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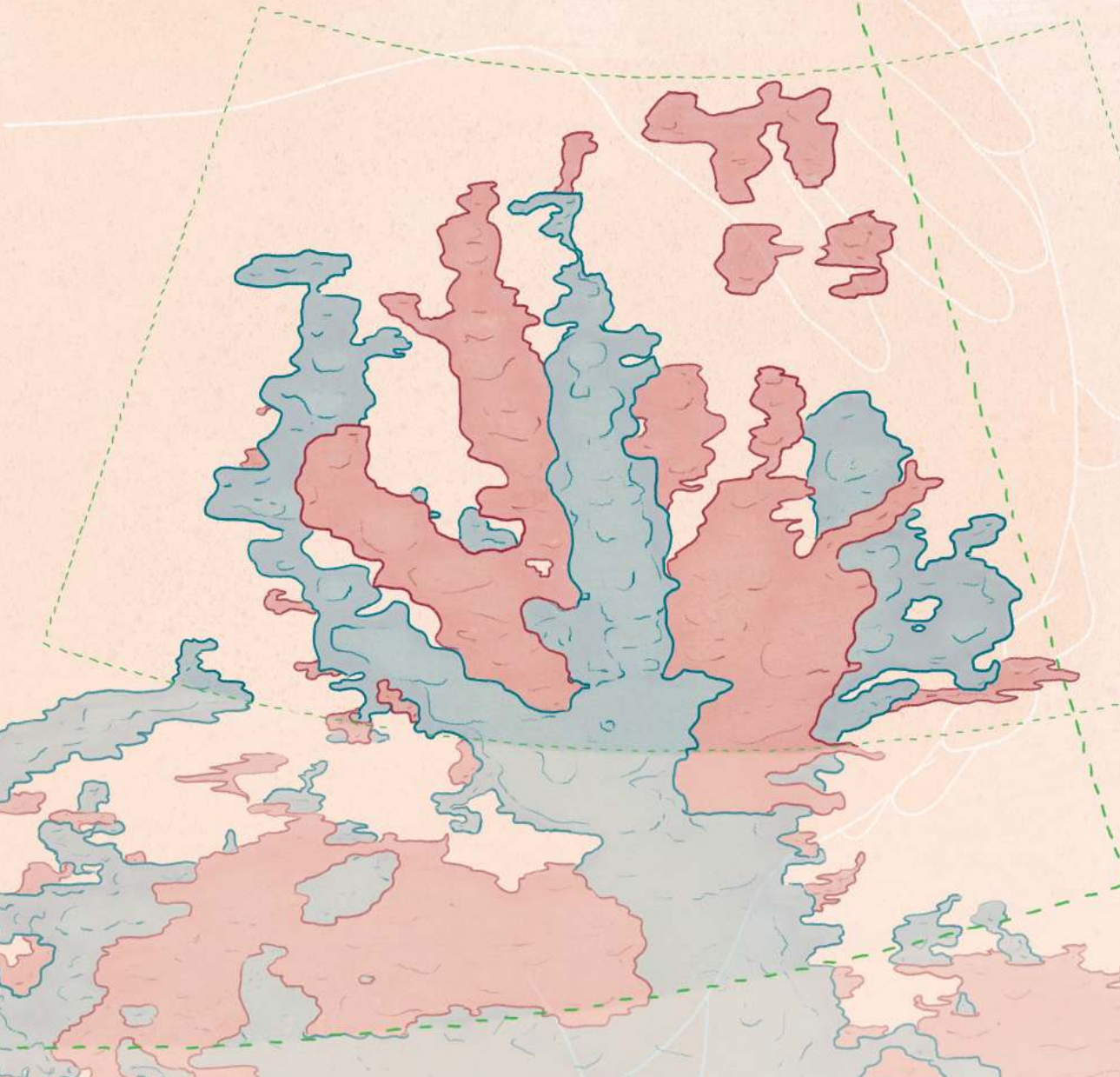
Nina C.J. Peters



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Prediction Of Postnatal Outcome In Foetuses At Risk For Chronic Lung Disease

Predictie van postnatale uitkomst in foetus met een verhoogd risico op chronische long ziekte

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Paranimfen

Ingrid Brussé
Rianne Hagens

Voor Noa en Milu

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CHAPTER 1

Introduction

INTRODUCTION

Foetal lung development takes place in five stages (embryonic, pseudoglandular, canalicular, saccular and alveolar)[1], during which the trachea and both lungs are formed from two avascular buds by a complex branching pattern. This process is controlled by a number of interacting genes and expression of transcription factors that determine normal or abnormal branching morphogenesis. If these processes do not occur at the correct moments in time, a variety of lung abnormalities may develop.[2, 3] Amongst others, foetuses with a congenital diaphragmatic hernia (CDH), giant omphalocele (GO) or congenital lung malformation (CLM) are at risk for pulmonary hypoplasia and/or development of pulmonary hypertension (PH).[4-11] These foetuses are also at risk for the development of chronic lung disease (CLD), which is associated with significant morbidity and mortality.[12-15 16]

In foetal life, a high pulmonary vascular resistance causes extrapulmonary shunting which results in low pulmonary blood flow (8-10% of total cardiac output). Immediately after birth, the pulmonary artery resistance drops, thereby allowing for increased blood flow throughout the pulmonary vascular system. In neonatal life, failure of the pulmonary system to reduce pressure in the pulmonary circulation at that moment can lead to PH.[17, 18] According to international criteria, postnatal PH is defined as a pulmonary wedge pressure above 20 mmHg proven by invasive cardiac catherization. Classically in pathology literature, pulmonary hypoplasia and/or PH are characterized by aberrant pulmonary and pulmonary vascular development including increased wall thickness due to muscular hypoplasia and thickened adventitia of small pulmonary arteries, reduced number of branches, relatively low lung weight and lung/body ratio and a low radial alveolar count.[19-22] Previous studies have shown that these vascular changes leading to PH are already present in foetuses with congenital anomalies associated with pulmonary hypoplasia.[2, 17, 18, 23-27]

Several studies have examined the value of two-dimensional (2D) and three-dimensional (3D) prenatal ultrasound predictors of abnormal pulmonary (vascular) development to improve the choice of intrauterine treatment and to estimate postnatal outcome for use in prenatal counselling.[28] Differences in lung growth,[29-34] diameter of the pulmonary artery,[35, 36] Doppler wave patterns,[37-39] decreased pulmonary vascular branching[40] and a decrease in pulmonary artery perfusion[41] have been described as possible predictors. None of these methods, so far, have been proven to have sufficient sensitivity and specificity to predict PH and/or CLD.[42]

Aims and outline of this thesis

In this two-part thesis we assessed the value of prenatal ultrasound predictors for postnatal outcome in foetuses with a congenital anomaly associated with pulmonary hypoplasia and an increased risk of postnatal development of PH and/or CLD.

The specific aims can be summarized as follows:

Part I

1. To develop prenatal tools for use in daily practice that would enable more patient-specific counselling regarding postnatal outcome.
2. To assess the value of currently used prenatal ultrasound prediction parameters for prediction of postnatal management, the need for pulmonary hypertension treatment and/or development of chronic lung disease.
3. To validate new methods for prenatal assessment of pulmonary development.

Part II

4. To examine differences in prenatal counselling between specialists of different disciplines based on the same prenatal characteristics.
5. To explore the possibilities to apply prenatal measurements in postnatal treatment protocols.

This introduction chapter is followed by a study on the development of the omphalocele circumference/abdominal circumference (OC/AC)-ratio for prediction of type of surgical closure in foetuses with an isolated omphalocele before 24 weeks' gestation (**Chapter 2**). The validation of this ratio for all foetuses with an omphalocele throughout gestation is reported in **Chapter 3**. In **Chapter 4,** a multicentre study is described that aimed to validate the observed-versus-expected lung-to-head ratio (O/E-LHR) in CDH in an era of standardized neonatal treatment. Subsequently, new techniques to assess pulmonary vascular development throughout gestation in foetuses with left-sided CDH are presented in **Chapter 5**. In the final chapter of this part of the thesis, prenatal parameters assessed in foetuses with a congenital lung malformation (CLM) for prediction of postnatal outcome are reviewed **(Chapter 6).**

Part II presents research on the application of prenatal prediction in postnatal management. First, we aimed to identify differences in the specialists' view on the patient population and differences with regard to the medical specialists' counselling of expectant parents with a foetus with an omphalocele **(Chapters 7 and 8). Chapter 9** describes the implications of the O/E-LHR ratio or postnatal management in foetuses with a left-sided CDH. **Chapters 10** and **11** provide, respectively, the general discussion and summary of this thesis.

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PART I

Prenatal prediction of postnatal outcome

CHAPTER 2

The relation between viscero-abdominal disproportion and type of omphalocele closure

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ABSTRACT

Objective

To investigate the relation between prenatal ultrasound measurements of viscero-abdominal disproportion and the expected type of postnatal surgical closure of an omphalocele.

Study design

Retrospectively, 24 fetuses diagnosed with an isolated omphalocele in the 2nd trimester of pregnancy were selected (period 2003–2013). An image of the axial plane of the abdomen at the level of the defect was retrieved. The ratio of omphalocele circumference to abdominal circumference (OC/AC), and the ratio of defect diameter to abdominal diameter (DD/DA) were calculated. Prognostic outcome was primary closure. Sensitivity and specificity and the corresponding area under the ROC curve of these ratios were calculated as measurements of prognostic accuracy.

Results

Primary closure was achieved in 15/24 cases. For the OC/AC-ratio a cut-off value of 0.82 successfully predicted outcome in 23/24 cases with an area under the ROC curve of 0.99. A cut-off value of 0.61 for the DD/DA-ratio successfully predicted type of closure in 20/24 cases with an area under the ROC curve of 0.88. In all cases without eviscerated liver tissue, the defect was primarily closed.

Conclusion

In prenatal isolated omphalocele cases, the OC/AC-ratio is better at predicting postnatal surgical closure than the DD/DA-ratio and can be used as a prognostic tool for expected type of closure in the 2nd trimester of pregnancy.

INTRODUCTION

An omphalocele is a congenital defect of the anterior abdominal wall, with a birth prevalence of approximately 1:12.5000.[1] Depending on the size of the defect, intestines, liver and/or gallbladder are herniated through the defect.[2] Additional congenital anomalies and/or syndromes, with or without abnormal karyotype, are found in approximately 80% of cases.[3] Associated anomalies rather than the omphalocele alone are decisive for treatment decision and determine clinical outcome.[4,5] Depending on gestational age at diagnosis and presence of associated abnormalities, termination of pregnancy (TOP) is performed in up to 83% of cases.[1,3,5–7]

In isolated cases postnatal outcome depends on type of surgical closure (primary or delayed).[8] Primary closure is defined as closure immediately after birth. Delayed closure is defined as late or even post-infancy closure after allowing the omphalocele to desiccate, contract and epithelialize with closure of the ventral hernia at a later stage. Type of surgical closure is determined by the size of the defect, evisceration of the liver,[9] intra-abdominal pressure, duration of mechanical ventilation, inspiratory oxygen fraction and clinical presentation of pulmonary hypoplasia.[10] Delayed closure is associated with increased co-morbidity and extended hospital stay.[11,12]

The vast majority of the omphaloceles is diagnosed in the first or second trimester of pregnancy. As there are no guidelines on case specific assessment, counseling on individual prognosis is not yet possible.[3,7,13–15] Individual counseling, however, enables parents to anticipate for a relative long period of hospitalization of their infant.[3,15] We report on additional ultrasound measurements for omphalocele closure which are relevant to the counseling period, i.e. prior to 24 weeks of gestation.

MATERIALS AND METHODS

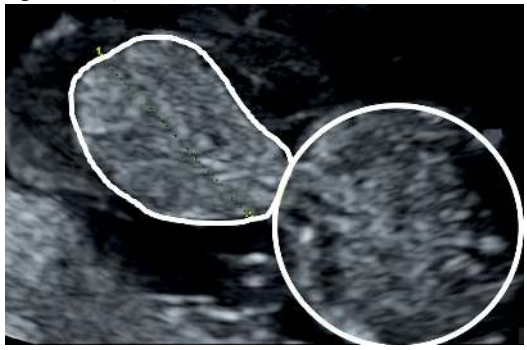
This retrospective cohort study was conducted in our tertiary referral center between January 2003 and December 2013. For the study we restricted ourselves to isolated omphaloceles diagnosed prior to 24 weeks of gestation. As a result, cases were not selected if they were diagnosed prenatally with major associated anomalies or karyotype with lethal prognosis (i.e. trisomy 13 or 18), which would influence type of postnatal closure. Cases diagnosed postnatal with additional anomalies were not excluded, since this information was unknown at the time of the prenatal diagnosis and counseling. Cases were excluded when parents had decided to terminate the pregnancy, an intrauterine fetal death (IUFD) had occurred, or infants had died shortly after birth before any attempt of surgical treatment. Also, cases were excluded if no ultrasound images

were available depicting the axial plane of the abdomen at the level of the defect for measuring the required ratios.

The primary outcome variable was type of closure (primary or delayed). The indications for the type of surgical closure were the same for all cases, according to the consensus of the Dutch society of pediatric surgery.[16] The following maternal and fetal characteristics of the included cases were obtained: gestational age at ultrasound examination, omphalocele contents, presence of other associated anomalies (detected prenatally or postnatally), fetal karyotype, and type of closure (Table 1). In cases where there was more than one ultrasound examination prior to 24 weeks of gestation we selected the one closest to 20 weeks of gestation.

We studied two ratios as candidate predictors of successful primary closure. The OC/AC-ratio was measured excluding the edema by dividing the omphalocele circumference by the abdominal circumference in the same ultrasound image at the level of the defect (Fig. 1.1). The OC/AC-ratio was measured to assess the size of an omphalocele in comparison to the fetal abdomen to quantify the degree of viscero-abdominal disproportion. This resembles the assessment by pediatric surgeons, who estimate the viscero-abdominal disproportion postnatally to determine whether a defect can be primarily closed.

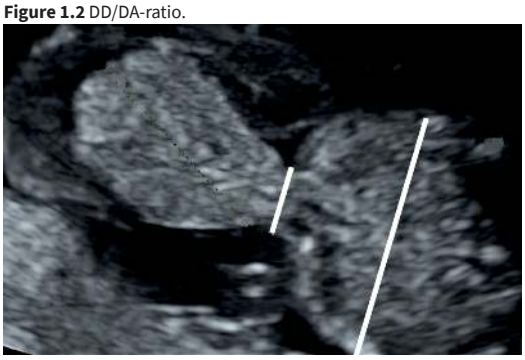
Figure 1.1 OC/AC-ratio.



An ultrasound image of an axial plane of the fetus at the level of the defect showing the method for the measurement of the OC/AC-ratio. The omphalocele circumference (OC) and the abdominal circumference (AC) are measured at the level of the defect in an axial plane. The omphalocele circumference is measured without umbilical cord and/or edema if present.

The DD/DA-ratio is the ratio of the diameter of the defect and the diameter of the abdomen measured parallel to each other at the level of the defect (Fig. 1.2). The DD/DA-ratio was measured to representthe relative size of the defect in relation to the abdominal size, hypothesizing that a large defect in relation to a narrow abdomen would be difficult to close primarily.

Figure 1.2 DD/DA-ratio.



An ultrasound image of an axial plane of the fetus at the level of the defect showing the method for the measurement of the DD/DA-ratio. The abdominal diameter (DA) is measured parallel to the defect diameter (DD) in an axial plane.

In both cases, higher ratios represent a larger defect relative to fetal size. The ratios were all measured by one investigator (T.E. Cohen-Overbeek).

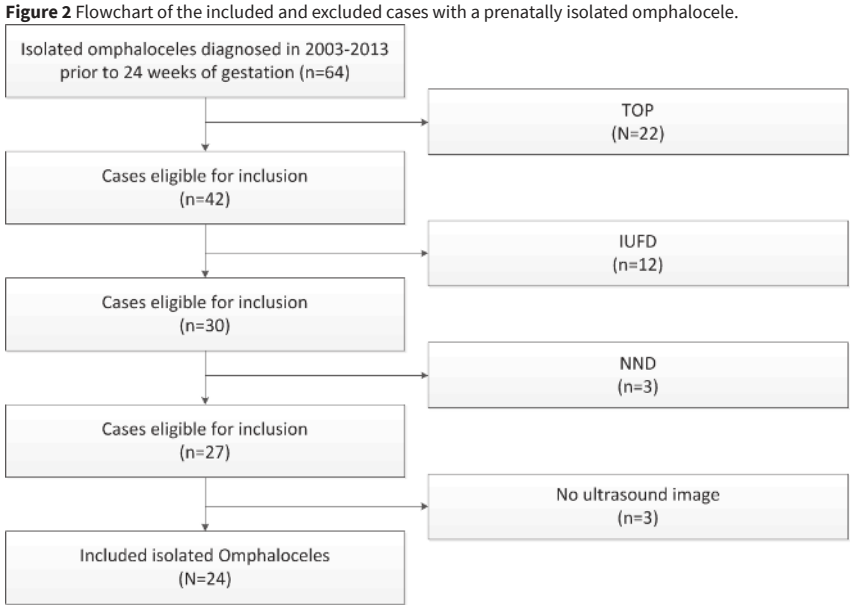
We calculated the sensitivity and specificity for 5 different cut-offs per ratio and used a receiver-operating characteristics (ROC) approach to establish which cut-offs would be most suitable if the ratio was used as predictor for type of closure. We assumed the best cut-off would be the one yielding the lowest sum of false positives (FP) and false negatives (FN), i.e. inaccurate predictions, giving equivalent weight to both inaccuracies. We calculated the area under the curve as a measure of predictive accuracy, where 0.5 reflects chance prediction and 1.0 reflects perfect prediction. All calculations and statistical analyses were performed using Microsoft Office Excel 2003 and SPSS statistics version 17.0. In SPSS the ROC is approximated following the non-parametric, trapezoidal rule.

RESULTS

Of the initial 146 cases diagnosed with an omphalocele in the selected period, 64 cases were prenatally isolated cases with an omphalocele diagnosed prior to 24 weeks of gestation. Thirty-seven cases were excluded because of TOP (n = 22), IUFD (n = 12) or a neonatal death (NND, n = 3). Three cases were excluded as the required image of the axial plane of the abdomen was unavailable, due to incomplete patient records and unrelated to the severity of the defect. Twenty-four cases remained (Fig. 2).

Table 1 displays the retrieved prenatal and postnatal data. Primary closure was performed in 15 of 24 cases. In 6 out of these 15 infants associated anomalies were detected after birth. Four infants were diagnosed with Beckwith–Wiedemann syndrome. One infant, prenatally diagnosed with Turner syndrome, showed a coarctation of the aorta

Figure 2 Flowchart of the included and excluded cases with a prenatally isolated omphalocele.



Abbrevations: IUFD, intra uterine fetal death; NND, neonatal death; TOP, termination of pregnancy.

after birth for which corrective surgery was performed. A ventricular septal defect was detected in one other infant. Delayed closure was planned in the 9 other cases. One infant with a postnatally detected Tetralogy of Fallot underwent corrective surgery. He died from therapy resistant pulmonary hypertension and subsequent right ventricular failure at 4 months after birth, prior to the scheduled closure of the defect. Two other infants were born prematurely at 30 weeks gestational age and both died from bronchopulmonary dysplasia in combination with pulmonary hypoplasia at 4 or 6 months after birth, before planned surgical closure. The remaining 6 infants showed long term survival; one was diagnosed with a mild aortic valve stenosis, one with a muscular ventricular septal defect and Beckwith–Wiedemann and another with a corpus callosum agenesis and a ventricular and atrial septal defect. The OC/AC-ratio and DD/DA-ratio ranged from 0.29 to 1.02, and 0.23 to 0.86, respectively (Figs. 3.1 and 3.2).

The five cut-offs calculated per ratio are presented in Table 2, with the number of true positive and true negative predictions per cut-off, the total number of correct predictions (accuracy) and the corresponding sensitivity and specificity with a 95% confidence interval.

With a cut-off value at 0.82 for the OC/AC-ratio, the type of closure is correctly predicted in 23 out of 24 cases. The number of true positives (TP) was 8 and the number of true negatives (TN) was 15, resulting in a sensitivity of 88.9% (95% CI 0.51–0.99) and a specificity of 100% (95% CI 0.75–1.00). The area under the curve is 0.99. For the

Table 1 Patient characteristics.

GA	Prenatal associated anomalies	Liver in omphalocele prenatally	OC/AC-ratio	DD/DA-ratio	Delivery mode, GA (weeks)	Birth weight (grams)	Type of surgery	Postnatal associated anomalies	Hospital stay (days)
19	-	no	0.53 (61/116)	0.6 (21/35)	VD, 39.4	4100	Primary	BWS	5
19	TS	no	0.53 (83/158)	0.37 (17/46)	VD, 35.0	1820	Primary	CoAo	57
19	SUA	no	0,57 (72/125)	0,53 (20/38)	VD, 38.5	2970	Primary	-	15
20	-	no	0.56 (103/184)	0.42 (28/66)	CS, 41.1	2830	Primary	-	7
20	-	no	0,39 (52/135)	0,41 (17/41)	CS, 35.5	2485	Primary	-	7
20	-	no	0,29 (34/116)	0,26 (10/38)	VD, 35.6	1919	Primary	-	15
20	-	no	0,48 (71/148)	0,25 (12/48)	CS, 33.5	2565	Primary	BWS	62
21	-	no	0,49 (82/166)	0,32 (17/54)	VD, 37.5	3650	Primary	BWS	9
22	-	no	0.72 (80/111)	0.23 (8/35)	VD, 37.1	3890	Primary	BWS	20
23	-	no	0,29 (51/176)	0,40 (12/52)	CS, 39.1	3195	Primary	-	5
23	-	no	0,4 (66/164)	0,29 (15/52)	VD, 39.0	3500	Primary	-	5
19	(twin)	yes	0.67 (78/118)	0.53 (17/32)	VD, 37.1	2200	Primary	-	9
20	-	yes	0.76 (97/128)	0.48 (20/42)	VD, 33.6	1960	Primary	Small VSD	18
20	-	yes	0.81 (122/150)	**0.7 (35/50)***	VD, 34.2	3430	Primary	-	20
21	-	yes	0.59 (86/145)	0.46 (21/46)	VD, 38.6	3100	Primary	-	25
16	-	yes	1 (60/60)	**0.52 (12/23)****	VD, 38.6	2730	Delayed	ACC, AVSD	100
19	-	yes	0.94 (117/124)	0,64 (23/36)	VD, 35.6	2600	Delayed	-	417
20	-	yes	1,02 (134/132)	**0,50 (21/42)****	VD, 30.6	1495	Delayed	-	106[a]
21	-	yes	0.90 (128/142)	0.65 (30/46)	VD, 35.4	1870	Delayed	ToF	57[a]
21	-	yes	0,95 (115/121)	0,73 (27/37)	CS, 38.5	3000	Delayed	-	49
22	-	yes	**0.74 (115/155)****	0.67 (30/45)	CS, 39.3	2140	Delayed	Mild AoVS	108
22	-	yes	0.91 (106/116)	0.86 (32/37)	CS, 30.0	1500	Delayed	-	192[b]
22	-	yes	0,83 (135/163)	0,69 (36/52)	CS, 39.1	5390	Delayed	BWS, mVSD	42
23	-	yes	0.93 (136/147)	**0.5 (22/44)****	VD, 38.6	2910	Delayed	-	23

[a]Infant death at 4 months, [b]Infant death at 6 months; *False positive (FP) or **False negative (FN) for type of closure after calculating the cut-offs.

Abbrevations: ACC, Agenesis of the corpus callosum; AoVS, Aortic valve stenosis; AVSD, atrial ventricular septal defect; BWS, Beckwith Wiedemann Syndrome; CoAo, Coarctation of the Aorta; CS, caesarean section; DD/DA, ratio of the defect diameter and the abdominal diameter; GA, gestational age in weeks. days; mVSD, musculous ventricular septal defect; OC/AC, the ratio of the omphalocele circumference and the abdominal circumference; SUA, Single umbilical artery; TS, Turner Syndrome; ToF, Tetralogy of Fallot; VD, vaginal delivery; VSD, ventricular septal defect.

Figure 3.1 Scatterplot of the OC/AC-ratio per type of closure and gestational age.

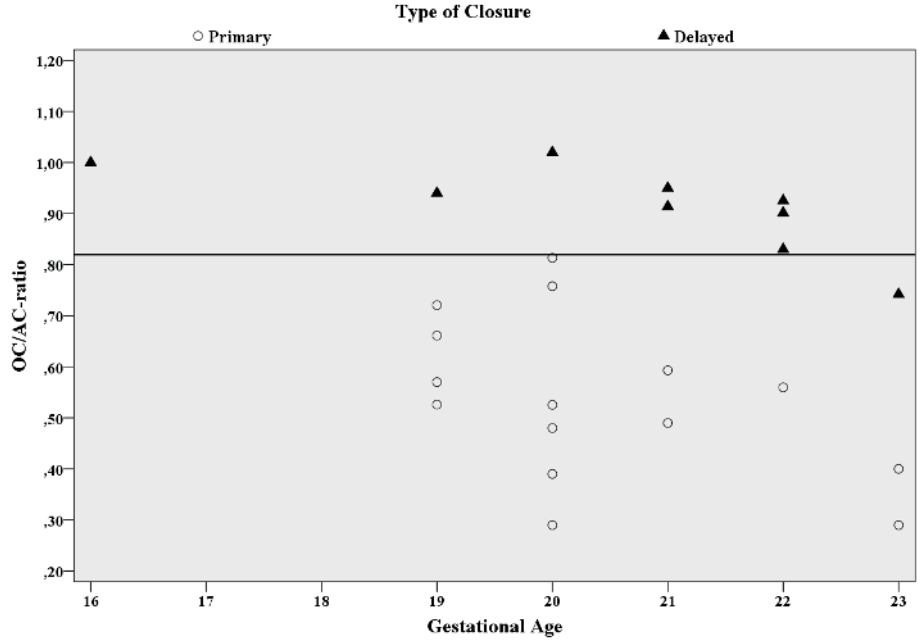


Figure 3.2 Scatterplot of the DD/DA-ratio per type of closure and gestational age.

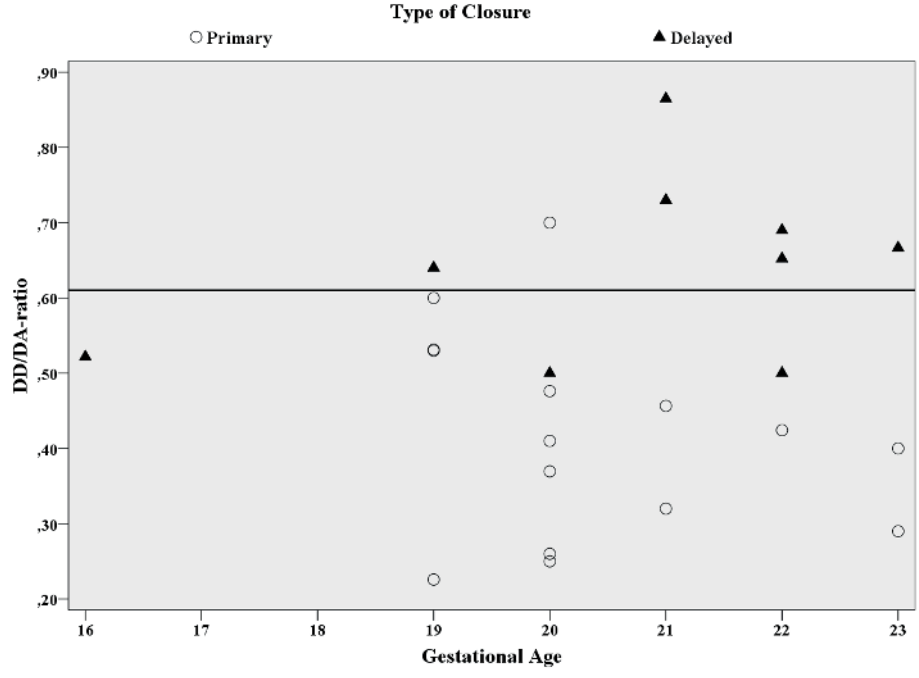


Table 2 Calculated cut-offs per ratio.
OC/AC ratio

Cut-off	True positive	True negative	Accuracy	Sensitivity	Specificity
0.63	9	11	20	100 (95% CI 0.62-1)	73 (95% CI 0.44-0.91)
0.73	9	13	22	100 (95% CI 0.63-1)	87 (95% CI 0.58-0.98)
0.79	8	14	22	89 (95% CI 0.51-0.99)	93 (95% CI 0.66-1)
0.82	**8**	**15**	**23**	**89 (95% CI 0.51-0.99)**	**100 (95% CI 0.75-1)**
0,87	7	15	22	78 (95% CI 0.40-0.96)	100 (95% CI 0.75-1)

DD/DA-ratio

Cut-off	True positive	True negative	Accuracy	Sensitivity	Specificity
0.41	9	8	17	100 (95% CI 0.63-1)	47 (95% CI 0.27-0.78)
0.51	7	11	18	78 (95% CI 0,40-0.96)	73 (95% CI 0.45-0.91)
0.57	6	13	19	67 (95% CI 0.31-0.91)	87 (95% CI 0.59-0.98)
0,61	**6**	**14**	**20**	**67 (95% CI 0.31-0.91)**	**93 (95% CI 0.66-1)**
0,65	4	14	18	44 (95% CI 0.15-0.77)	93 (95% CI 0.66-1)

The bold lines are the cut-offs with the highest number of accurate predictions.
Abbrevations: CI, Confidence Interval; DD/DA, ratio of the defect diameter and the abdominal diameter; OC/AC-ratio, the ratio of the omphalocele circumference and the abdominal circumference.

DD/DA-ratio a cut-off value at 0.61 provided the most favorable number of TP (n = 6) and TN (n = 14) with regard to primary closure. Using this cut-off we correctly predicted the type of closure in 20 of 23 cases. Sensitivity is 66.7% (95% CI 0.31–0.91) and specificity is 93.3% (95% CI 0.66–1.00). The area under the curve was 0.88. The corresponding ROC graphs of both ratios are presented in Figs. 4.1 and 4.2. All cases without liver (n = 11) in the omphalocele could be closed primarily as shown in Table 1.

COMMENTS

We demonstrated that 2 ultrasound based ratios, in particular the OC/AC-ratio, are predictive for the type of postnatal surgical closure of an omphalocele. Both ratios are easily obtained independent of fetal size. They may support prenatal counseling of the parents, attributing towards case specific counseling.

In 10 out of 24 cases associated anomalies were detected after birth, which were not known prenatally. This is an important finding which is included in prenatal counseling.[3] Despite the presence of postnatally detected anomalies, the cases were by intent included in this study, since there was no knowledge of these anomalies prenatally and these parents would be counseled accordingly (intention-to-treat like approach). The influence of these associated anomalies on the type of closure cannot be disregarded, however. In one case a fetus was born with the Tetralogy of Fallot and the infant died

prior to the scheduled surgery to close the defect. Another two infants were born prematurely at 30 weeks of gestation, which is a known complication of fetuses with an omphalocele.[17] Severe prematurity influences postnatal management as immaturity of the lungs in combination with some degree of pulmonary hypoplasia may prevent any type of surgical procedure. Note that the OC/AC-ratio in these censored cases was very large, indicating a lower probability of primary closure should they have survived.

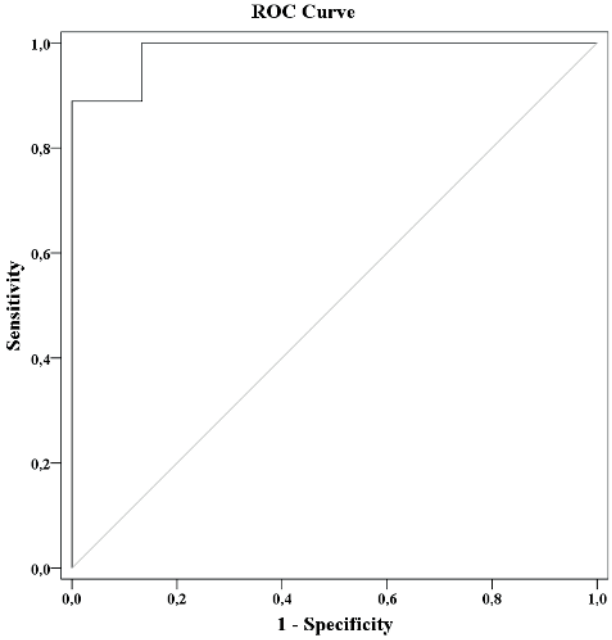
Location of the liver was identified in all cases. In our study, all cases (11/24) without liver herniation were closed primarily. In remaining 13/24 (54%) cases, the liver was present in the omphalocele. Four of these 13 cases (31%) were primarily closed confirming the observation made by Heider et al.[18] that liver present in the omphalocele is associated with a decreased rate of primary closure. Based on their OC/AC-ratio, the 4 cases were correctly predicted for primary closure independent of the presence of liver herniation. The OC/AC-ratio proves to be a valuable measure in addition to the knowledge about the location of the liver.

The use of a ROC curve needs careful interpretation. In our study the ROC represents the calculated sensitivity and specificity for all possible cut-offs per ratio: in other words the number of correct predictions of type of closure. In our study a false negative (FN) result would imply that a predicted delayed closure actually closes primarily, while a false positive (FP) prediction result implies the reverse. The conventional ROC approach assigns equal weight to a FN and a FP case. One could hypothesize that a FP prediction has a more negative impact on future parents than a FN prediction. To account for this a weight can be applied for FP and FN predictions. Since in our study the goal was to establish the most reliable cut-off per ratio, we did not apply differential weights in the ROC analysis.[19] For future studies regarding counseling purposes, evaluation of patients' preferences can be incorporated by assigning various differential weights for FN and FP predictions.

In the years 2003–2013, postnatal care with respect to decisions on type of closure did not change. On the other hand, duration of artificial ventilation is nowadays often prolonged because normal postnatal growth is strived after. This may in turn complicate the staged closure of larger defects.[3,15] This change in protocol was reason to refrain from artificial ventilation as a parameter in our study. Length of stay and time to full enteral feeding co-depend on type of closure, therefore we chose not to include these as outcome parameters in our study.[3]

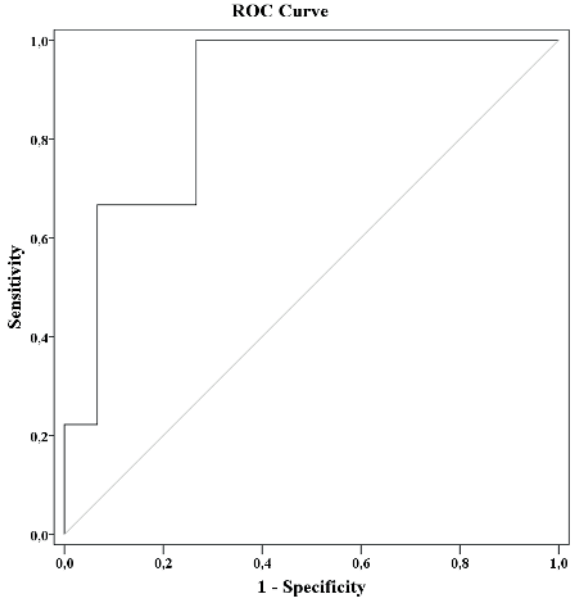
A number of ratios, including the OC/AC-ratio, have been previously investigated and our findings are supported in these papers.[7,20] Montero et al. found the O/HC-ratio (maximum omphalocele diameter divided by the fetal head circumference) most predictive for the type of surgical closure.[7] Although this ratio might be independent of gestational age it

Figure 4.1 ROC-curve (receiver operating characteristics curve) of the OC/ACratio.



The image depicts the plotted ROC-curve of the sensitivity and 1-specificity of the OC/AC-ratio with an area under de curve (AUC) of 0.99.

Figure 4.2 ROC-curve (receiver operating characteristics curve) of the DD/DA-ratio.



The image depicts the plotted ROC-curve of the sensitivity and 1-specificity of the DD/DA-ratio with an area under de curve (AUC) of 0.88.

does not reflect the viscero-abdominal disproportion. Since omphaloceles present in all different shapes and sizes and seldom as a perfect circle, the circumference of the omphalocele, instead of the maximum diameter, should be more representative.

In contrast to the previous studies[7,20] we limited our cases to being diagnosed prior to 24 weeks gestational age. Parents are counseled about postnatal outcome based on information avail- able at time of diagnosis, which in most cases is during first trimester screening or at the routine 20 week ultrasound scan. There is no evidence that the ratios and the cut-offs are the same throughout all gestational ages and that the predictive value remains constant.

The number of TOP and IUFD in our study is comparable to other omphalocele studies[1,3,5–7,18,20–22] and has attributed to a high attrition rate which resulted in a small number of cases with available postnatal surgical outcome. Test performance in our study was established using an outcome measure which requires being live-born, therefore we initially excluded the IUFD and TOP cases since there was no knowledge of type closure. The predictive value of calculating the ratios is, therefore, applicable to live-born cases. Standard obstetric care does, however, also involve counseling prior to 24 weeks of gestation on the possible occurrence of IUFD and on expected postnatal outcome of these cases. The data presented in a study by Kleinrouweler et al.,[20] revealed that the OC/AC-ratio is predictive for the type of closure (area under the ROC curve of 1.00), but is not helpful in predicting specifically an IUFD. In order to establish the most reliable cut-offs and their wide-scale applicability, as well as to decide whether gestational age is of an influence on these ratios, a prospective case-control study is required.

We studied two ratios and their predictive value for type of postnatal surgical closure of an omphalocele. We concluded that the OC/AC-ratio is better at predicting postnatal surgical closure than the DD/DA-ratio and can be used as a prognostic tool for expected type of closure prior to 24 weeks of gestation. The OC/AC-ratio can be helpful in individual counseling about the expected postnatal course.

CONDENSATION

The OC/AC-ratio is better at predicting postnatal surgical closure of an omphalocele than the DD/DA-ratio and can be used as a prognostic tool in the 2nd trimester of pregnancy.

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CHAPTER 3

The validity of the viscero-abdominal disproportion ratio for type of surgical closure in foetuses with an omphalocele

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ABSTRACT

Objective

To determine the predictive value of the fetal omphalocele circumference/abdominal circumference (OC/AC)-ratio for type of surgical closure and survival and to describe the trajectory of OC/AC-ratio throughout gestation.

Methods

This cohort study included all live-born infants prenatally diagnosed with an omphalocele in our tertiary centre (2000–2017) with an intention to treat. The OC/AC-ratio and liver position were determined using 2D ultrasound at three periods during gestation (11–16, 17–26, and/or 30–38 weeks). Primary outcome was type of closure; secondary outcome was survival. In the secondary analyses, the predictive value of the OC/AC-ratio trend for type of closure and survival was assessed.

Results

Primary closure was performed in 37/63 (59%) infants, and 54/63 (86%)survived. The OC/AC-ratio was predictive for type of closure and survival in all periods. Optimal cut-off values for predicting closure decreased throughout gestation from 0.69 (11–16 weeks) to 0.63 (30–38 weeks). Repeated OC/AC-ratio measurements were available in 33 (73%) fetuses. The trend of the OC/AC-ratio throughout gestation was not significantly associated with type of closure. All infants without liver herniation underwent primary closure.

Conclusion

Type of omphalocele surgical closure and survival can be predicted prenatally on the basis of the OC/AC-ratio and liver herniation independent of associated anomalies.

Learning objective

The reader will be able to use the OC/AC-ratio throughout gestation in all omphalocele cases for prediction of type of closure and survival and thus patient counselling

INTRODUCTION

An omphalocele is a congenital anomaly characterized by herniation of the abdominal viscera through the abdominal wall at the umbilicus covered by a membrane.[1] It is reported to occur in 1 to 2 per 10 000 live births.[2] Multiple congenital anomalies (MCAs) are observed in 30% to 70% of fetuses with an omphalocele, and chromosomal abnormalities are present in 10% to 30%.[1,3,4] Infants with MCA or chromosomal abnormalities carry a significantly higher risk of comorbidity than those with an isolated omphalocele.[1,3-6] In the Netherlands, in up to 74% of cases, depending on the presence of associated anomalies and gestational age at diagnosis, the pregnancy is terminated.[7]

A small (or minor) omphalocele can be closed primarily, ie, within 48 hours after birth. If the postnatal defect size equals or is larger than 5 cm, with liver (partly) protruding,[8] closure is usually delayed in view of the viscero-abdominal disproportion.[9] These infants with a "giant" omphalocele are at risk for chronic lung disease (CLD), feeding problems, prolonged hospital stay, and a lower chance of survival, besides the difficulty of closure of the abdominal wall defect.[10-13]

Today, around 90% of omphaloceles and most of the additional anomalies are detected by prenatal ultrasound from 11 week gestation onwards.[2,14] Previous studies have shown that ultrasound parameters can predict postnatal outcome in fetuses with an omphalocele.[15-19] More recent studies showed that the ratio between the omphalocele circumference (OC) and the abdominal circumference (AC) — the OC/AC-ratio — predicts the method of postnatal surgical closure.[17,20] These studies were mostly limited to single measurements and infants whose omphalocele was assumed to be isolated at prenatal ultrasound. Still, in approximately one-third of such cases, additional anomalies are detected after birth.[4,21] These additional anomalies may influence postnatal outcome, including type of closure.

The primary aim of this study was to evaluate the predictive value of the OC/AC-ratio as either cross-sectional or a repeated measurement in all fetuses with an omphalocele (isolated and non-isolated) and a postnatal intention to treat. Secondarily, we examined the predictive value of the OC/AC-ratio for survival before and after birth.

METHODS

Study population

We analysed prospectively stored data of live-born infants, who were prenatally diagnosed with an omphalocele in our tertiary referral centre from January 2000 up to and

including December 2017. On a postnatal intention-to-treat basis, those infants were included for whom at least one prenatal ultrasound image was available. Fetuses with a rare abdominal wall defect (e.g, body stalk anomaly, pentalogy of Cantrell, or amniotic band syndrome) and infants lost to follow-up were excluded. Data of pregnancies resulting in intrauterine fetal death (IUFD) or neonatal death (NND; defined as death during the first 28 days) were stored in a separate database. Fourteen of the included isolated cases have previously been studied to validate the OC/AC-ratio measured prior to 24-weeks gestation.[4,17] The Medical Ethical Review Board waived approval because data obtained during routine care were retrospectively analysed (MEC-2015-308).

Prenatal measurements and parameters

The OC and AC were measured, if possible, at three time periods during gestation: at the beginning of the second trimester (11- to 16- week gestation; US1), mid-second trimester (17- to 26-week gestation; US2), and in the third trimester (30- to 38-week gestation; US3). Based on availability of data, the OC/AC-ratios were calculated according to a previously described method.[17] We included three examples of third trimester measurements of the OC/AC-ratio as Figure S1. All measurements were performed in retrospect by two experienced physicians (TECO and NCJP), who were unaware of post- natal outcome. We retrieved data on content of the omphalocele, presence of fetal growth restriction, polyhydramnios (defined as an amniotic fluid index (AFI) of >24 cm), presence of chromosomal abnormalities, and MCA. Those MCAs that required surgery or multiple follow-up visits were regarded as major.

Postnatal parameters

We retrieved data on delivery mode, gestational age (GA) at delivery, birth weight, and Apgar score at 5 minutes. Preterm birth was defined as delivery prior to 37-week gestation. The method of closure was recorded as either primary or delayed. Delayed treatment included both initial epithelization and later surgical closure.[9,10] Additional data retrieved were the durations of parenteral feeding, length of hospital stay (LOS), and supplemental oxygen dependency during the initial hospital stay after birth as well as the presence of CLD, defined as oxygen supplementation for at least 28 days.[10,22] A giant omphalocele was defined as a postnatal defect size of at least 5 cm, with liver (partly) protruding. Survival was defined as survival until at least 1 year of age. Infant death is defined as a death greater than 28 days after birth.

Statistical analysis

Patient characteristics are described as number (%) for categorical data and median (interquartile range, IQR) for continuous data.

Prenatal and postnatal parameters were compared between neonates with primary and delayed closure and between survivors and non-survivors using the chi-square or Fisher exact tests (nominal or ordinal variables) or Mann–Whitney tests (continuous variables). The mean OC/AC-ratios at the three time periods were compared using a general linear model that accounts for the within-subject correlations. The association between OC/AC-ratio at these three time periods and type of closure, survival, or presence of CLD was evaluated using univariable logistic regression analysis. The association between OC/AC-ratio at these three time periods and LOS was evaluated using Spearman's rank correlation coefficient.

The intraclass correlation coefficient (ICC) was used to quantify the interobserver agreement. TECO and NCJP both measured the OC/AC-ratio in 20 randomly selected cases, where they were blinded to each other's result. For good agreement, the ICC has to be .75, and for excellent agreement, the ICC has to be higher than .90. The ICC was calculated in a two-way mixed model with absolute agreement and reported as single measures.

To calculate the predictive value of the OC/AC-ratio for type of postnatal closure and for survival, a receiver-operating characteristic (ROC) curve was made for each time period separately. Data are presented as area under the curve (AUC) with a 95% confidence interval (95% CI). The cut-off with the highest value of the Youden index (sensitivity plus specificity minus 1) was regarded as the most suitable.

To examine the trend in the OC/AC-ratio throughout gestation, we performed a linear regression of the OC/AC-ratio at the three time periods for each patient separately, with GA (coded as a continuous variable) as the only independent variable. To summarize the longitudinal data of the OC/AC-ratio, we used an estimated level (intercept in the linear regression) and time trend (slope in the linear regression). This analysis concerned only fetuses for whom two or three OC/AC-ratios were available. The resulting estimates of the intercept and slope in the linear regressions served as independent variables in logistic regressions for type of closure. The slope is calculated per 1-day difference in gestation.

Logistic regressions were performed to predict type of closure and survival rate only in fetuses with liver herniation with the OC/AC-ratio as independent variable, for the time periods US2 and US3 separately.

For the purpose of the secondary aim, i.e., to examine the predictive value of the OC/AC-ratio for survival before birth, we included data of fetuses with an IUFD or NND — referred to as "fetuses without intention to treat." Those who were live-born and survived

past 1 month (i.e., not an IUFD or NND) are referred to as “fetuses with an intention to treat” for this analysis.

All odd ratios are related to the occurrence of either a delayed closure when the outcome is type of postnatal surgical closure or mortality when the outcome is survival. All calculations were performed using SPSS version 21.0 for Windows and Windows Excel 2010. A two-sided *p* value of less than .05 was considered statistically significant.

RESULTS

Study population

Sixty-three live-born infants with an intention to treat were eligible for analyses (Figure 1).

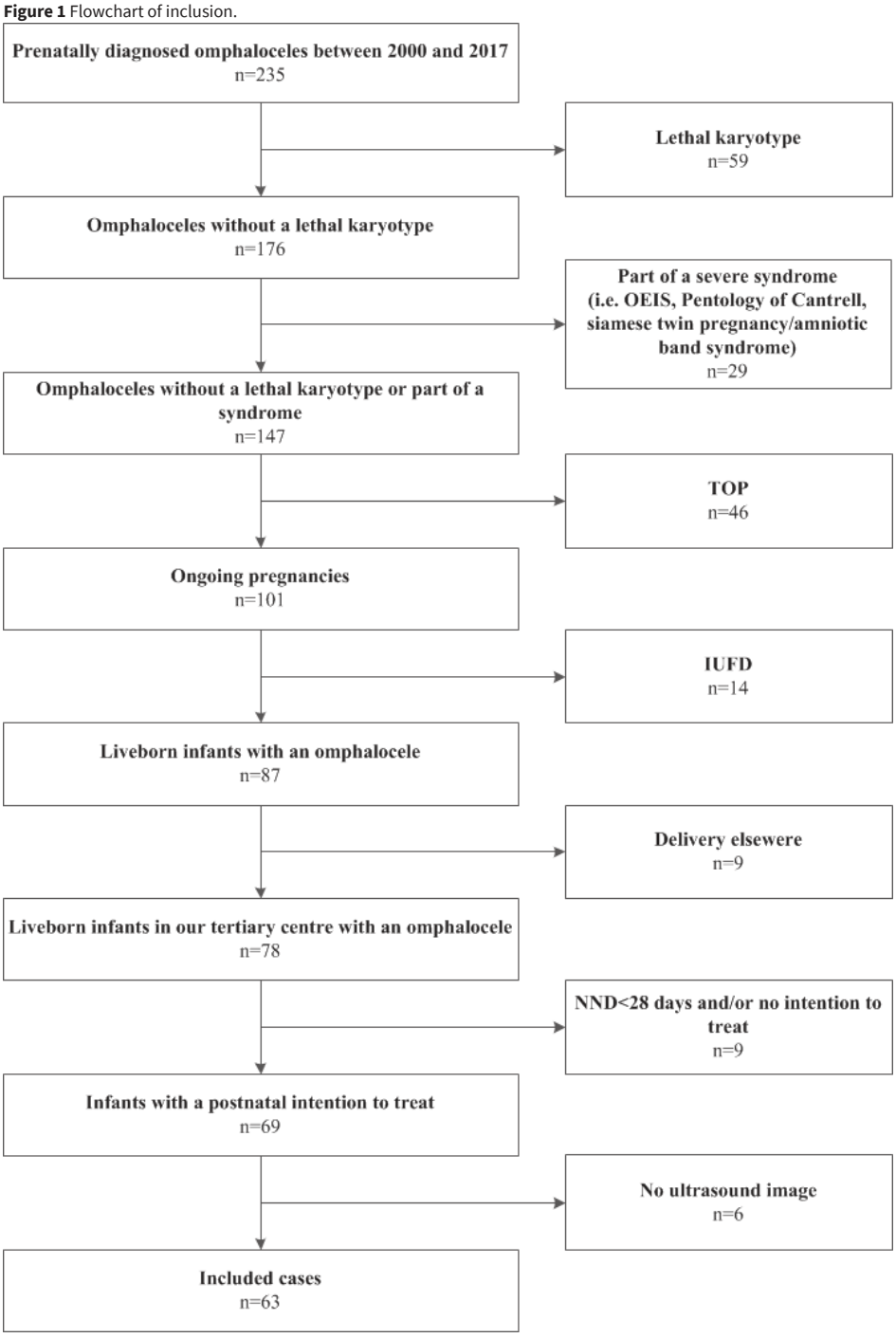
Primary closure had been performed in 37 (59%) infants. Fifty-four (86%) infants survived. The OC/AC-ratio could be calculated for 22 fetuses at US1, for 50 at US2, and for 58 at US3. Two or three OC/AC-ratios were available for 48 (76%) fetuses. The required image for measurement of the OC/AC-ratio was not available for two fetuses at US1 and two fetuses at US3. There were no differences between the assessments of liver location (extra abdominal vs intra-abdominal) at the different time periods per fetus. Interobserver agreement calculations resulted in an ICC of .966 (95% CI, 0.917– 0.986), representing excellent agreement. Patient characteristics are summarized in Table 1.

Additional anomalies were diagnosed in 19/63 (30%) of fetuses in the prenatal period. In nine out of 44 (20%) cases where the omphalocele was assumed isolated, additional anomalies were detected after birth. In six of these cases, the anomalies were major (Table 2). Eleven fetuses were diagnosed with a clinically significant syndrome and/or chromosomal abnormality; nine of them had Beckwidth-Wiedemann syndrome (BWS). The OC/AC-ratio in these fetuses ranged from 0.20 to 0.63 at US2 or US3. In 10 (91%) cases, there was no herniation of the liver through the defect (p = 0.006 comparedwith fetuses without a syndrome or chromosomal abnormality). In the case with liver herniation, only a very small slip of liver was present in the omphalocele. In all cases with a syndrome or chromosomal abnormality, a primary closure was performed (p = .002, compared with fetuses without a syndrome or chromosomal abnormality). Three (33%) of the nine fetuses with BWS had shown polyhydramnios.

Type of surgical closure

At all three time periods, the OC/AC-ratio was significantly positively associated with the probability of requiring a delayed closure (Figure 2, Table S1 for logistic regression).

Figure 1 Flowchart of inclusion.



Based on ROC curve analysis, the type of closure was predicted correctly by the OC/AC-ratio with optimal cut-off values of 0.69 at US1 (sensitivity 0.93 and specificity 0.90; AUC 0.96, 0.88–1.00; $p < .001$), 0.66 at US2 (sensitivity 0.88 and specificity 0.93; AUC 0.98, 0.95–1.00; $p < .001$), and 0.63 at US3 (sensitivity 0.95 and specificity 0.94; AUC 0.98, 0.95–1.00; $p < .001$) (Figure 3).

Table 1 Patient characteristics.

	Primary Closure (*n* = 37)	Delayed Closure (*n* = 26)	*p* value
Prenatal parameters			
US 11–16 weeks			
GA (w^{+d})	13^{+1} (12^{+4}–15^{+4})	16^{+1} (13^{+5}–16^{+6})	**.02**
OC/AC-ratio (*n* = 22; *P* = 9/D = 13)	0.51 (0.44–0.68)	0.94 (0.79–1.00)	**<.001**
Liver herniation (*n* = 21; *P* = 8/D = 13)	2 (25)	13 (100)	**.001**
US 18–26 weeks			
GA (w^{+d})	20^{+4} (20^{+0}–21^{+5})	20^{+5} (19^{+5}–21^{+2})	.63
OC/AC-ratio (*n* = 50, *P* = 28/D = 22)	0.46 (0.30–0.56)	0.84 (0.76–0.92)	**<.001**
Liver herniation (*n* = 51, P = 28/D = 23)	5 (18)	23 (100)	**<.001**
US 30–38 weeks			
GA (w^{+d})	31^{+4} (30^{+4}–32^{+1})	31^{+1} (30^{+1}–32^{+0})	.58
OC/AC-ratio (*n* = 58, *P* = 36/D = 22)	0.40 (0.32–0.46)	0.77 (0.72–0.88)	**<.001**
Liver herniation (n = 58, *P* = 35/D = 23)	5 (14)	23 (100)	**<.001**
Liver herniation	5 (14)	26 (100)	**<.001**
Isolated	23 (62)	23 (89)	**.02**
Postnatal parameters			
GA at delivery (w^{+d})	38^{+1} (36^{+3}–38^{+6})	38^{+3} (35^{+6}–38^{+6})	.93
Delivery <32-week GA	3 (8)	3 (12)	.65
Spontaneous vaginal delivery	25 (68)	15 (58)	.42
Apgar score at 5 min	9 (8–10)	8 (6–9)	**.002**
Birthweight (g)	2960 (2433–3330)	2815 (1994–3378)	.40
Gender: female	21 (57)	12 (46)	.41
Isolated	19 (51)	17 (66)	.19
Giant omphalocele	2 (5)	24 (92)	**<.001**
Survival	36 (97)	18 (69)	**.002**
CLD	7 (19)	15 (58)	**.002**
LOS (d)	10 (7–35)	52 (19–107)	**<.001**

Data are presented as median (interquartile range) or numbers (%). Statistical significance was tested via the chi-square/Fisher exact test (nominal or ordinal variables) or Mann–Whitney U test (continuous variables). Per US period, the number of cases (n) are described per analysis for the total group and per type of closure, where the P represents primary closure and the D represents delayed closure. A giant omphalocele is defined as a postnatal defect size of at least 5 cm, with liver included. Survival was defined as survival until at least 1 year of age. The statistically significant results (*p*-value <0.05) are printed in bold.

Abbreviations: CLD, chronic lung disease defined as need for supplemental oxygen for greater than or equal to 28 days; d, days; GA, gestational age; g, grams; LOS, length of initial hospital stay; OC/AC-ratio, omphalocele circumference/abdominal circumference ratio; US, ultrasound; w^{+d}, weeks+days.

Figure 2 The omphalocele circumference/ abdominal circumference (OC/AC)-ratio throughout gestation per type of postnatal closure.

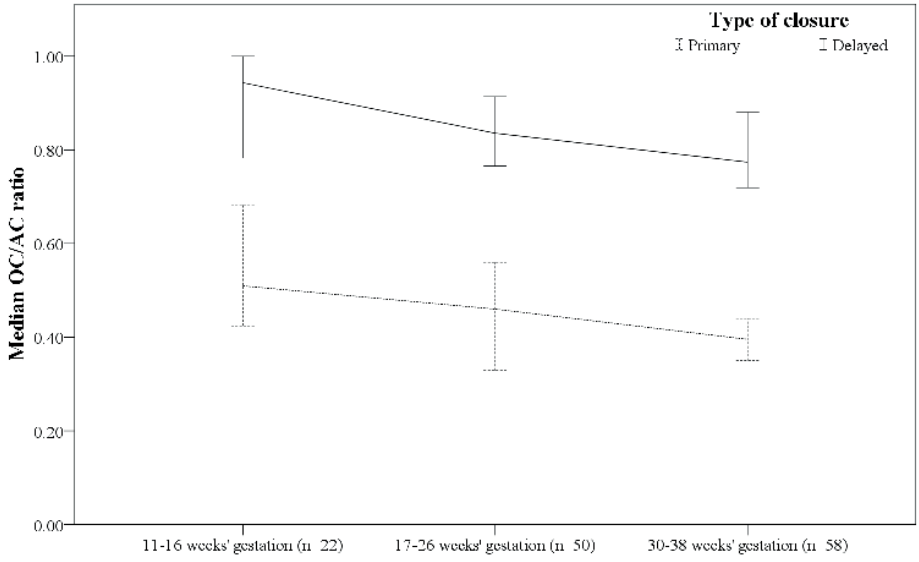


Figure 3 Receiver-operating characteristic (ROC) analysis of the omphalocele circumference/abdominal circumference (OC/AC)-ratio at the different time periods for type of closure.

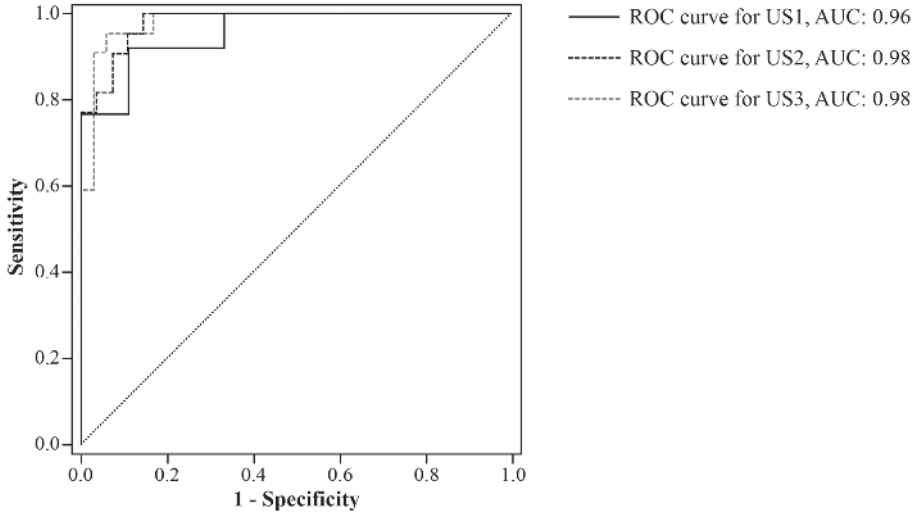


Table 2 Omphalocele cases with additional anomalies detected prenatally and postnatally.

OC/AC-Ratio US1	OC/AC-Ratio US2	OC/AC-Ratio US3	Survival	Prenatal Liver	Type of Closure	Prenatal Anomalies	Postnatal Anomalies
	0.31	0.4	Yes	No	Primary	Suspicion of BWS	BWS
	0.53	0.44	Yes	No	Primary	Suspicion of BWS	BWS
		0.46	Yes	No	Primary	Suspicion of BWS	BWS, naevues flammeus glabella eyelid
	0.56	0.61	Yes	No	Primary	Suspicion of BWS	BWS
	0.63	0.61	Yes	No	Primary	Suspicion of BWS	BWS
0.51	0.2	0.22	Yes	No	Primary	mVSD, suspicion of CoAo, X-linked ALAS2 mutatie[c]	Bicuspid aorticvalve, X-linked ALAS2 mutatie
		0.29	Yes	No	Primary	Multicystic left kidney	BWS, unilateral kidney agenesis/ urethrocystocele, mPVS
0.33	0.49	0.4	Yes	No	Primary	Bilateral schisis, ToF, Blake's pouch, SUA	Bilateral schisis, ToF, Blake's pouch[d]
	0.52	0.65	No	No	Primary	AVSD, ToF, suspicion of small intestine atresia	AVSD, ToF, TAPVR, hiatus hernia, asplenia, UPJ stenosis
	0.56		Yes	No	Primary	SUA, Paternal microdeletion 16p13.11	Paternal microdeletion
	0.72	0.42	Yes	No	Primary	Turner syndrome[e]	Turner syndrome[e]
		0.78	No	Yes	Delayed	Dilated right atrium (cardiomegalie)	Dilated right atrium and ventricle
0.8	0.66	0.85	No	Yes	Delayed	Postaxial polydactyly[a]	Postaxial polydactyly
	0.37	0.35	Yes	Yes	Primary	Femurlength <p5	BWS, soft palate schisis
		0.39	Yes	No	Primary	Suspicion of small intestine atresia	Small intestine atresia, bilateral polydactyly
		0.5	Yes	No	Primary	Suspicion of BWS	BWS, bowel volvulus
	0.74	0.65	Yes	Yes	Delayed	Thoracic situs inversus, ascites	Dextrocardia, ASD, VSD, ODB, desmoid torticollis
0.96	0.81		Yes	Yes	Delayed	SUA with umbilical cord cyst	Hydro-urether, hydronephrosis, ASD
	0.9	0.75	Yes	Yes	Delayed	Narrow thorax, dilated stomach	Bicuspid aorticvalve with stenosis/ insufficience
0.46	0.3	0.32	Yes	No	Primary	-	Pierre Robin, sliding hernia
	0.37	0.31	Yes	No	Primary	-	BWS[f]
		0.4	Yes	No	Primary	-	Clasped thumb
0.52	0.56	0.42	Yes	No	Primary	-	BWS, two mVSDs[f]

OC/AC-Ratio US1	OC/AC-Ratio US2	OC/AC-Ratio US3	Survival	Prenatal Liver	Type of Closure	Prenatal Anomalies	Postnatal Anomalies
	0.66	0.74	Yes	Yes	Primary	-	Mild pelvic dysplasia[b]
0.89	0.81	0.78	Yes	Yes	Delayed	-	Aplasia cutis congenital Morgagni hernia, ASD type 2[f]
0.76	0.91	0.73	No	Yes	Delayed	-	Large pVSD with overriding aorta, ODB[f]
1	1.05		No	Yes	Delayed	-	Small ASD and VSD (clinically not relevant), CCA[f]
		1.11	No	Yes	Delayed	-	ToF, Esophageal atresia with fistula[f]

Cases are ranked by concordance between prenatal and postnatal associated anomalies, severity of the anomalies, and OC/AC-ratio. [a]DiTri triplet. [b]Monochorionic twin pregnancy, sIUGR. [c]Mutation causing congenital sideroblastic anemia. [d]CHARGE-syndrome. [e]Prenatal with MCA: enlarged NT 4.1 mm, suspicion of CoAo with LV < RV, dilated bowel, IUGR, and postnatal with MCA: CoAo, bicuspid aortic valve, bilateral dilated renal pelvis, dysplastic ears. [f]Fetus prenatally assumed isolated with postnatally major associated congenital anomalies.

Abbreviations: ASD, atrial septal defect; AVSD, atrial ventricular septal defect; BWS, Beckwith-Wiedemann syndrome; CCA, corpus callosum agenesis; CoAo, Coarctation Aortae; LV and RV, left ventricle and right ventricle; MCA, multipel congenital anomalies; mPVS, mild pulmonary valve stenosis; mVSD, musculous ventricular septal defect; NT, nuchal translucency; ODB, open Ductus Botalli; pVSD, perimembranous ventricular septal defect; sIUGR, selective intra uterine growth restriction; SUA, single umbilical artery; TAPVR, total anomalous pulmonary venous return; ToF, Tetralogy of Fallot; UPJ, uteropelvic junction; VSD, ventricular septal defect.

The mean OC/AC-ratio differed significantly between the three time periods (p = .002), showing a decreasing trend throughout gestation. On the basis of the different optimal cut-offs per time period, the prediction of the type of closure at the first time period did not change for 43/48 (90%) fetuses for whom multiple OC/AC-ratios were available. The type of closure would have been predicted correctly at all time periods for 42/48 (88%) fetuses but incorrectly for one fetus (primary closure predicted; delayed closure performed). In the remaining five fetuses, the predicted method of closure differed between the time periods; in four out of five, a primary closure was performed.

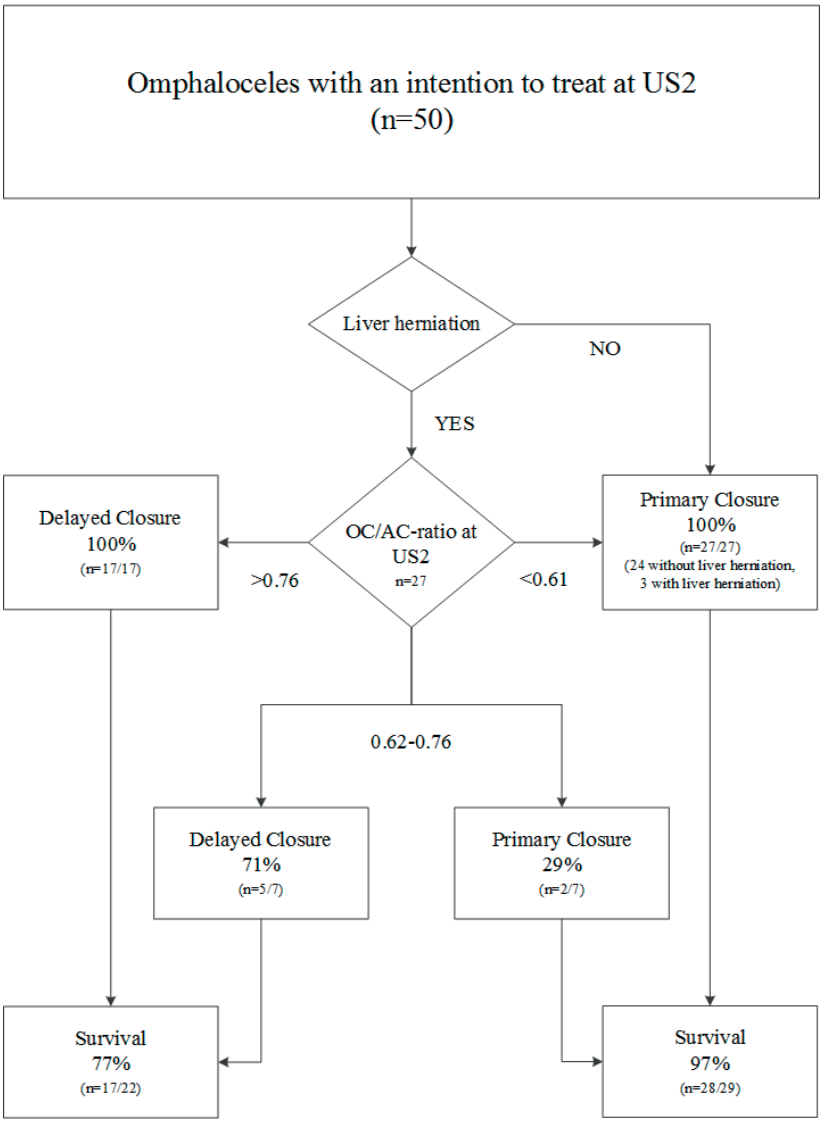
With the use of multivariable logistic regression analyses, we found a significant association between the intercept of the OC/AC-ratio and type of closure (OR 1.31; p = .006) but not for the slope (OR 0.82; p = .79), i.e., no association was found between the trend in OC/AC-ratio throughout gestation and type of postnatal closure (Figure S2).

The presence of MCA prenatally was found predictive of type of surgical closure (p = .02), and the presence of MCA postnatally was not significantly predictive of type of surgical closure (p = .18). In the group of infants with delayed closure, we found a significantly lower median Apgar score at 5 minutes, longer LOS, more frequent CLD, more often a giant omphalocele, and worse survival rates compared with infants who underwent primary closure (Table 1). With the use of logistic regression analysis, we found a significant association between the OC/AC-ratio at US2 and US3 and presence of CLD (p = .01 and p = .003, respectively). With the use of Spearman's rank correlation, we also found a significant correlation between the OC/AC-ratio at US2 and US3 and LOS (p < .001 and p < .001, respectively).

Liver herniation

The omphalocele was closed primarily in all 32 infants without liver herniation, and 31 infants survived. Not having liver herniation, independent of the OC/AC-ratio, was a perfect predictor for primary closure. We selected only fetuses with liver herniation (n = 31) for the logistic regression analysis. The OC/AC-ratio was available for 15 fetuses at US1, for 27 at US2, and for 27 at US3. Two or three measurements were available for 26/31. We found a statistically significant difference between the OC/AC-ratio and type of surgical closure at both US2 (p = .001) and US3 (p = .04). The number of cases at US1 was too small for a meaningful statistical analysis. Since the parental counselling period coincides with US2, we designed a flowchart for prediction of type of closure and survival based on OC/AC-ratio at US2 (n = 59). In 5/27 (21%) infants with an available OC/AC-ratio at US2 and herniated liver, the defect was closed primarily; they all survived. All of these infants had an OC/AC-ratio < 0.76 at US2 and a relatively large defect diameter, which enabled an uncomplicated return of the abdominal organs back into the abdominal cavity. The other 22 all required delayed closure, and 17 (77%) survived (Figure 4).

Figure 4 Counselling flowchart for type of surgical closure and survival rate according to prenatal liver position and the omphalocele circumference/abdominal circumference (OC/ AC)-ratio in fetuses with an omphalocele and an intention to treat.



Survival

Separate ROC analyses (data not shown) for each of the three measurement time periods revealed a statistically significant negative association between the OC/AC-ratio and survival at US2 and US3. The ROC at US1 had an AUC of 0.72 (with a 95% CI of 0.48–0.96;*p* = .15), at US2 an AUC of 0.81 (with a 95% CI of 0.61–1.00; *p* = .01), and at US3 an AUC of 0.89 (with a 95% CI of 0.79–0.98; *p* = .001).

Thirty-six (97%) of the 37 infants who underwent primary closure of the defect survived. One infant who did not survive had MCA, including a congenital heart defect with a total abnormal pulmonary venous return and severe insufficiencies over the atrioventricular valves. All non-survivors (*n* = 9) had CLD, and eight (89%) of them showed herniation of the liver.

In univariable logistic regression analyses, we found a significant association between the slope (OR 13.9 with a 95% CI of 2.13–91.18; *p* = .006) of the OC/AC-ratio for survival and for the intercept (OR 1.07 with a 95% CI of 1.01–1.13; *p* = .015). Patient numbers were insufficient for multivariable analysis. In fetuses who survived, the decline in OC/AC-ratio throughout gestation was steeper than in fetuses who did not survive, especially between US1 and US2 (Figure S3).

IUFD and NND

In a secondary analysis of data of 11 fetuses, we evaluated whether the OC/AC-ratio of IUFD (n = 9) or NND (*n* = 2) differed from that of live-born fetuses who survived at least 28 days, i.e., fetuses with an intention to treat (Figure S4). For four out of nine IUFD cases, no cause for the intrauterine demise was found other than the presence of an omphalocele. For the remaining five cases, other factors next to the omphalocele contributed to the cause of death (Table S2). The median (IQR) OC/AC-ratio at US1 was 0.74 (0.50–0.91) and at US2 0.55 (0.48–0.73). Five of 11 (46%) fetuses had liver herniation. The two NND cases were born at 27- and 28-week GA. The median OC/AC-ratios of the IUFD or NND cases at US1 or US2 were not statistically different from those of fetuses with an intention to treat, *p* = .76 and *p* = .75, respectively.

DISCUSSION

In this cohort of fetuses with an omphalocele, the OC/AC-ratio throughout the second and third trimesters of pregnancy proved an important determining factor for the prediction of both type of postnatal surgical closure and survival. The OC/AC-ratio decreased significantly throughout gestation, resulting in different cut-offs during gestation for prediction of type of surgical closure. The most reliable period for this prediction was the third trimester. The OC/AC-ratio time trend was not significantly associated with type of surgical closure. Fetuses without liver herniation underwent primary closure. In infants with a syndrome or chromosomal abnormality, more often a small omphalocele was present, and primary closure was possible.

In previous studies, a number of ratios have been investigated,[15,16,18-20] including the OC/AC-ratio.[17,20] Differing outcome parameters and study population inclusion cri-

teria hamper comparison. The cut-offs we found in the current study are lower than previously reported[17] in a group of 24 isolated omphalocele cases but comparable with those reported by Kleinrouweler et al.[20] In the latter cross-sectional study, the predictive value of the OC/AC-ratio for type of closure was examined in all (isolated and non-isolated) omphalocele cases. Since the cut-offs are comparable in these two separate patient populations, we expect a good clinical applicability. In line with our finding, Kleinrouweler et al also found a decreasing OC/AC-ratio with increasing GA, which resulted in different cut-offs per GA.[20] Kiyora et al[18] and Montero et al,[15] however, found no difference in ratios per GA. The latter study[15] used fetal growth parameters (AC, femur length, and head circumference), which remained relatively constant throughout gestation. The suggested ratios resulted in a lower predictive value for the prediction of postnatal closure (AUC 0.67–0.72) than the OC/AC-ratio in our study (AUC 0.96–0.98), as did all ratios including omphalocele diameter instead of circumference.[16,18,19] Additional research should make clear whether correction for GA could result in a constant cut-off throughout gestation, without negatively affecting the predictive value.

An omphalocele is usually diagnosed prior to 24-week GA, and parents prefer counselling shortly thereafter.[23-25] At US1, the result of the invasive prenatal testing is not immediately available, which influences prenatal counselling of future parents. In addition, we found that type of closure and survival can be more accurately predicted by the OC/AC measurements in the late second (US2) and third trimester (US3). The latter especially in cases where around 24-week gestation, the OC/AC-ratio is measured between 0.62 and 0.76, and the liver is herniated. Parents should be informed about this early in pregnancy. Although the predictive value of the OC/AC-ratio at US3 is limited for counselling purposes as referred to in the previous article,[17] it is beneficial for both perinatal planning and preparing parents for the period after birth. When a case predicts delayed closure, both physicians and patients can prepare for a higher mortality and neonatal morbidity (e.g., longer hospital stay, increased risk of feeding problems, increased risk of respiratory problems). To our knowledge, there are no previous studies evaluating the value of repeated measurements throughout gestation per case. Although we did not find a significant association between the trend of the OC/AC-ratio and type of surgical closure, we did find an association between the intercept of the OC/AC ratio and type of closure. Since the intercept describes the average OC/AC-ratio throughout gestation, it is more precise than a single measurement. Therefore, we do advise repeated measurements to improve prenatal counselling.

The occurrence of an omphalocele is not seldomly (80%) associated with additional anatomical and/or chromosomal abnormalities that may influence the postnatal outcome.[1,3-7,21,26,27] We also know from previous studies[4,17] that in approximately 20% of prenatally assumed isolated cases, postnatally associated anomalies are detected.

Although we found a statistically significant association between type of surgical closure and MCA prenatally, this was not confirmed postnatally. The presence of associated anomalies in a neonate may therefore not influence type of surgery, which should be considered when counselling future parents. In our study, based on the OC/AC-ratio and liver position, delayed closure and a lower chance of survival would have been predicted for all but one fetus with major MCA, thus irrespective of the presence of these additional anomalies. This is in contrast to fetuses with a syndrome or chromosomal abnormality, who showed a relatively small OC/AC-ratio, less liver herniation, and primary closure.

Like Kleinrouweler et al, we were unable to identify prenatal parameters predictive for the occurrence of IUFD or NND.[20] It is highly likely that the sample sizes were too small (13 and 11 cases, respectively), especially since in only four out of 11 cases in our study, there was no apparent cause found for the occurrence of an IUFD and/or NND. Further multicentre studies in larger cohorts are needed to verify this outcome.

In all cases without liver herniation, the defect was closed primarily, irrespective of the OC/AC-ratio. Previous studies[17,20,27,28] confirm our findings of lower survival and a higher occurrence of delayed closure in fetuses with liver herniation. Still, our findings show that predicting type of closure and survival in fetuses with liver herniation and an OC/AC-ratio between 0.62 and 0.76 around 24-week gestation remains challenging; in our study, 29% of these neonates underwent a primary closure. The group of patients with an OC/AC-ratio between 0.62 and 0.76 around 24-week gestation warrants further investigation.

CONCLUSION

In fetuses with an omphalocele, the OC/AC-ratio determined from ultrasound measurements in the late second and third trimesters, combined with position of the liver, predicts the type of postnatal surgical closure and survival. The predictive value increases with increas- ing GA and can be used throughout pregnancy with different cut-offs for different time periods in pregnancy. The OC/AC-ratio can be a valuable predictive tool in the counselling of parents.

ACKNOWLEDGEMENT

Ko Hagoort provided editorial advice.

What's already known about this topic?

- In fetuses with an isolated omphalocele, the OC/AC-ratio is less than 24 weeks; gestation is of predictive value for postnatal type of closure.

What does this study add?

- The OC/AC-ratio is predictive for type of surgical closure and survival in all fetuses with an omphalocele.
- This report is the first concerning the trend of the OC/AC-ratio throughout gestation.
- The OC/AC-ratio best predicts type of closure and survival in the third trimester of pregnancy.

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SUPPLEMENTAL MATERIAL

Supplemental Figure 1 Examples of ultrasound measurement of the OC/AC-ratio at US3

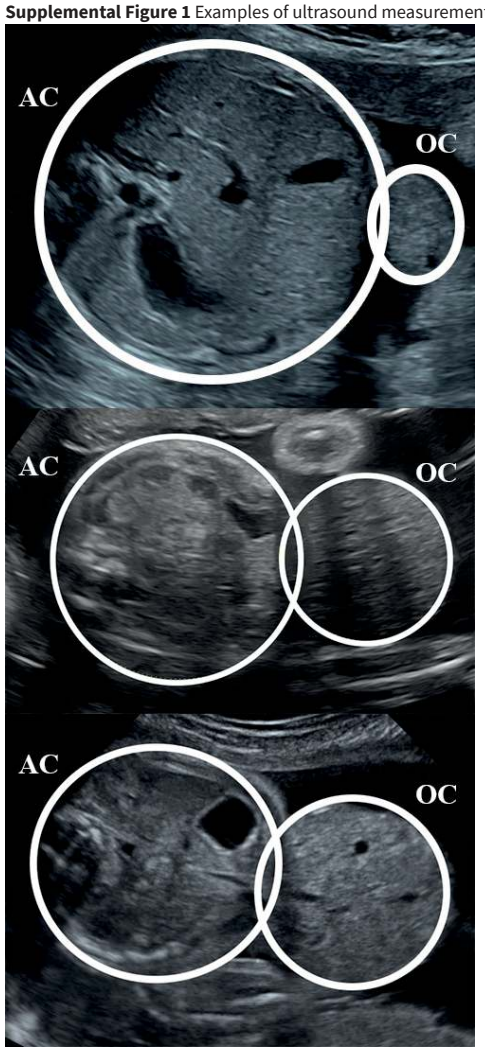


Figure showing three examples of measurement of the OC/AC-ratio at US3. The circle on the left is the measurement of the abdominal circumference (AC) and the circle on the right is the measurement of the omphalocele circumference (OC). The OC/AC-ratio of these cases at US3 is 0.29, 0.69 and 0.77 (from top to bottom)
Abbreviations OC/AC-ratio: omphalocele circumference / abdominal circumference-ratio; US3: ultrasound examination between 30-38 weeks gestational age.

Supplemental Figure 2 The OC/AC-ratio throughout gestation per type of postnatal closure and per case

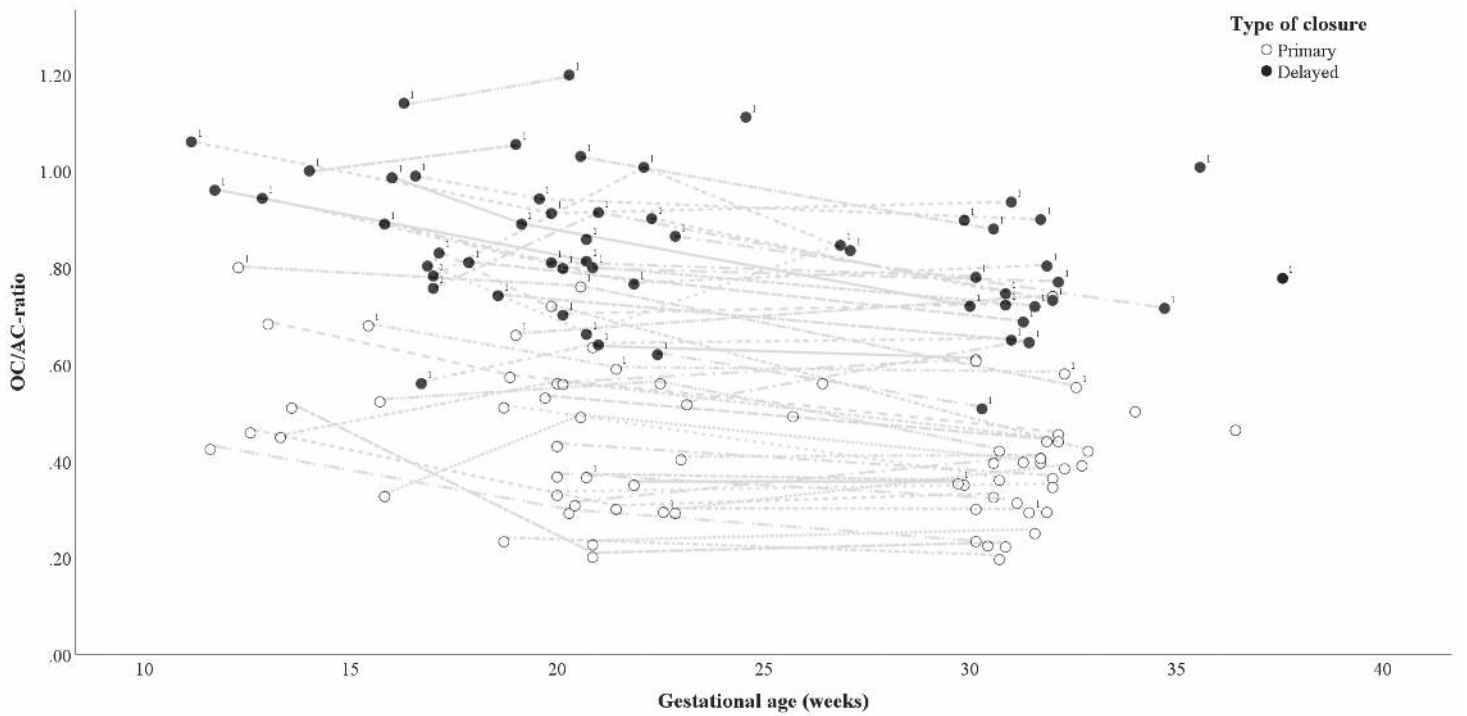
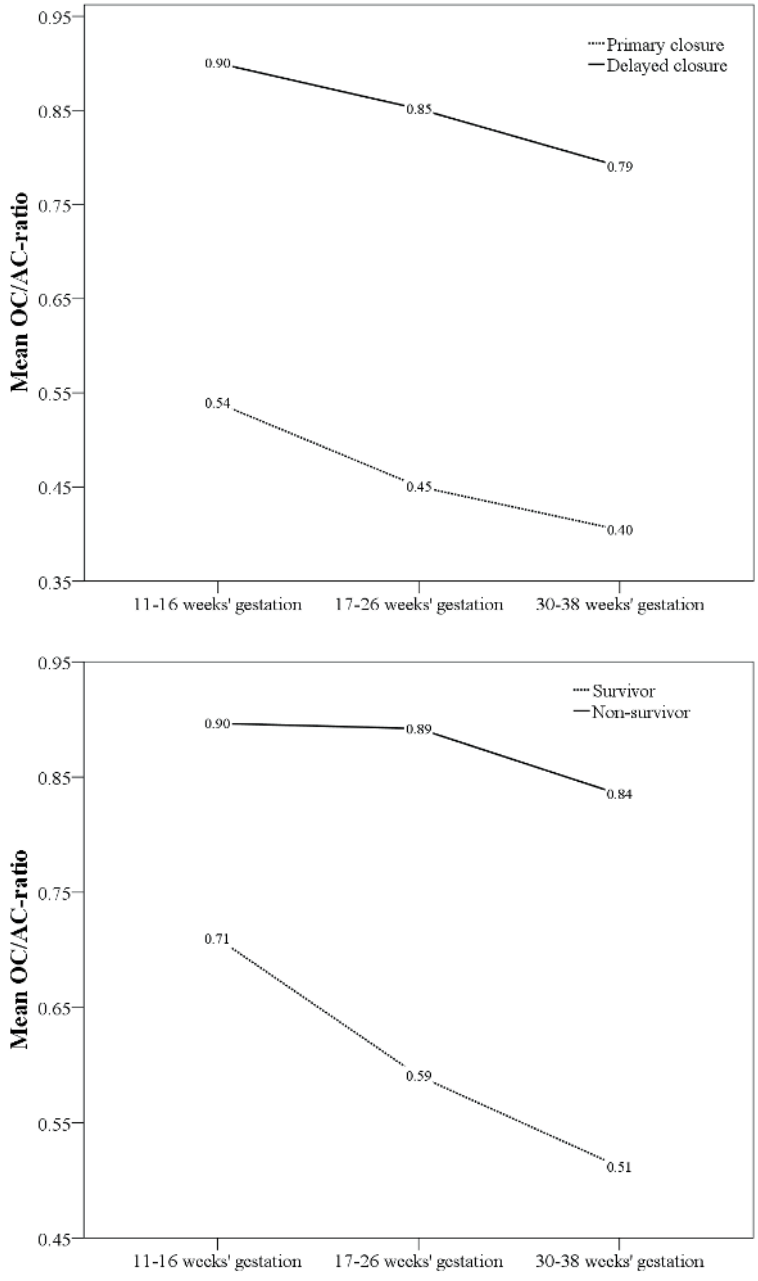


Figure showing the trend of the OC/AC-ratio per case throughout gestation per type of postnatal surgical closure. The open dots are cases with a postnatal primary closure, the solid black dots represent cases with a delayed closure. The grey lines represent the trend of the OC/AC-ratio throughout gestation in cases with ≥2 measurements. Cases with liver herniation are marked with number one.

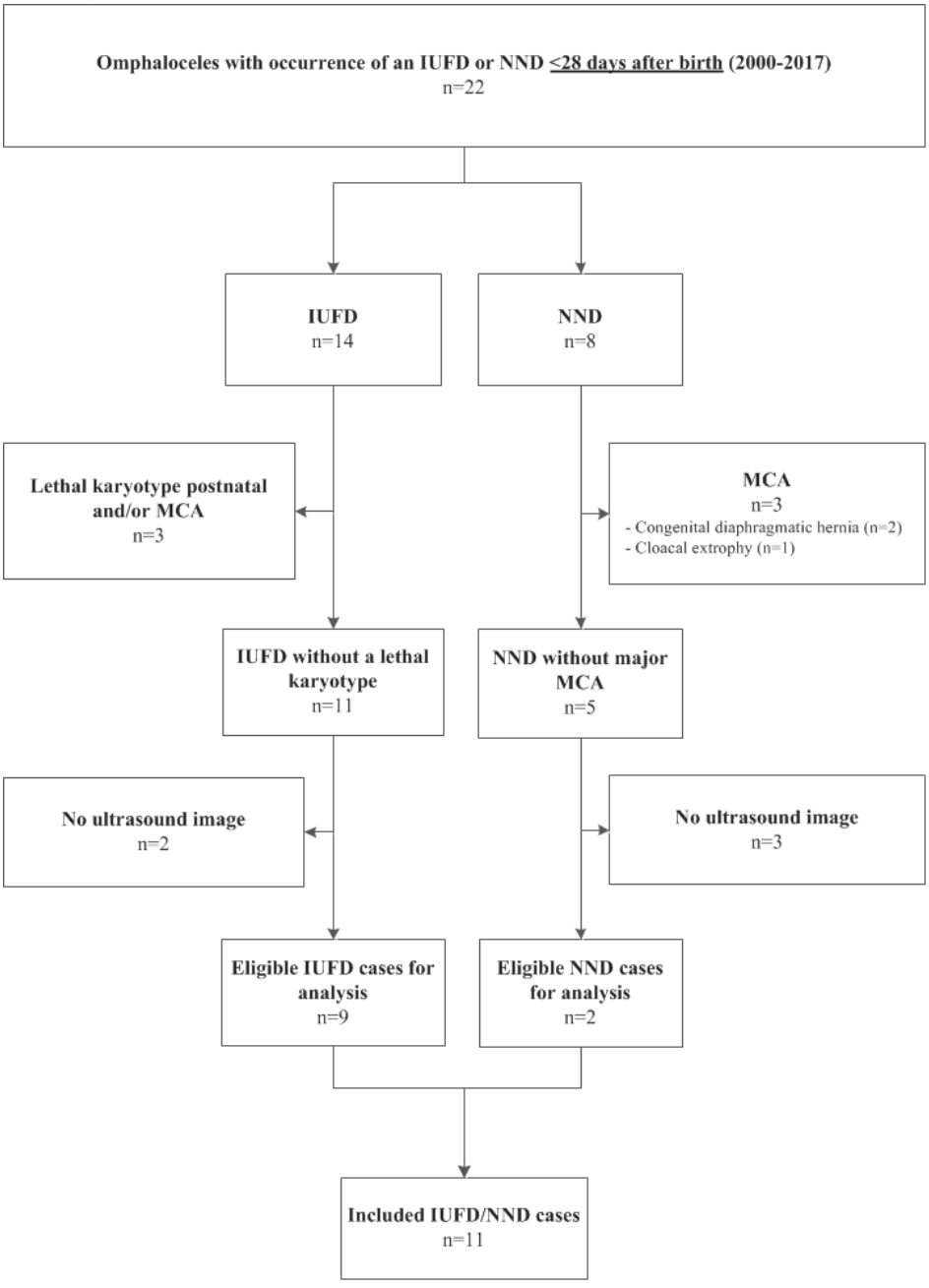
Abbreviations OC/AC-ratio: omphalocele circumference / abdominal circumference-ratio.

Supplemental Figure 3 The slope of the mean OC/AC-ratio throughout pregnancy for type of closure and survival



Data are presented as mean OC/AC-ratio, per ultrasound time period and stratified for type of closure (top figure) and survival (bottom figure). The dashed line represents cases with a primary closure (top figure) or survivor (bottom figure). The solid line represents cases with a delayed closure (top figure) or non-survivor (bottom figure).
Abbreviations OC/AC-ratio: omphalocele circumference / abdominal circumference-ratio.

Supplemental Figure 4 Inclusion flowchart of fetuses diagnosed with an omphalocele and occurrence of an IUFD or NND (2000-2017)



Abbreviations IUFD: intra uterine fetal death; NND: neonatal death within 28 days after birth; MCA: multiple congenital anomalies.

Supplemental Table 1 Logistic regression analysis for the OC/AC-ratio for type of closure and survival

	Outcome		
Variable	**OR**	**95% CI**	***p*-value**
		Type of closure	
OC/AC-ratio US1: 11-16 weeks GA	1.14	1.03-1.27	0.014
OC/AC-ratio US2: 17-26 weeks GA	1.24	1.09-1.42	0.002
OC/AC-ratio US3: 30-38 weeks GA	1.23	1.09-1.40	0.001
		Survival	
OC/AC-ratio US1: 11-16 weeks GA	1.04	0.99-1.11	0.14
OC/AC-ratio US2: 17-26 weeks GA	1.07	1.01-1.12	0.02
OC/AC-ratio US3: 30-38 weeks GA	1.08	1.02-1.15	0.01

The OR relate to delayed closure or mortality.

Abbrevations OR: odds ratio; OC/AC-ratio: omphalocele circumference / abdominal circumference-ratio; US: ultrasound; GA: gestational age;

Supplemental Table 2 Omphalocele cases and their cause of death

OC/ AC-ratio US1	OC/AC-ratio US2	OC/AC-ratio US3	Liver hernia-tion	GA at birth	AS 5 min	Giant	Sex	Type of closure	CLD	LOS	Time of death	MCA	Cause of death
	0.66		No		N/A	N/A	Male	N/A	N/A	N/A	IUFD (30)	-	Unknown[1]
0.5	0.55		No		N/A	N/A	-	N/A	N/A	N/A	IUFD (29+0)	Anencephaly	MCA
0.83			Yes		N/A	N/A	Male	N/A	N/A	N/A	IUFD (27+0)	SUA	Unknown
1.26			Yes		N/A	N/A	Female	N/A	N/A	N/A	IUFD (26+4)	(deviated heart axis)	Unknown
	0.54		No		N/A	N/A	Male	N/A	N/A	N/A	IUFD (24+5)	-	Early IUGR with placental redistribution
	0.93		Yes		N/A	N/A	-	N/A	N/A	N/A	IUFD (21+2)	-	Unknown
0.91			Yes		N/A	N/A	Male	N/A	N/A	N/A	IUFD (18+4)	Unilateral MCKD	PROM with CHIV
0.3			No		N/A	N/A	Male	N/A	N/A	N/A	IUFD (15+1)	Trisomy 21	MCA
0.68			No		N/A	N/A	Female	N/A	N/A	N/A	IUFD (13+0)	Umbilical cord cysts	MCA
	0.48		No	27+6	7	No	Female	N/A	N/A	0	NND (0)	BWS	Circulatory failure
0.74	0.48		Yes	28+5	7	Yes	Male	N/A	Severe	9	NND (9)	TTTS[2]	Pulmonary hypoplasia and pulmonary hypertension
		0.78	Yes	37+4	6	Yes	Male	delayed	Severe	36	Infant death (91)	Dilated right atrium and ventricle	Pulmonary hypertension
		1.11	Yes	32+3	7	Yes	Male	delayed	Severe	54	Infant death (54)	ToF and EA with fistula	MCA, septic shock, respiratory failure
		0.9	Yes	37+0	4	Yes	Male	delayed	Severe	84	Infant death (84)	-	Respiratory failure

OC/ AC-ratio US1	OC/AC-ratio US2	OC/AC-ratio US3	Liver hernia-tion	GA at birth	AS 5 min	Giant	Sex	Type of closure	CLD	LOS	Time of death	MCA	Cause of death
1	1.05		Yes	38+6	6	No	Male	delayed	Severe	101	Infant death (101)	Small ASD and VSD (clinically not relevant), CCA	Pulmonary hypertension
1.14	1.2		Yes	30+6	7	Yes	Male	delayed	Severe	106	Infant death (106)	-	Pulmonary hypoplasia and pulmonary hypertension
0.8	0.66	0.85	Yes	27+0	5	Yes	Male	delayed	Severe	111	Infant death (111)	Postaxial polydactyly	Pulmonary hypertension[3]
	0.52	0.65	No	39+1	9	No	Male	primary	Severe	126	Infant death (126)	AVSD, ToF, TAPVR, hiatus hernia, asplenia, UPJ stenosis	MCA, insufficient cardiac circulation with hypoxia, no treatment options
0.76	0.91	0.73	Yes	35+5	6	No	Female	delayed	Mild	156	Infant death (156)	Large pVSD with overriding aorta, ODB	MCA, cardiac failure and pulmonary hypertension
0.78	1.01	0.84	Yes	30+0	6	Yes	Male	delayed	Severe	192	Infant death (192)	-	Cardiac and respiratory failure

Cases are ranked by time of death and length of stay. [1]Dichorionic twin pregnancy; [2]monochorionic twin pregnancy; [3]dichorionic triamniotic triplet. A giant omphalocele is defined as a postnatal defect size of at least 5 cm, with liver included. NND: neonatal death is defined ad <28 days after birth. Infant death is defined as a death >28 days after birth.

Abbreviations OC/AC-ratio: omphalocele circumference / abdominal circumference-ratio; US: ultrasound; CLD: chronic lung disease defined as need for supplemental oxygen for ≥28 days; LOS: length of initial hospital stay; GA: gestational age; w+d: weeks+days; MCA: multiple congenital anomalies; N/A: not applicable; IUFD: intra uterine fetal death; SUA, single umbilical artery; IUGR: intre uterine growth restriction; MCKD: multicystic kidney disease; PROM: premature rupture of membranes; CHIV: chronic chronic histiocytic intervillositis; BWS: Beckwith-Wiedemann syndrome; TTTS: twin-to-twin transfusion syndrome; ToF: Tetralogy of Fallot; EA: esophageal atresia; ASD: atrial septal defect; VSD: ventricular septal defect; CCA: corpus callosum agenesis; AVSD: atrial ventricular septal defect; TAPVR: total anomalous pulmonary venous return; UPJ: uteropelvic junction; pVSD: perimembranous ventricular septal defect; ODB: open Ductus Botalli;

CHAPTER 4

The validity of the observed-to-expected lung-to-head ratio in congenital diaphragmatic hernia in an era of standardized neonatal treatment; a multicenter study

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ABSTRACT

Objective

To assess the predictive value of observed-to-expected lung-to-head ratio (O/E LHR) for survival and chronic lung disease (CLD) in survivors of left-sided congenital diaphragmatic hernia (CDH) in an era of standardized neonatal treatment, and to evaluate the predictive value of the O/E LHR trajectory for survival.

Methods

This retrospective cohort study was performed in two high-volume CDH centers in the Netherlands in prenatally detected, isolated left-sided CDH patients born between 2008 and 2014. O/E LHR and liver position were determined using 2D-ultrasonography at three time points during gestation from 19 weeks onwards. Ultrasound measurements were performed on stored ultrasound data by one single experienced operator blinded to postnatal outcome.

Results

Of the 122 included cases, 77.9% survived of whom 38.9% developed CLD. A significant association was found between the first measured O/E LHR and survival and development of CLD in survivors. Prenatal liver position did not have additional predictive value. No significant association was found between the trajectory of the O/E LHR and survival.

Conclusion

In an era of standardized neonatal treatment for neonates with CDH, the first measured O/E LHR per patient significantly predicts survival and development of CLD in survivors in isolated left-sided CDH infants.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in 2200 live births.[1] Although the survival rate has significantly increased to about 70–80%,[2,3] CDH is still a life-threatening congenital anomaly.[4] Various parameters are related to a worse prognosis like a right-sided CDH, intrathoracic liver herniation, and associated congenital and/or chromosomal malformations.[5–7]

Metkus *et al.* were the first (1996) who described the predictive value of lung-to-head ratio (LHR) in fetuses with CDH.[8] Because the LHR increases exponentially with gestation in healthy fetuses,[9] the observed-to-expected LHR (O/E LHR) was introduced in 2007 by Jani *et al.* after a multicenter study in 354 isolated CDH fetuses.[10] Thereafter, several studies have demonstrated that the O/E LHR is a useful predictor of postnatal outcome.[11–14]

In fetuses with left-sided severe CDH *(O/E LHR < 25%)* and fetuses with moderate CDH (*O/E LHR 25–34.9% or O/E LHR 35–44.9% with intrathoracic liver herniation*), the benefit of fetoscopic endotracheal occlusion (FETO) is currently being investigated in randomized controlled studies (NCT01240057 and NCT00763737). Groups are based on survival rates according to Deprest *et al.*[15] and Jani *et al.*,[10] which is the largest study to date.[10] However, in that period, there was still a lack of postnatal standardization of treatment, which has proven to influence postnatal outcome, reaching survival rates up to over 80%.[3] Secondly, in their study, each of the participating centers provided the data. Information concerning inter-observer reproducibility was not available and variability in prenatal ultrasound measurements may have influenced the results. Thirdly, up to date, there has not been a longitudinal evaluation of the O/E LHR per individual patient during pregnancy.

From 2008 onwards, all patients born in participating centers of the CDH EURO Consortium have been treated according to a standardized neonatal treatment protocol which was published in 2010 and recently actualized.[16,17] Subsequent high survival rates might influence validity of the 'original' cut-offs and their value for prenatal counseling. Therefore, we evaluated the predictive value of the prenatally measured O/E LHR on postnatal survival and development of chronic lung disease (CLD), when neonates receive standardized treatment in the two Dutch CDH designated centers with extracorporeal membrane oxygenation (ECMO) availability. Moreover, we performed longitudinal analyses of the O/E LHR measurements per patient during gestation.

METHODS

All patients with a prenatal diagnosis of CDH, born between January 2008 and December 2014, and treated in the Erasmus University Medical Centre, Rotterdam, The Netherlands or the Radboud University Medical Centre, Nijmegen, The Netherlands were included in this observational retrospective cohort study. Because all infants from the Netherlands with a CDH are referred to one of the two CDH centers, this represents a nationwide cohort. Both centers are high-volume centers (defined as >10 CDH patients per year).[18] Exclusion criteria were defined as: right-sided CDH, termination of pregnancy, premature birth <30 weeks gestational age (GA), FETO, and associated major structural or chromosomal anomalies. Because subjects are not being submitted to any handling, nor are there rules of human behavior being imposed, Institutional Review Board approval was waived by the ethical committee of the Erasmus Medical Center, Rotterdam, The Netherlands (MEC-2015-517).

The original ultrasound image of a transverse plane of the fetal chest at the level of the four-chamber view of the heart was retrieved from patient records and used for measurement of the contralateral (right) lung. The lung area was measured by manual tracing of the limits of the lung (mm^2), if possible in multiple images per examination and preferably in an image recorded for measurement of lung area. Liver position (intrathoracic or intra-abdominal) was determined by visual assessment in a transversal plane, as well as a coronal or sagittal plane if available. The head circumference (mm) was retrieved from medical records. The O/E LHR was then calculated as described by Jani *et al.*[19] Ultrasound measurements were performed on stored images reloaded on a GE Voluson E8 or E10 system (GE Medical Systems, Zipf, Austria) at the Department of Obstetrics and Gynecology, Division of Obstetrics and Prenatal Medicine at the Erasmus University Medical Centre. The original images where obtained using the GE Voluson 730/E8 system (GE Medical Systems, Zipf, Austria). All measurements were performed by one single operator (N. C. J. Peters) with 5 years of experience measuring the O/E LHR,[20] who was unaware of postnatal outcome. If there was no image available meeting the requirements as described by Jani *et al.*[21] a measurement was regarded as missing. Ultrasound measurements were performed in the second and third trimester of pregnancy and were categorized as follows; ultrasound 1: 19^{+0}–24^{+0} weeks' gestational age (GA), ultrasound 2: 24^{+1}–29^{+6} weeks' GA, and ultrasound 3: ≥30^{+0} weeks' GA. Postnatal patient characteristics were retrieved from medical records. Patient demographics included: gestational age at birth, birth weight, gender, associated major structural or chromosomal anomalies, side of diaphragmatic hernia, liver position (intrathoracic/intra-abdominal) at surgical repair, diaphragmatic defect size (A/B/C/D, with 'A' being the smallest and 'D' being the largest defects),[2] need for ECMO, survival, and presence

of CLD in survivors. Survival was defined as survival after the first year of life. CLD was defined as oxygen dependency (>0.21) at day 28 of life.[22] Since 2008, all patients have been treated according to a standardized neonatal treatment protocol, which was published in 2010 and recently updated in 2016.[16,17] ECMO therapy was available for patients born after >34 weeks of gestation, with a birth weight above 2000 grams during the complete study period, without a change in indications for ECMO during this period. Severity of CDH was divided according to the same groups as proposed by Deprest *et al.*[15]: extreme CDH (O/E LHR <15%), severe CDH (O/E LHR 15–25%), moderate CDH (O/E LHR 26–35% or O/E LHR 36–45% with intrathoracic liver position), and mild CDH (O/E LHR 36–45% and liver down or O/E LHR ≥46%).

Statistical analysis

Patient characteristics were described as numbers (%) for categorical data, or median (interquartile range; IQR) for continuous data because they were not normally distributed. The first measured O/E LHR per patient was selected and used for all analyses, except for the longitudinal analyses for which all measurements per individual patient were evaluated. O/E LHR was compared between survivors and non-survivors, and survivors with and without development of CLD, and comparison between centers using Mann–Whitney tests. Associations between O/E LHR and mortality, and CLD in survivors were evaluated using univariable logistic regression modeling. Multivariable logistic regression analyses with prenatal liver position and O/E LHR as independent variables were then used to evaluate their combined predictive value on survival and development of CLD in survivors. The calibration of the multivariable logistic regression models was assessed using the Hosmer–Lemeshow goodness-of-fit test. The association between O/E LHR and postnatal defect size was evaluated using the Jonckheere–Terpstra test, whereas the association between prenatal liver position and postnatal defect size was evaluated using a linear-by-linear association chi-square test. Multivariable ordinal logistic regression analysis was used to determine the association between postnatal defect size (dependent variable) and the O/E LHR and prenatal position of the liver (independent variables). An univariable logistic regression analysis was performed to assess the association between the gestational age at diagnosis and survival. Receiver operating characteristic (ROC) curves were used to evaluate the prognostic value of O/E LHR for survival and development of CLD in survivors. Data were presented as areas under the ROC curves (AUC); [95% CI]. Optimal cut- off values were determined by maximizing the Youden index (sensitivity plus specificity minus 1). Missing observations of O/E LHR could conceivably be *missing not at random,*[23] if the more severe cases of CDH are more likely to be detected early on during pregnancy. To test this hypothesis, univariable logistic regression analysis was repeated in a selection of patients in whom the CDH was detected before 24 weeks GA. Results from this group were compared with

the results of the complete study group to assess whether the O/E LHR observations are missing at random.[23] Then, for the evaluation of the predictive value of the trajectory of O/E LHR over time on survival, missing data of O/E LHR 19^{+0}–24^{+0} weeks GA (n = 64 patients), O/E LHR between 24^{+1}–29^{+6} weeks GA (n = 70), and O/E LHR >30^{+0} weeks GA (n = 11 patients), were imputed using multiple imputation by chained equations in SPSS with 100 imputations. Using the multiple imputation data set, a linear regression of the O/E LHR at the three time points was performed for each patient separately, with GA (coded as a continuous variable) as the only independent variable. The purpose of this analysis was to summarize the longitudinal data of O/E LHR using an estimated level (intercept in the linear regression) and time trend (slope in the linear regression). The resulting estimates of the intercept and slope in the linear regressions were used as independent variables in logistic regressions for survival and CLD in survivors. The linear regressions were performed using MICROSOFT EXCEL 2010, and all other analyses were performed using SPSS version 21.0 for Windows. A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

During the study period, 238 CDH patients were born alive with a CDH in one of the two CDH centers in the Netherlands. In 176 (74%) patients, the CDH was prenatally detected. Reasons for exclusion from the study are summarized in Figure 1. In total, 122 patients with a prenatal diagnosis of an isolated left CDH were included. In the study group, 95 (77.9%) patients survived, and 37 (38.9%) of the survivors developed CLD (Table 1). Thirty-eight (31%) neonates received ECMO treatment, of which 21 died (55%). For 73 (60%) patients, more than one measurement was available, so 73 patients with a total of 190 measurements were available for the longitudinal analyses. The first measured O/E LHR and survival rate of patients with CDH were not significantly different between the two centers with survival rates of 78.2% at the Erasmus University Medical Center and 77.1% at the Radboud University Medical Center (p = 0.90). In non-survivors and survivors, the median O/E LHR was 35.9% (IQR 29.2–43.0) and 45.7% (IQR 40.5–55.9), respectively (p < 0.001). The median of the O/E LHR was 44.0% (IQR 36.0–48.8) in survivors with CLD and 48.8% (IQR 41.8–57.7) in survivors without CLD (p = 0.03).

Figure 2 shows the relationship between the O/E LHR and gestational age for each patient, stratified by survival status. There was no significant association between survival and GA at diagnosis (p = 0.30) nor between the first measured O/E LHR and the GA at diagnosis (p = 0.05).

Table 1 Background characteristics of CDH patients.

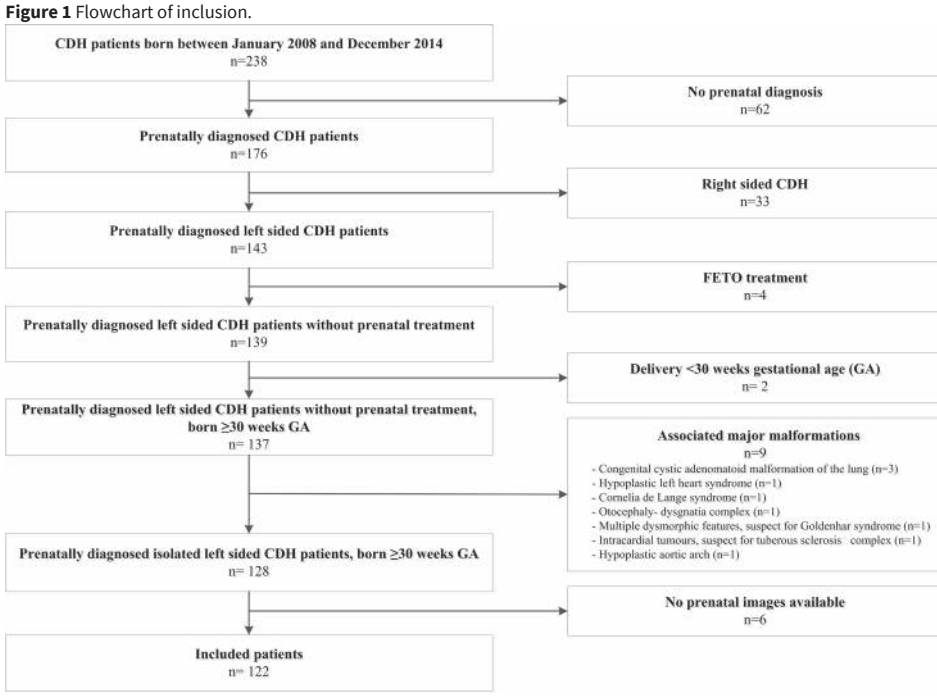
Variables	CDH patients (n=122)
Gestational age at delivery (weeks)	38^{+2} (37^{+5}- 38^{+5})
Birth 30-34 weeks GA	5 (4.1%)
Birth 34-37 weeks GA	18 (14.8%)
Birth weight (grams)	3000 (2700- 3200)
Gender: male	63 (51.6%)
Prenatal liver position	
Intra-abdominal	67 (54.9%)
Intrathoracic	52 (42.6%)
Unknown/ missing	3 (2.5%)
Postnatal liver position (during surgery)	
Intra-abdominal	65 (53.3%)
Intrathoracic	50 (41.0%)
No repair	5 (4.1%)
Unknown/ missing	2 (1.6%)
Defect size[2]	
A	10 (8.2%)
B	28 (23.0%)
C	56 (45.9%)
D	10 (8.2%)
No repair	5 (4.0%)
Unknown/ missing	13 (10.7%)
ECMO	38 (31.1%)
Survival after first year of life	95 (77.9%)
CLD (in survivors)	37 (38.9%)

Data are presented as numbers (%) or median (interquartile range). Defect size was classified according to Lally et al.[2] with "A" being defects entirely surrounded by muscle, "B" defects having a small (<50%) and "C" defects having a large (>50%) portion of the chest wall devoid of diaphragm tissue, and "D" patients having complete or near complete absence of the diaphragm.

Abbreviations: GA: gestational age; ECMO: extracorporeal membrane oxygenation; CLD: chronic lung disease.

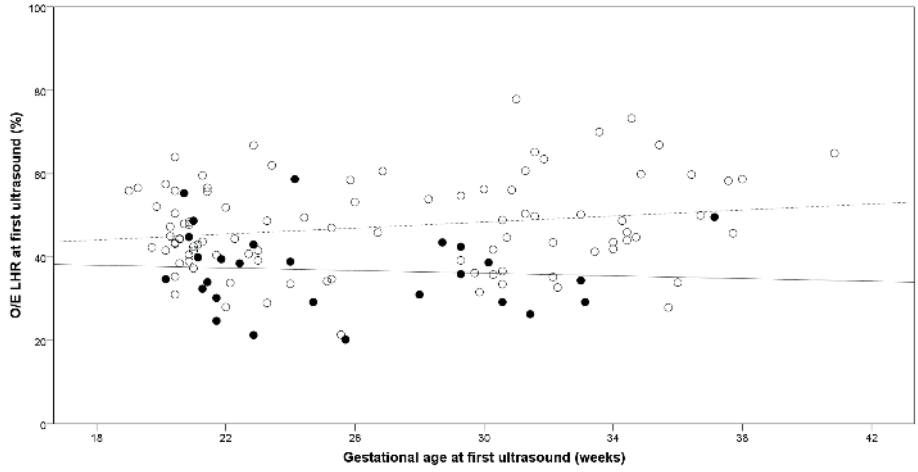
The relationship between O/E LHR and survival, stratified by prenatal liver position in each group is shown in Figure 3. None of our patients belonged to the extreme CDH group *(O/E LHR < 15%)*. Only one of four patients (25%) with severe CDH *(O/E LHR ≤ 25%)* survived. In the moderate group *(O/E LHR 26–35% or O/E LHR 36–45% with intrathoracic liver position)* 29/43 patients (67.4%) survived. In the mild group *(O/E LHR 36–45% and liver down or O/E LHR ≥ 46%)*, 65/75 patients (86.7%) survived. Fetuses with an O/E LHR of 36–45% with liver up show no statistically significant difference in survival rate in comparison with fetuses with an O/E LHR of 36–45% and liver down, respectively 82% and 76% ($p = 0.63$).

Figure 1 Flowchart of inclusion.



Abbrevations: CDH, congenital diaphragmatic hernia; FETO, fetoscopic endotracheal occlusion; GA, gestational age.

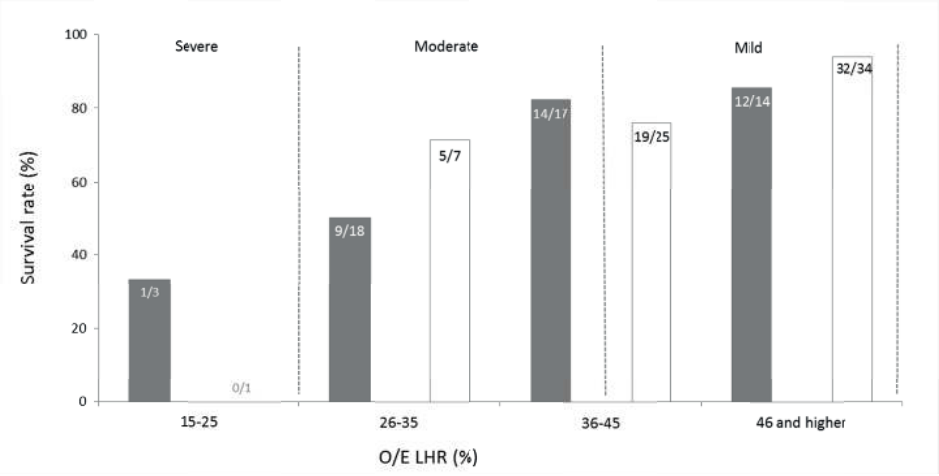
Figure 2 Relationship between the first measured observed to expected lung to head ratio (O/E LHR) and gestational age.



This figure shows the O/E LHR measured at the first ultrasound examination per patient. The closed circles represent the neonates that died, and the open circles represent the survivors. The solid and dashed lines are linear regression lines for the neonates that died and the survivors, respectively.

In Figure 3, 42 instead of 43 patients are in the moderate group and 73 instead of 75 patients in the mild group. Those differences are explained by the fact that in the moderate group for one patient prenatal liver position was unknown, and in the mild group for two patients, the prenatal liver position was unknown.

Figure 3 Survival rate according to the fetal observed to expected lung to head ratio (O/E LHR) and fetal liver position in fetuses with isolated left-sided diaphragmatic hernia.



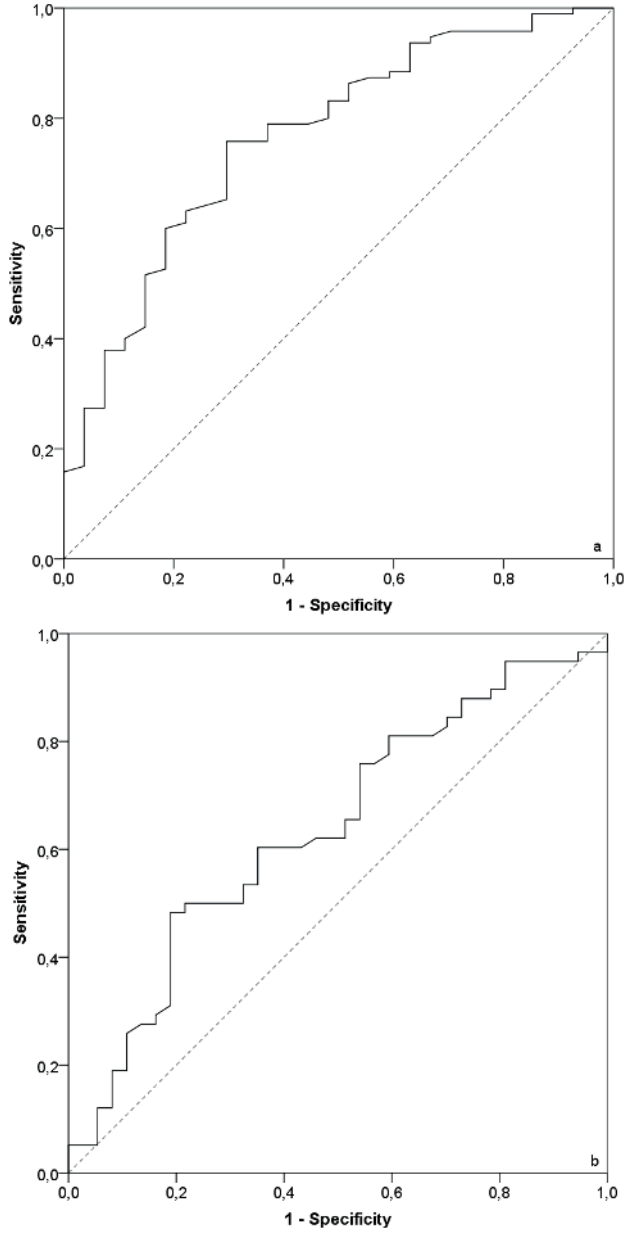
The filled bars represent fetuses with intrathoracic herniation of the liver and the open bars represent those without herniation. The numbers inside the bars represent the absolute numbers of survived patients/total number of patients within that specific group. The areas between the dashed lines represent the division according to Deprest *et al.* into groups of estimated severity of pulmonary hypoplasia based on the O/E LHR in combination with liver position.[24] The difference in patient numbers between this figure and the total group is explained by the fact that in the moderate group for one patient prenatal liver position was unknown and in the mild group for two patients the prenatal liver position was unknown.

Table 2 Logistic regression analyses for the O/E LHR with outcomes survival and chronic lung disease in survivors

Variable	Univariable analyses			Multivariable analyses		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
		Survival			**Survival**	
O/E LHR (%)	1.11	1.052-1.168	<0.001	1.11	1.048-1.172	<0.001
Liver position	2.26	0.944-5.425	0.07	0.83	0.310-2.213	0.71
		CLD in survivors			**CLD in survivors**	
O/E LHR (%)	0.96	0.919-0.997	0.04	0.94	0.902-0.988	0.01
Liver position	1.23	0.520-2.925	0.63	0.55	0.214-1.414	0.21

For the multivariable analyses prenatal liver position (intrathoracic versus intra-abdominal) was added into the model.
Abbreviations: O/E LHR: observed-to-expected lung-to-head ratio; OR: odds ratio; CI: confidence interval.

Figure 4 Receiver operating characteristic (ROC) curve for survival (a) and chronic lung disease (b)



(a) ROC curve for the prediction of survival in neonates with isolated left-sided congenital diaphragmatic hernia according to cut-off values of observed-to-expected lung area to head circumference ratio (continuous line). The dashed line is the reference line. Area under the curve: 0.77. (b) ROC curves for the prediction of chronic lung disease in surviving neonates with isolated left-sided congenital diaphragmatic hernia according to cut-off values of observed-to-expected lung area to head circumference ratio (continuous line). The dashed line is the reference line. Area under the curve: 0.64.

Univariable logistic regression analysis showed that a lower O/E LHR was significantly associated with mortality and with the development of CLD in survivors (Table 2). Multivariable logistic regression analysis with correction for prenatal liver position resulted in the same conclusions and showed that liver position was not of additional value for prediction of outcome (Table 2). *P*-values of the Hosmer–Lemeshow test were larger than 0.05, indicating an adequate model calibration.

Based on ROC analysis, mortality was predicted correctly by the O/E LHR with an optimal cut-off value of 40.2% (sensitivity 0.76 and specificity 0.70, AUC 0.77; [0.666–0.866], $p < 0.01$) (Figure 4a). Development of CLD in survivors was predicted by the O/E LHR (AUC 0.64; [0.522–0.751], $p = 0.03$) with an optimal cut-off value of 49.9% (sensitivity 0.48 and specificity 0.81) (Figure 4b).

In a separate univariable analysis in patients with a known postnatal defect size ($n = 104$), a statistically significant positive association was found between the O/E LHR and postnatal defect size ($p = 0.02$) as well as between the presence of CLD in survivors and postnatal defect size ($p = 0.002$). No statistically significant association was found between liver position and postnatal defect size ($p = 0.25$). The multivariable ordinal regression analyses showed that the addition of prenatal liver position was not relevant in the association between O/E LHR and postnatal defect size ($p = 0.41$).

The category of CDH severity based on O/E LHR measurements and prenatal liver position per patient remained stable for 58 patients (79.5%) of the 73 patients with at least two ultrasound measurements during the second and third trimester of pregnancy. In the univariable logistic regression analysis, no differences were found in predictive value of the O/E LHR on survival between the selected group of patients in whom the CDH was detected before 24 weeks of gestational age and the total patient population. Therefore, multiple imputation was performed. Longitudinal analyses of the trajectory of O/E LHR measurements during gestation showed no significant association with survival ($p = 0.18$).

DISCUSSION

In this nationwide study performed in an era of standardized neonatal treatment, we demonstrated that the first prenatally measured O/E LHR per patient can predict survival in isolated left-sided CDH infants. Survival within the different O/E LHR categories was comparable with data from Jani *et al.*, the largest multicenter study concerning the predictive value of the O/E LHR,[10] when no international consensus in standardization of postnatal therapeutic modalities had been reached and/or had been made available.

A lower O/E LHR was significantly associated with development of CLD in survivors. The O/E LHR remained stable over time during gestation.

The rationale for the use of O/E LHR is that it provides an indirect assessment of contralateral lung volume, and therefore the likelihood of pulmonary hypoplasia.[25] Adequate prenatal counseling, considering the indication for prenatal treatment (FETO) and expected postnatal prognosis, requires accurate prediction tools. Jani *et al.* retrospectively evaluated the predictive value of O/E LHR in a multicenter study of 354 isolated CDH patients (of whom 329 left-sided), who were treated without a standardized protocol in a large number of centers with both high-volume and low-volume case load on a yearly base.[18] A difference between the two studies is, next to different patient numbers and the presence of standardized treatment, a different inclusion period (2008–2014 in the present study vs 1996–2005 in the study by Jani *et al.*). The presented survival rates in the different categories (severe, moderate and mild) of O/E LHR in our study are comparable with the previous studies. Because inclusion criteria in the Tracheal Occlusion To Accelerate Lung (growth) trial (moderate CDH (NCT01240057) and severe CDH (NCT00763737)) are based on these previous studies, it is important that we can conclude that those criteria are still valid following a nationwide evaluation in The Netherlands in an era of standardized neonatal treatment protocol. Improving neonatal therapy is, however, a moving target explaining that may contribute to the different overall survival rates between the two study periods (76% in the present study vs 65% in the study by Jani *et al.*). Our data also show that fetuses with an O/E LHR of 36–45% have a survival chance equal to fetus in the mild group irrespective of liver position. Position of the liver seems more relevant in fetus with an O/E LHR between 26 and 35%. In the multivariable logistic regression analysis, however, prenatal liver position was not significantly associated with survival, postnatal defect size nor with development of CLD in survivors after adjustment for O/E LHR. In our study, we assessed the liver position as being a dichotomous variable (intrathoracic or not intrathoracic). Previous studies have shown, however, that quantification of the extent of liver tissue herniation by ultrasound or MRI and/or position of the stomach in the thorax are more predictive for survival, even independent of the O/E LHR.[26–30] The primary aim of our study was to investigate the validity of the currently used O/E LHR for survival in an era of standardized neonatal treatment and quantification of herniated liver tissue was not part of the study design.

We found an AUC for survival of 0.77, which is comparable with previous studies (AUC 0.76 in the study by Jani *et al.*,[10] AUC 0.78 in the study by Ruano *et al.*,[31] and AUC 0.84 in the study by Kehl *et al.*[32]). The relevance for clinical practice of the cut-off values based on the Youden index is debatable, because the weight of a possible false positive or false negative prediction has not been taken into consideration Before assigning differential

weights to the predictions, evaluation of parents preferences should, however, be further investigated.

In our study, we found a difference in the significance of the association between survival and GA at diagnosis (p0.30) and the association between the first measured O/E LHR and GA at diagnosis (p0.05). This indicates that a higher absolute difference in percentage O/E LHR at a later time during gestation does not immediately result in an overall higher survival. Deprest *et al.*[15] proposed a division of patients into categories (extreme/severe/moderate/mild). Because our data show that 80% of the patients remain in the same O/E LHR category during the second and third trimester of pregnancy, those categories rather than absolute percentages seem more suitable for prenatal counseling.

We found that a lower O/E LHR was significantly associated with development of CLD in survivors. The only studies that have also evaluated the prognostic value of the O/E LHR for the development of CLD[10,14] found the same result. In addition, we have shown that a lower O/E LHR is associated with a larger postnatal defect size as classified by the Boston scale and these larger defects are associated with the development of CLD in survivors. Therefore, it is likely that prenatally assessed size of the contralateral lung is not only a predictor of mortality, but also for pulmonary morbidity.

The strengths of this study are the inclusion of a large cohort of isolated left CDH patients in a relatively short inclusion period who were all treated according to the same standardized treatment protocol including the same ECMO protocols, in addition to standardized prenatal measurements. Because one single experienced operator performed all measurements on stored ultrasound data, inter-observer variability could not have influenced our results. Cruz-Martinez *et al.* showed that there is a learning curve for performing O/E LHR measurements, which emphasizes the importance of an experienced operator.[20] We used the tracing method to calculate the O/E LHR which was shown to be superior to the anteroposterior diameter method in predicting postpartum survival in isolated left-sided CDH.[21,32]

A limitation of this study may be that, although O/E LHR was measured by one observer, measurements were performed on stored ultrasound images, which may not have been the perfect section of the cross-sectional view of the fetal thorax at the level of the four-chamber view of the heart. However, if an image did not meet the criteria for measurement of the lung area as described by Jani *et al.*,[21] a measurement was regarded as missing.

CONCLUSIONS

In isolated left-sided CDH patients, O/E LHR predicts survival and development of CLD in survivors in an era of a standardized neonatal treatment protocol, and the previously established categories of severe, moderate and mild CDH remain valid. Prenatal liver position ('liver up' vs 'liver down') was not significantly associated with survival nor with development of CLD in survivors after adjustment for O/E LHR.

ACKNOWLEDGEMENTS

We thank Dagmar de Bruijn from the Radboud University Medical Centre, Nijmegen, The Netherlands for her help with data collection.

What's already known about this topic?

- The O/E LHR ratio is currently used for prenatal prediction of postnatal outcome in fetuses with CDH.

What does this study add?

- An evaluation of the predictive value of the O/E LHR ratio for survival and development of chronic lung disease in fetuses with CDH in an era of standardized neonatal treatment.
- Insight into the predictive value of the O/E LHR trajectory throughout gestation.

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CHAPTER 5.1

Power Doppler rendering of fetal bilateral accessory renal arteries in virtual reality

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The renal arteries normally arise from the abdominal aorta proximal to the bifurcation. Known anatomic variations in renal arteries, for example accessory renal arteries, are present in 20 – 30% of the general population and show different places of origin and various courses.[1] Accessory renal arteries are embryonic mesonephric arteries that failed to degenerate.[2] Accessory renal arteries may be parallel to the main renal arteries, this being the most common anatomic variation.[2] Other known variations include a divergent, convergent or crossed trajectory of the renal arteries on the same side.[1]

We observed, in a fetus at 26 weeks' gestation, two normal kidneys with bilateral accessory renal arteries. Three-dimensional (3D) power Doppler datasets were obtained using a GE Voluson E8 system (GE Medical Systems, Zipf, Austria). These datasets were analyzed in 4D view and by use of a virtual reality system to render images in the Barco I-space[3]. The Barco I-space is a CAVE-like virtual reality system, which, by use of the V-scope volume rendering application, creates a hologram from a 3D dataset. The hologram, projected onto the walls and floor of a dark room, is analyzed wearing 3D glasses and using a special joystick. By making use of the third dimension, 'depth perception', virtual reality enabled us to visualize the fetal vascular anatomy in more detail. The different kinds of voxels (3D pixels), i.e. power Doppler and gray-scale voxels, can easily be separated, allowing visualization of Doppler images of the fetal vasculature with and without the internal organs.

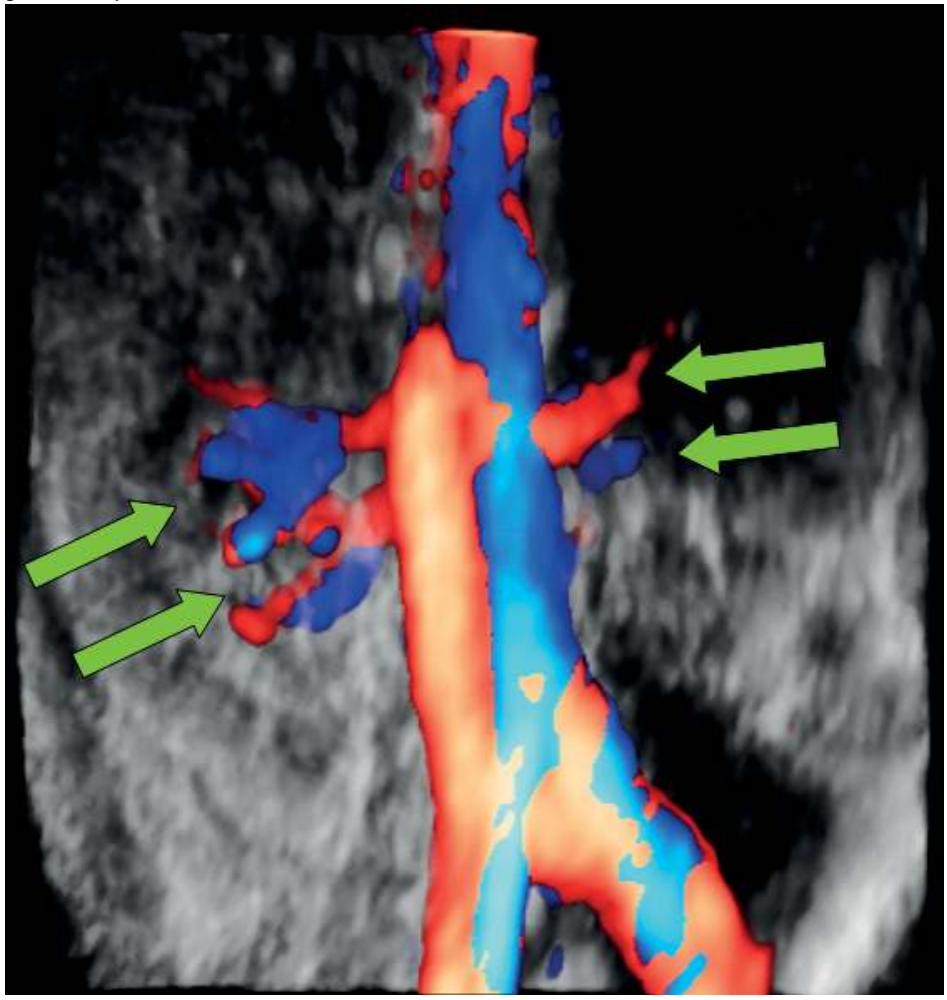
The fetal vascular system, including the bilateral accessory renal arteries, is shown in Figure 1 as seen in 4D View and in Figure 2a as a hologram as seen in the Barco I-Space; Figure 2b is a schematic representation of Figure 2a.

Visualization of 3D images on a two-dimensional (2D) screen has technical limitations. In contrast to assessment in 4D View, the virtual reality system offers the real third dimension: depth perception. It has been shown previously that the Barco I-space improves visualization of fetal anatomical structures.[3,4] 3D virtual reality power Doppler imaging of the fetal vasculature is a novel addition that improves the assessment of variations in the vascular system in relation to the internal organs.

Access to more detailed knowledge about variations in the fetal vascular system might be useful for surgical procedures later in life, for example, renal transplantation.[1] Possible comorbidities of accessory renal arteries as a result of differences in size, length and/or course have been described previously. Possible comorbidities include an increased risk of hydronephrosis or of developing arterial hypertension later in life.[2,5] In the Barco I-space, the course, length, width, number of bifurcations and relationship with the surrounding structures of (renal) vessels can easily be evaluated in detail, which could contribute to a risk estimate for these comorbidities.

In conclusion, advanced imaging techniques such as 3D virtual reality ultrasound provide the opportunity to enhance the visualization of Doppler images of the fetal vasculature, and can be used in addition to the conventional 2D ultrasound examination.

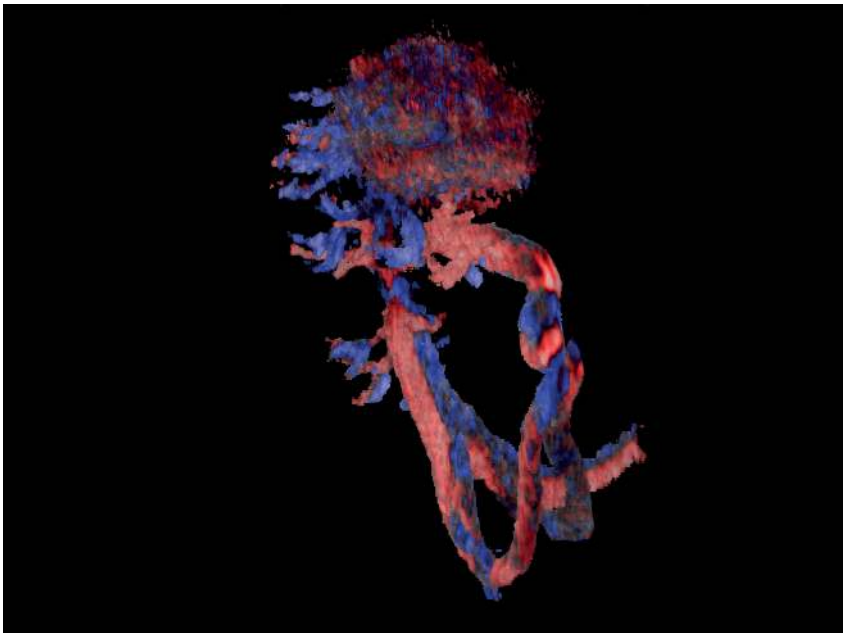
Figure 1 Three-dimensional power Doppler image (dorsal view) of fetal bilateral accessory renal arteries at 26 weeks' gestation analyzed in 4D View.



Arrows indicate the bilateral accessory and main renal arteries, which run parallel and enter the hilum of each kidney.

Figure 2 (a) Two-dimensional image of the hologram derived from the three-dimensional power Doppler image of the bilateral accessory renal arteries in a fetus at 26 weeks' gestation in a deviated frontal view in the Barco I-space. (b) Schematic view of Figure 2a indicating the different fetal anatomical structures. Red, fetal heart and pulmonary vessels; purple, vena cava and aorta bifurcating in the femoral vessels; blue, umbilical arteries; turquoise, umbilical vein and liver vessels; bright green, renal arteries arising from the aorta on each side.

a



b

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CHAPTER 5.2

Assessment by 3D-VR ultrasonography of pulmonary vascular development in fetuses with isolated congenital diaphragmatic hernia and healthy controls

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In submission

ABSTRACT

Objectives

To study pulmonary vascular development in fetuses with an isolated left sided congenital diaphragmatic hernia (L-CDH) and healthy controls by measurement of the pulmonary vascular volume of the right lung (R-PVV) using three-dimensional (3D) virtual reality (VR) ultrasound. In addition, associations were studied with survival, need for treatment for pulmonary hypertension (PH) and presence of chronic lung disease (CLD) in fetuses with an isolated L-CDH born >34 weeks' gestation.

Methods

3D volumes of the contralateral right lung (measured with and without Power Doppler) were obtained at 20-24 (US1), 24-30 (US2) and/or 30-36 (US3) weeks' gestation in all included fetuses (2012-2018). Right lung volumes (R-LV) were measured by rotational analysis in 4DView. R-PVV measurements were analysed in the BARCO I-Space Virtual Reality system. To correct for lung size the R-PVV was divided by the R-LV to calculated the R-PVV/LV-ratio. R-LV, R-PVV and R-PVV/LV-ratio measurements were compared between healthy controls and isolated L-CDH fetuses matched for gestational age.

Results

Fifty-one fetuses with an isolated L-CDH, of whom 48 born >34 weeks' gestation, and 72 healthy controls were included. Survival rate within the L-CDH group was 38/48 (79%) and 23/48 (48%) were treated for PH. Seventeen (45%) of the L-CDH survivors developed CLD. The median observed-versus-expected lung-to-head ratio [interquartile range] was 41.7% [34.2-52.3], indicating an overall moderate to mild pulmonary hypoplasia within the L-CDH group. The interobserver agreement and intraobserver agreement (ICC) for the R-PVV was 0.99 and 1.00, respectively, representing excellent agreement. R-LV, R-PVV and R-PVV/LV-ratio were significantly smaller in isolated L-CDH fetuses compared to healthy controls. Mean R-PVV at US1 in non-survivors within the isolated L-CDH group was significantly lower than that in survivors (p=0.001). No associations between the R-PVV, R-LV or R-PVV/LV-ratio and the need for treatment for PH and development of CLD were found.

Conclusion

The contralateral pulmonary vascular volume in fetuses with an isolated L-CDH was smaller than that in healthy controls when corrected for lung size. The R-PVV can be reliably measured by 3D-VR ultrasound.

INTRODUCTION

Although survival rates in neonates with congenital diaphragmatic hernia (CDH) have increased significantly in the last decade to about 70-80%,[1-3] CDH is still a life-threatening congenital anomaly associated with long-term morbidity. Fetuses are at risk for the development of clinical relevant pulmonary hypertension (PH) of variable duration after birth. Many surviving fetuses at risk for PH develop chronic lung disease (CLD) as an acquired secondary morbidity.[4-9] Previous studies have investigated the use of fetal MRI and two-dimensional (2D) and three-dimensional (3D) ultrasound techniques for the prediction of PH, with the ultimate aim to optimize prenatal counselling of parents and improve selection for intrauterine treatment.[10-24] As MRI is not widely available, and not invaluable in prognosis prediction in CDH, we have concentrated on ultrasound parameters that might predict an increased risk of PH in fetuses with CDH.[25-27] These include the observed-versus-expected lung-to-head ratio (O/E LHR),[10-12] 3D lung volume measurements,[13] position of the liver (intra-abdominal versus intrathoracic),[14-16] stomach position (grade A-D) within the thorax,[17, 18, 24] pulmonary artery size[19-21] and pulmonary artery and vein velocity measurements.[22, 23] None of these methods, so far, proved to have sufficient sensitivity and specificity to assess vascular development and predict PH.

PH is the result of increased pulmonary vascular resistance. Morphologically, it is characterized by a relatively low lung weight, a low radial alveolar count, reduced branching of the small pulmonary arteries and increased medial wall thickness due to increase muscularization even at the level of the arterioles.[28-33] Previous studies have shown that these factors are already present in the fetal period.[34-36] We hypothesized that the volume of the fetal pulmonary vasculature differs significantly between healthy controls and left sided (L-) CDH patients, and that 3D-virtual reality (VR) ultrasound could precisely assess the pulmonary vascular development in fetal life.[37-41] To confirm this hypothesis, we calculated the contralateral pulmonary vascular volume (PVV) from 3D-VR ultrasound images in fetuses with an isolated L-CDH and in gestational age matched healthy controls. In addition, we assessed the predictive value of the PVV of isolated L-CDH patients for survival, need for treatment for neonatal PH and development of CLD in survivors.

METHODS

Patient selection

For this case-control study, the case group consisted of live-born fetuses with a prenatal diagnosis of an isolated L-CDH between April 2012 and June 2018 in the Erasmus Univer-

sity Medical Centre in Rotterdam, The Netherlands.[24] The Medical Ethics Review Board waived approval since data, which were obtained prospectively during routine care, were retrospectively analysed (MEC-2014-016). Exclusion criteria were multiple pregnancies, major multiple congenital anomalies, presence of chromosomal abnormalities, prenatal diagnosis/first referral >33 weeks' gestation, termination of pregnancy, intrauterine fetal death, no intention to treat and/or loss to follow-up.

Controls were recruited from the FLOW study (Fetal Lung Observations and ultrasound Waveforms), a prospective case-control study embedded in a hospital-based birth cohort study from preconception onwards with follow- up to 1 year after birth.[42] The control group of the FLOW study consists of fetuses who did not show congenital anomalies on the 20-week anomaly scan. Exclusion criteria for the control group were: no written informed consent, multiple pregnancies, prenatal or postnatal presence of structural and/or chromosomal abnormalities, development of preeclampsia, preterm birth <34 weeks' gestational age (GA), fetal growth restriction (defined as an estimated fetal weight below the 10th percentile), termination of pregnancy, intra uterine fetal death, death during the first 28 days of life) and/or loss to follow-up. Multiple congenital anomalies were defined as major when surgery or multiple postnatal follow-up visits were required.

Prenatal parameters

We retrieved data for both cases and controls on maternal BMI, parity, presence of polyhydramnios (defined as an amniotic fluid index (AFI) of >24 cm), presence of associated congenital anomalies and/or chromosomal abnormalities, presence of fetal growth restriction, placenta location (anterior versus other localisations). For fetuses with L-CDH, we also retrieved the O/E LHR and prenatal position of the liver (intra-abdominal or intrathoracic).

The O/E LHR was calculated as described by Jani et al.[10] by the tracing method on one of the GE Voluson E8 or E10 systems (GE Medical Systems, Zipf, Austria) in our centre. Ultrasound measurements were categorized into three ultrasound (US) periods: 19^{+0}-24^{+0} weeks' gestation (US1), 24^{+1}-29^{+6} weeks' gestation (US2), and $\geq 30^{+0}$ weeks' gestation (US3). Based on availability of images, one single experienced operator (NP), who was unaware of postnatal outcome, measured pulmonary volume of the right lung (R-LV) and pulmonary vascular volume of the right lung (R-PVV).

Pulmonary volume and vascular volume measurements

Ultrasound volumes of the fetal thorax were obtained with either a Voluson E8 or E10 ultrasound machine (Kretztechnik, Zipf, Austria) with a 1-7 MHz RM6C transducer for 3D volume scanning. Volumes were recorded at a transverse section of the fetal thorax

at the level of the four-chamber view. In order to include the entire fetal thorax, the angle of volume sampling varied throughout gestational age with a maximal limit of 70 degrees in the third trimester. Dynamic contrast was adjusted to improve differentiation between the lung and adjacent structures.

R-LV was measured on stored 3D-US volumes by use of specialized 3D computer software (4D View, GE Medical Systems, Zipf, Austria) and the virtual organ computer-aided analysis (VOCAL, GE Medical Systems, Zipf, Austria) measuring application.[43] The transverse plane served as a reference. This plane was rotated around the 'z-axis' in 6 steps of 30°; in each step the lung was traced manually until completion of a 180° rotation. The 3D R-LV was created and checked for possible inconsistencies. The software then calculated R-LV (figure 1).

A 3D Power Doppler US scan was performed to visualise the pulmonary arteries and veins. Each Power Doppler scan was recorded using standardized settings of the ultrasound machine: pulse repetition frequencies (PRF) of 1.3 kHz, gain of -8.0, quality 'high1' and wall motion filter on 'low'. If needed, the woman was instructed to hold her breath during the recording. The 3D Power Doppler volume was then uploaded in 4D View (figure 2), where the right lung was selected to fit within the borders of the render plane. Only the data within the borders of the render plane were saved as a Cartesian volume for offline measurement with the use of our V-Scope software in the BARCO I-Space VR system.[40]

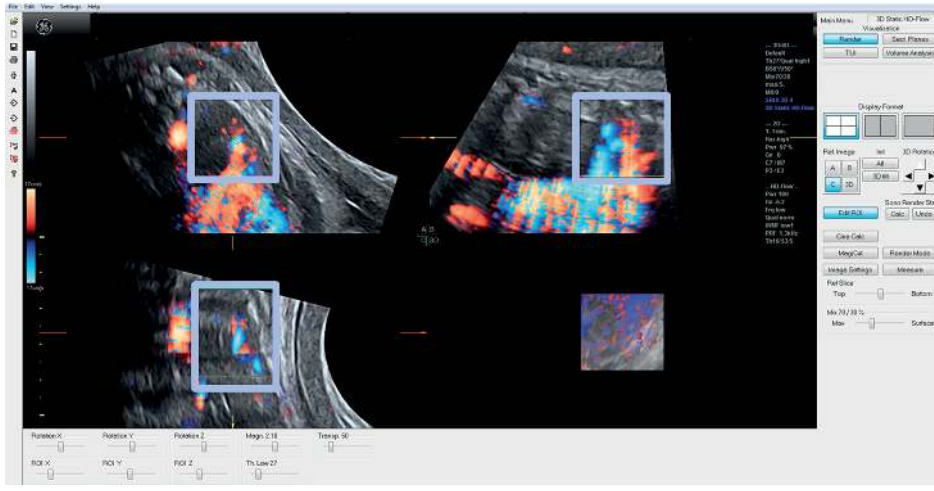
In this four-walled CAVE™-like VR system, the main pulmonary vascular branch at the level of the left atrium was sought out (figure 3). The V-Scope settings in the BARCO I-Space VR system were uniform for all measurements: the lower-Doppler voxel threshold was set to 120 in order to count only voxels with a value between 120 and 255; for uniform assessment of the R-PVV, the deviation threshold was set to the maximum (255) in order to include only the voxels connected to the main pulmonary branch. By 'planting a seed', i.e. selecting a voxel within the main pulmonary vascular branch, a semi-automatic volume measurement of all connected voxels with a Doppler value above the threshold was obtained (supplemental video).[40]

To account for differences in lung volume between fetuses, we calculated the vascular volume to lung volume ratio (R-PVV/LV-ratio) by dividing the R-PVV by the R-LV, and multiplying the result by 100, in order to express the ratio as a percentage.

Figure 1 Measurement of the right lung volume in 4DView.

Image of the three-dimensional (3D) volume measurement of the right lung (R-LV) in a case with a left-sided congenital diaphragmatic hernia at 27 weeks' gestation. The transverse plane served as a reference (plane A). This plane was rotated around the 'z-axis' in 6 steps of 30°; in each step the lung was traced manually until completion of a 180° rotation. The 3D R-LV was created and checked for possible inconsistencies. The software then calculated R-LV.

Figure 2 Selection of pulmonary vasculature within 4D View for measurement of pulmonary vascular volume in the BARCO I-Space.



The acquired 3D Power Doppler volume is uploaded in 4D View, where the right lung is selected to fit within the borders of the render plane (purple square); only the data within this square were then saved as a Cartesian volume.

Figure 3 Measurement of the pulmonary vascular volume in the BARCO I-Space.

Photograph showing the offline measurement of the pulmonary vascular volume in a healthy control patient (A) and a foetus with L-CDH (B) at 26 weeks' gestational age in the BARCO I-Space Virtual Reality system using our V-Scope software.[40] In this four-walled CAVE™-like system, the main pulmonary vascular branch at the level of the left atrium is sought out. By 'planting a seed'; i.e., selecting a voxel within the main pulmonary vascular branch, a semi-automatic volume measurement of all connected voxels (maximum deviation threshold) with a Doppler value meeting the pre-set threshold (120-255) was obtained (C).

Postnatal parameters

During the study period, L-CDH patients postnatally have been treated according to a standardized neonatal treatment protocol.[8,44] For all included patients, we retrieved data on delivery mode, GA at birth, birthweight, gender, Apgar score at 5 minutes, presence of associated major structural or chromosomal anomalies, and survival. For fetuses with L-CDH we also registered need for treatment of PH (defined as being treated for PH with inhaled nitric oxide and/or intravenous sildenafil), need for extracorporeal membrane oxygenation (ECMO), mode of surgery (thoracoscopy or laparotomy), need for a patch, liver position (intrathoracic/intra-abdominal) at surgical repair, diaphragmatic defect size (A/B/C/D, with 'A' being the smallest and 'D' being the biggest defects),[3] survival, and presence of CLD in survivors. Postnatal patient characteristics were retrieved from medical records; information on the pregnancy outcome for healthy controls was received from the midwife or gynaecologist.

Preterm delivery was defined as birth prior to 34 weeks' GA for both cases and controls. Survival was defined as alive after the first year of life. CLD was defined as need for increased oxygen requirement at the age of >28 days after birth in infants born >32 weeks' GA.[45] ECMO therapy was available for all patients born after >34 weeks' GA and a birth weight above 2000 grams.

Statistical analysis

Patient characteristics are described as number (%) for categorical data and median (interquartile range, IQR) for continuous data. For the analysis on prediction of postnatal outcome (i.e., survival, treatment for PH), we selected only isolated L-CDH cases born >34 weeks' gestational age. For the analysis for prediction of CLD, we selected only isolated L-CDH survivors born >34 weeks' gestation.

Prenatal and postnatal parameters were compared between 1) healthy controls and isolated L-CDH cases, and 2) surviving and non-surviving isolated L-CDH neonates using chi-square or Fisher exact tests (nominal or ordinal variables) or Mann-Whitney tests (continuous variables). The association between the R-LV and R-PVV at the three time periods separately and the presence of an isolated L-CDH, survival and treatment for PH within isolated L-CDH cases or presence of CLD in isolated L-CDH survivors were evaluated using univariable logistic regression analyses. For the multivariable logistic regression analyses, maternal BMI was added to the model for analysis at US1 and US2. Maternal BMI as well as GA at US3 were added to the model for analysis at US3. Logistic regression analysis was only performed if the sample size was adequate (i.e. >5 cases/events per variable).

The intraclass correlation coefficient (ICC) was used to quantify the interobserver and intraobserver agreements. Regarding the interobserver agreement, NCJP and ADR both measured the PVV in 15 randomly selected cases, blinded to each other's result. Regarding the intra-observer agreement, NCJP measured the PVV in 15 randomly selected cases at a 6-month interval. The ICCs were calculated in a two-way mixed model with absolute agreement, and reported as single measures. An ICC between 0.75 and 0.90 indicates good agreement; an ICC > 0.90 indicates excellent agreement.

The distributions of the R-PVV, R-LV and R-PVV/LV-ratio were compared between time periods (i.e.; US1, US2 and US3) using Mann-Whitney tests, and these analyses were stratified by patient group (controls as well as survivors and non-survivors in the L-CDH group). An additional longitudinal analysis was performed to determine whether the growth rate (i.e. the relative change per day of R-PVV, R-LV and R-PVV/LV-ratio) differed between the time interval US1 to US2 versus the interval US2 to US3. To analyse these growth rates, the R-LV, R-PVV and R-PVV/LV-ratio were log-transformed. General linear models for repeated measurements were then run, with logR-LV, logR-PVV and logR-PVV/LV-ratio at the three time periods as the dependent variable. The independent variables were gestational age in days and a variable that was defined as the difference in gestational age between US2 and US3 for observations at US3, and as 0 for observations at US1 and US2. A Wald test for the latter variable served to determine whether there

was a significant change in growth rate between the two time intervals. An unstructured covariance matrix was used to model the within-subject correlations.

To analyse the association between trends in R-LV and R-PVV throughout gestation and outcome parameters, we summarized the longitudinal data of the log transformed R-LV, R-PVV and R-PVV/LV-ratio of each patient using an estimated level (intercept) and time trend (slope). The intercept and slope were obtained from a linear regression of log transformed R-LV, R-PVV and R-PVV/LV-ratio on the gestational age (as a continuous variable), for each patient separately. The slope was calculated per day difference in GA. This analysis was only performed for fetuses for whom two or three measurements were available. The resulting estimates of the intercept and the slope in the logistic regressions served as independent variables in multivariable logistic regressions for 1) presence of an isolated L-CDH, 2) survival or treatment for PH in isolated L-CDH cases, and 3) presence of CLD in isolated L-CDH survivors.

All odds ratios are related to prenatal diagnosis of an isolated L-CDH in all cases, survival and treatment of PH only in isolated L-CDH cases born >34 weeks GA, or presence of CLD in isolated L-CDH survivors born >34 weeks GA. All calculations were performed using SPSS version 25.0 for Windows and Windows Excel 2010. A two-sided p-value of <0.05 was considered to indicate statistical significance.

RESULTS

Study population

During the study period, 77 healthy control patients and 75 singleton isolated L-CDH patients were eligible for inclusion. The applied exclusion criteria are summarized in the flowchart (supplemental figure 1). Data of 72 live-born healthy control patients and 51 isolated L-CDH patients with an intention to treat were eligible for analysis. Four fetuses with a L-CDH showed multiple congenital anomalies after birth. These anomalies included one fetus with a pre-auricular tag and coronal hypospadias, another with a postnatal hydrocephalus for which a drain was needed, a third neonate showed polysplenia and the final neonate showed a renal duplex system.

R-LV could be measured in 320/368 (87%) of the acquired 3D volumes. On average 192/203 (95%) of volumes in the control group were of sufficient quality, versus 105/117 (90%) (n=105/117) of volumes in the case group. At US1 (p=0.001) and US2 (p=0.01), significantly more volumes were of sufficient quality for the measurement of the R-LV in the control group (67/69 (97%) and 66/69 (96%, respectively), than in the case group (28/31 (90%) and 37/41 (90%), respectively). The number of volumes available for meas-

urement of R-LV at US3 did not significantly differ between these groups (n=59/65 (91%) and n=40/45 (89%), respectively). Overall, the quality of the volumes for measurement of the R-LV did not significantly differ between US1, US2 and US3 (p=0.68).

R-PVV could be measured in 305/367 (83%) of the acquired 3D volumes. Overall, 81% 158/196 (81%) of volumes in the control group and 68/109 (62%) of volumes in the case group were of sufficient quality. R-PVV could be measured for significantly more control patients compared to cases at US1 (63/69 (91%) and 13/28 (46%); p<0.001, respectively), US2 (50/66 (76%) and 25/39 (64%); p=0.006, respectively) and US3 (45/61 (74%) and 30/42 (71%); p<0.001, respectively). Overall, no significant difference was found in quality of the volumes for measurement of the R-PVV between US1, US2 and US3 (p=0.70).

Multiple measurements (i.e. two or three) of the R-LV were available for 108 (88%) of the included patients (controls (n=70) and L-CDH cases (n=36)), and 104 (84%) had multiple measurements available of the R-PVV (controls (n=68) and L-CDH cases (n=34)). This resulted in a total of 318 R-LV and 292 R-PVV measurements being available for the longitudinal trend analysis.

Intraobserver and interobserver agreement calculations of the R-PVV resulted in an ICC of 1.000 (95% CI: 1.000-1.000) and 0.992 (95% CI: 0.977–0.997), respectively, both representing excellent agreement.

Healthy controls versus isolated L-CDH cases

Baseline characteristics compared between healthy controls (n=72) and isolated L-CDH cases (n=51) are summarized in table 1.

We found expected differences in GA at delivery, vaginal delivery, Apgar score at 5 minutes, umbilical cord blood pH, birthweight, presence of associated anomalies and survival between healthy controls and isolated L-CDH cases. In addition, maternal BMI in the healthy control group was significantly lower than that in the case group (p=0.03). Mean GA at US3 was significantly lower in the healthy control group compared to the case group (p=0.001), due to late referral and/or diagnosis in the latter group.

Both median R-LV and R-PVV in controls were significantly larger compared to isolated L-CDH cases of the same GA at US1, US2 and US3 (p<0.001; table 1, figure 4.1 and 4.2). The R-PVV/LV-ratio was significantly larger in controls compared to isolated L-CDH cases at US1 and US3 (p=0.001 and p=0.02, respectively; table 1, figure 4.3), but not at US2 (p=0.07; table 1).

Table 1 Patient characteristics compared between healthy controls and isolated L-CDH cases.

	n	Controls n=72	n	L-CDH n=51	*p* value
Prenatal characteristics					
US1: 19^{+0}-24^{+0} weeks GA					
GA (w^{+d})	69	22^{+0} (20^{+6}-22^{+3})	33	21^{+5} (20^{+5}-22^{+5})	0.93
R-PVV (mm^3)	69	350 (220-495)	26	58 (33-171)	**<0.001**
R-LV (mm^3)	70	8213 (6493-9872)	31	4311 (3344-6238)	**<0.001**
R-PVV/LV-ratio (%)	70	4.00 (2.42-6.29)	25	1.94 (0.38-4.60)	**0.001**
US2: 24^{+1}-29^{+6} weeks GA					
GA (w^{+d})	71	26^{+1} (25^{+4}-26^{+6})	44	26^{+2} (25^{+5}-27^{+0})	0.14
R-PVV (mm^3)	64	675 (240-1148)	38	270 (78-466)	**<0.001**
R-LV (mm^3)	69	16874 (12808-20910)	40	9156 (6446-11861)	**<0.001**
R-PVV/LV-ratio (%)	64	4.16 (1.30-6.95)	36	2.81 (1.32-4.98)	0.07
US3: ≥30^{+0} weeks GA					
GA (w^{+d})	71	30^{+3} (30^{+0}-30^{+5})	50	30^{+6} (30^{+2}-31^{+4})	**0.001**
R-PVV (mm^3)	53	650 (345-1295)	42	260 (77-577)	**<0.001**
R-LV (mm^3)	65	26888 (22096-31721)	44	15248 (12772-20402)	**<0.001**
R-PVV/LV-ratio (%)	50	2.94 (1.44-4.97)	41	1.66 (0.77-3.61)	**0.02**
Maternal BMI	70	23 (20.6-25.1)	51	25.0 (21.7-28.5)	**0.03**
Maternal Age	72	32.5 (29-37)	51	32 (27-35)	0.21
Nullipara	72	41 (57)	51	24 (47)	0.28
Polyhydramnios	72	0 (0)	51	13 (26)	**<0.001**
FGR	72	0 (0)	51	2 (4)	0.09
Placental location: anterior	72	34 (47)	51	23 (45)	0.18
Postnatal characteristics					
Gestational age at delivery (w^{+d})	62	39^{+2} (38^{+2} – 40^{+2})	51	38^{+1} (37^{+4} – 38^{+3})	**<0.001**
Delivery <34 weeks GA	72	0 (0)	51	3 (6)	0.07
Delivery <37 weeks GA	72	3 (4)	51	6 (6)	0.16
Vaginal delivery	67	50 (75)	51	36 (71)	**<0.001**
Apgar score at 5 minutes	61	10 (9-10)	47	7 (6-9)	**<0.001**
Umbilical cord blood pH	43	7.24 (7.20-7.30)	48	7.29 (7.23-7.33)	**0.02**
Birth weight (grams)	65	3400 (3075-3855)	47	3000 (2800-3300)	**<0.001**
Gender female	68	35 (52)	51	25 (49)	0.79
MCA	72	0 (0)	51	4 (8)	**0.02**
Survival	72	72 (100)	51	40 (78)	**<0.001**

We compared prenatal, perinatal and postnatal characteristics between neonates with a left-sided congenital diaphragmatic hernia (L-CDH) and healthy controls, using chi-square or Fisher's exact tests (categorical variables) and Mann-Whitney tests (continuous variables). Data are described as number (%) or median (interquartile range, IQR), as appropriate. The MCA within the L-CDH group included one foetus with a pre-auricular tag and coronal hypospadias, one with a postnatal hydrocephalus for which a drain was needed, one neonate showed polysplenia and the final neonate showed a renal duplex system.

Abbreviations L-CDH: left-sided congenital diaphragmatic hernia; US: ultrasound; GA: gestational age; w^{+d}: weeks+days; R-LV: lung volume right lung; R-PVV: pulmonary vascular volume right lung; FGR: fetal growth restriction (defined as an estimated fetal weight <10^{th} percentile); MCA: multiple congenital anomalies.

Table 2 shows the results of the univariable and multivariable logistic regression analyses. The latter showed that at US1 and US2 a lower R-LV, R-PVV and R-PVV/LV-ratio were significantly associated with the presence of an isolated L-CDH, independent of maternal BMI. At US3, the multivariable logistic regression analysis with correction for maternal BMI and GA at US3 showed a significant association of both R-LV and R-PVV for the prediction of the probability of an isolated L-CDH.

Table 2 Univariable and multivariable logistic regression analyses for the pulmonary vascular volume and lung volume for presence of an isolated left-sided congenital diaphragmatic hernia (L-CDH).

	Univariable regression analysis			**Multivariable regression analysis**		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
US1: 19^{+0}-24^{+0} weeks GA*						
R-PVV (mm3)	0.994	0.991-0.997	**<0.001**	0.994	0.991-0.997	**<0.001**
BMI				1.048	0.940-1.168	0.40
R-LV (mm3)	0.473	0.352-0.636	**<0.001**	0.479	0.357-0.644	**<0.001**
BMI				1.051	0.946-1.166	0.35
R-PVV/LV-ratio (%)	0.78	0.645-0.951	**0.01**	0.791	0.654-0.956	**0.02**
BMI				1.057	0.952-1.172	0.30
US2: 24^{+1}-29^{+6} weeks GA*						
R-PVV (mm3)	0.998	0.996-0.999	**<0.001**	0.998	0.996-0.999	**0.001**
BMI				1.025	0.935-1.124	0.59
R-LV (mm3)	0.719	0.632-0.818	**<0.001**	0.723	0.636-0.822	**<0.001**
BMI				1.071	0.969-1.183	0.18
R-PVV/LV-ratio (%)	0.863	0.748-0.994	**0.04**	0.882	0.761-1.023	0.10
BMI				1.054	0.965-1.151	0.24
US3: ≥30^{+0} weeks GA**						
R-PVV (mm3)	0.998	0.996-0.999	**<0.001**	0.998	0.996-0.999	**0.001**
GA at US3				2.954	1.346-6.482	**0.007**
BMI				1.051	0.9658-1.144	0.26
R-LV (mm3)	0.780	0.710-0.857	**<0.001**	0.757	0.677-0.847	**<0.001**
GA at US3				2.816	1.168-6.789	**0.02**
BMI				1.200	1.048-1.375	**0.01**
R-PVV/LV-ratio (%)	0.798	0.653-0.974	**0.03**	0.818	0.659-1.016	0.07
GA at US3				2.624	1.295-5.317	**0.01**
BMI				1.088	0.998-1.18 7	0.06

*multivariable analyses were adjusted for maternal BMI; **multivariable analyses were adjusted for maternal BMI and GA at US.

Abbreviations L-CDH: left-sided congenital diaphragmatic hernia; OR: odds ratio; CI: confidence interval; R-LV: lung volume right lung; R-PVV: pulmonary vascular volume right lung; US: ultrasound; GA: gestational age; BMI: Body Mass Index.

Survival in L-CDH cases

Forty-eight fetuses with isolated L-CDH were born alive after 34 weeks' gestation, and thus were eligible for analysis. Survival within this group was 79% (n=38). Baseline characteristics stratified by survival status are summarized in table 3. We found a significant higher O/E LHR at US1, US2 and US3 and a lower number of cases with intrathoracic liver in surviving isolated L-CDH cases compared to non-surviving isolated L-CDH cases. Laparotomy instead of thoracoscopy was less often performed in surviving isolated L-CDH cases. Surviving isolated L-CDH cases had a smaller defect size at surgery and less often needed a patch. They were also less likely to receive treatment for PH or required ECMO treatment, and had a lower median length of hospital stay (table 3).

Table 3 Prenatal and postnatal characteristics of isolated left-sided congenital diaphragmatic hernia (L-CDH) cases born after >34 weeks' gestation, stratified for survival status.

	n	Survivors L-CDH n=38	n	Non-survivors L-CDH n=10	*p* value
Prenatal characteristics					
US1: 19^{+0}-24^{+0} weeks GA					
GA (w^{+d})	26	21^{+5} (20^{+4}-22^{+5})	5	21^{+6} (20^{+5}-22^{+2})	0.65
O/E LHR	26	44 (40-53)	7	29 (21-40)	**0.006**
R-PVV (mm^3)	22	82 (41-198)	3	3 (N/A)	**0.001**
R-LV (mm^3)	25	4687 (3431-6488)	5	3344 (1965-3818)	**0.02**
R-PVV/LV-ratio (%)	21	2.1 (1.0-5.4)	3	0.1 (N/A)	**0.001**
US2: 24^{+1}-29^{+6} weeks GA					
GA (w^{+d})	32	26^{+2} (25^{+5}-26^{+6})	10	26^{+5} (25^{+5}-27^{+2})	0.54
O/E LHR	32	43 (37-55)	9	31 (24-38)	**0.001**
R-PVV (mm^3)	28	275 (112-493)	8	100 (48-338)	0.15
R-LV (mm^3)	29	10563 (7206-13638)	9	6398 (5018-8436)	**0.004**
R-PVV/LV-ratio (%)	26	2.8 (1.7-5.2)	8	1.9 (0.7-4.2)	0.35
US3: ≥30^{+0} weeks GA					
GA (w^{+d})	38	30^{+5} (30^{+2}-31^{+2})	10	30^{+6} (30^{+4}-32^{+3})	0.32
O/E LHR	37	46 (37-56)	10	34 (30-38)	**0.001**
R-PVV (mm^3)	34	262 (120-585)	6	178 (73-628)	0.67
R-LV (mm^3)	36	16809 (13865-21068)	6	10264 (8451-12156)	**<0.001**
R-PVV/LV-ratio (%)	33	1.7 (0.6-3.6)	6	1.6 (0.8-5.3)	0.64
Maternal BMI	38	24 (21-27)	10	28 (24-35)	0.09
Maternal Age	38	31 (27-35)	10	33 (26-34)	0.93
Nullipara	38	21 (55)	10	1 (10)	**0.01**
Liver up	38	19 (50)	10	9 (90)	**0.03**
Hydrops	38	0 (0)	10	0 (0)	N/A
Polyhydramnios	38	8 (21)	10	4 (40)	0.41
FGR	38	1 (3)	10	1 (10)	0.38
Placental location: anterior	38	17 (45)	10	5 (50)	1.00

	n	Survivors L-CDH n=38	n	Non-survivors L-CDH n=10	*p* value
Postnatal characteristics					
Gestational age at delivery (w^{+d})	38	38^{+1} (37^{+5} – 38^{+3})	10	38^{+0} (37^{+5} – 38^{+3})	0.73
Delivery <37 weeks GA	38	3 (8)	10	0 (0)	1.00
Vaginal delivery	38	29 (76)	10	6 (60)	0.71
Apgar score at 5 minutes	35	7 (7-9)	9	7 (5-8)	0.14
Umbilical cord blood pH	37	7.30 (7.23-7.34)	9	7.29 (7.21-7.31)	0.29
Birth weight (grams)	35	3000 (2800-3240)	9	3000 (2650-3450)	0.93
Gender female	38	17 (45)	10	6 (60)	0.51
Isolated	38	36 (95)	10	9 (90)	1.00
Type of surgery (laparotomy)	33	19 (58)	3	3 (100)	**<0.001**
Use of patch	34	24 (71)	3	3 (100)	**<0.001**
Defect size	38		4		**<0.001**
A		5 (13)		0	
B		14 (37)		0	
C		15 (40)		3 (75)	
D		4 (11)		1 (25)	
Treatment for PH	38	14 (37)	10	9 (90)	**0.004**
ECMO	38	3 (8)	10	6 (60)	**0.001**
Length of hospital stay (days)	38	22 (21-23)	10	12 (2-30)	**0.001**
CLD	38	17 (45)	N/A		N/A

Prenatal, perinatal and postnatal characteristics of foetuses with a left-sided congenital diaphragmatic hernia stratified for survival status. Chi-square or Fisher's exact tests were used for categorical variables and Mann-Whitney tests for continuous variables. Data are described as number (%) or median (interquartile range, IQR), as appropriate.
Abbreviations L-CDH: left-sided congenital diaphragmatic hernia; US: ultrasound; GA: gestational age; w^{+d}: weeks+days; R-LV: lung volume right lung; R-PVV: pulmonary vascular volume right lung; BMI: body mass index; FGR: foetal growth restriction (defined as an estimated foetal weight <10^{th} percentile); PH: pulmonary hypertension (defined as receiving treatment with sildenafil or NO; ECMO: extracorporeal membrane oxygenation; CLD: chronic lung disease (defined as a need for increased oxygen requirement at the age of >28 days after birth in infants born after 32 weeks gestational age (GA).

Median R-LV at US1, US2 and US 3 in survivors was significantly larger than in non-survivors (p=0.02, p=0.004 and p<0.001, respectively). At US1, both the median R-PVV and the R-PVV/LV-ratio were significantly larger in survivors compared to non-survivors (p=0.001 for both parameters). At US2 and US3, no significant differences were found in median R-PVV and the R-PVV/LV-ratio between survivors and non-survivors (table 3, figures 4.1-4.3).

Univariable logistic regression analyses showed a significant positive association between R-LV at US3 and survival in isolated L-CDH cases (p=0.03; table 4). Univariable logistic regression analysis at US 1 and multivariable logistic regression analysis were not possible due to small sample size.

Presence of CLD in isolated L-CDH survivors

Seventeen (45%) of the isolated L-CDH survivors developed CLD. Only median R-LV at US3 and the O/E LHR were significantly lower in those 17 compared to those who did not develop CLD (p=0.02 and p=0.01, respectively). A significantly higher proportion of isolated L-CDH who developed CLD received treatment for PH (p=0.02).

Univariable logistic regression analysis showed a significant association between R-LV at US3 and development of CLD in isolated L-CDH survivors (p=0.04). No significant association was found at US1, US2 or US3 between R-PVV or R-PVV/LV-ratio and development of CLD in isolated L-CDH survivors (table 4).

Treatment for PH in isolated L-CDH cases

Twenty-three (48%) neonates with isolated L-CDH born after 34 weeks' gestation received treatment for PH. They had a significantly lower O/E LHR at US2 and US3 (p=0.04 and p=0.001, respectively) compared to those who did not receive treatment for PH. Univariable logistic regression analysis showed a significant association between R-LV and the need for treatment for PH (p=0.04) at US3, but not at US1 (p=0.06) and US2 (p=0.13). No association was found between R-PVV or R-PVV/LV-ratio and the need for treatment for PH at US1, US2 or US3 (table 4).

Pulmonary (vascular) volume trends

The median R-PVV, R-LV and R-PVV/LV-ratio of healthy controls and isolated L-CDH survivors and non-survivors per US period are plotted in figures 4.1-4.3. In both controls and isolated L-CDH cases, the median R-PVV was significantly different between US1 and US2 (p<0.001 and p=0.01, respectively), but not between US2 and US3 (p=0.29 and p=0.48, respectively). The median R-LV was significantly different in both controls and isolated L-CDH cases between US1 and US2 (p<0.001 in both groups) as well as between US2 and US3 (p<0.001 in both groups). The median R-PVV/LV-ratio did neither differ significantly for both controls (p=0.08) and isolated L-CDH cases (p=0.08) between US2 and US3, nor between US1 and US2 (p=0.63 and p=0.23, respectively).

Using a general linear model for repeated measurements we did not find a significant difference in the overall growth per day GA between US1/US2 compared to between US2/US3 for the R-PVV (p=0.35), but we did find a significant difference for the logRLV (estimate: -0.014, indicating smaller growth between US2/US3 compared to between US1/US2; p=0.004)

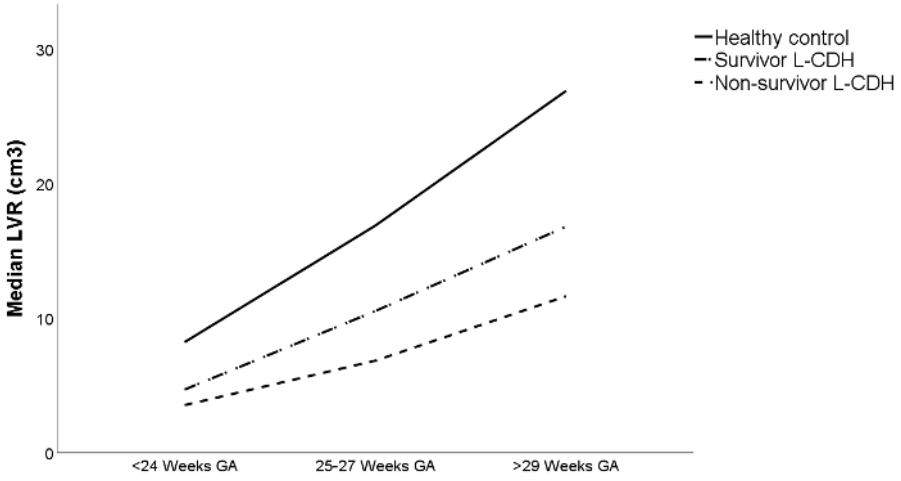
Using multivariable logistic regression analyses we found a significant association between the slope and the intercept of the log R-LV and presence of an isolated L-CDH; i.e., a lower value and a smaller increase of the log R-LV in patients with isolated L-CDH com-

Table 4 Univariable logistic regression analyses for the pulmonary vascular volume (PVV) and lung volume (LV) of the right lung with survival, treatment for PH and presence of CLD in cases with isolated L-CDH born after 34 weeks' gestation.

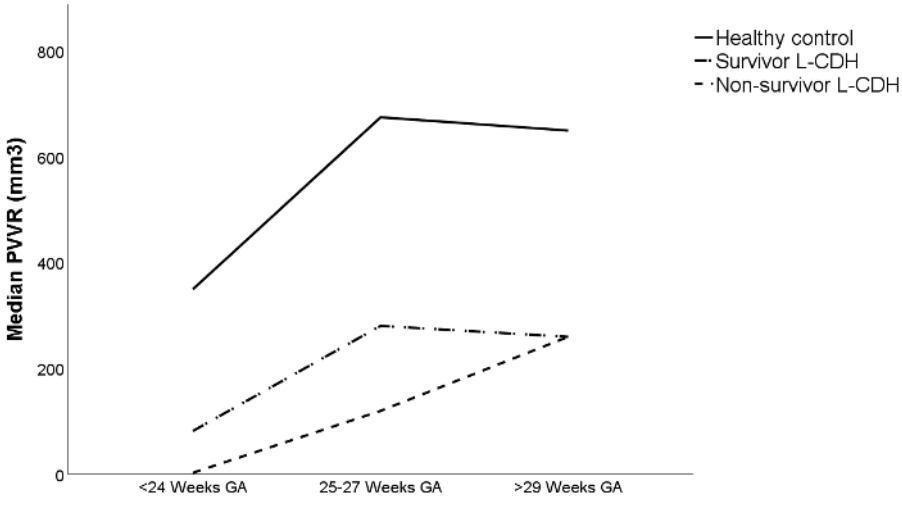
	OR	95% CI	*p*-value
	Survival in L-CDH		
US2: 24-30 weeks GA			
R-PVV	0.997	0.992-1.001	0.15
R-LV	0.663	0.468-0.938	**0.02**
R-PVV/LV-ratio	0.822	0.561-1.206	0.32
US3: 30-36 weeks GA			
R-PVV	0.999	0.997-1.002	0.71
R-LV	0.542	0.366-0.867	**0.03**
R-PVV/LV-ratio	1.164	0.771-1.757	0.47
	Treatment for PH in L-CDH		
US1: 20-24 weeks GA			
R-PVV	1.000	0.996-1.003	0.83
R-LV	0.652	0.415-1.025	0.06
R-PVV/LV-ratio	0.994	0.765-1.293	0.97
US2: 24-30 weeks GA			
R-PVV	1.000	0.998-1.002	0.75
R-LV	0.887	0.761-1.035	0.13
R-PVV/LV-ratio	1.102	0.832-1.460	0.50
US3: 30-36 weeks GA			
R-PVV	1.000	0.998-1.002	0.82
R-LV	0.830	0.717-0.961	**0.01**
R-PVV/LV-ratio	1.151	0.832-1.591	0.40
	CLD in L-CDH survivors		
US1: 20-24 weeks GA			
R-PVV	1.001	0.997-1.005	0.79
R-LV	0.710	0.445-1.132	0.15
R-PVV/LV-ratio	1.162	0.860-1.571	0.33
US2: 24-30 weeks GA			
R-PVV	1.000	0.998-1.003	0.65
R-LV	0.938	0.798-1.103	0.44
R-PVV/LV-ratio	1.123	0.826-1.526	0.46
US3: 30-36 weeks GA			
R-PVV	1.001	0.999-1.003	0.38
R-LV	0.843	0.716-0.993	**0.04**
R-PVV/LV-ratio	1.382	0.928-2.058	0.11

Abbreviations L-CDH: left-sided congenital diaphragmatic hernia; OR: odds ratio; CI: confidence interval; US: ultrasound; GA: gestational age; R-LV: lung volume right lung; R-PVV: pulmonary vascular volume right lung.

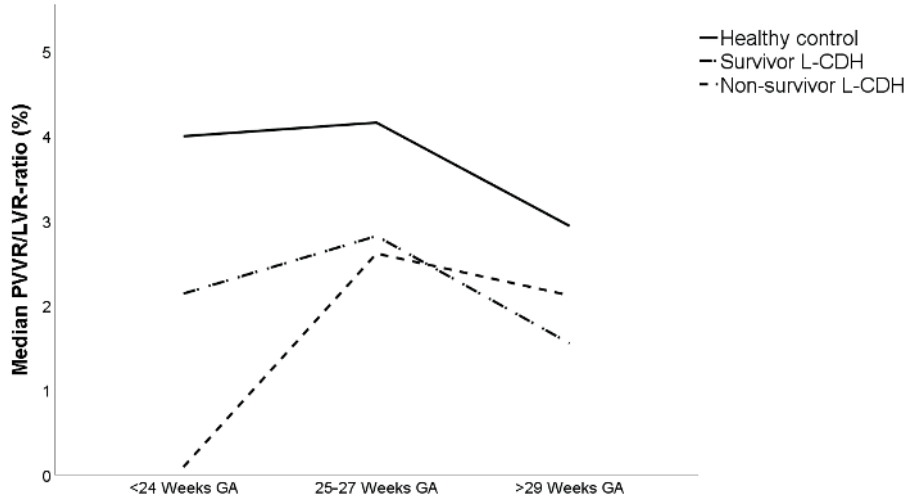
Figure 4 Median pulmonary vascular volume, lung volume and their ratio stratified per patient category (healthy controls, isolated L-CDH survivors and non-survivors) throughout gestation.



Median R-LV at US1, US2 and US 3 was significantly larger in healthy controls compared to isolated L-CDH foetuses ($p<0.001$ at all US time periods) and in isolated L-CDH survivors compared to non-survivors ($p=0.02$, $p=0.004$ and $p<0.001$, respectively).



Median R-PVV was significantly larger in healthy controls compared to isolated L-CDH cases at all time periods ($p<0.001$). At US1, the median R-PVV was significantly larger in survivors compared to non-survivors ($p=0.001$). At US2 and US3, no significant differences were found in median R-PVV between isolated L-CDH survivors and non-survivors ($p=0.15$ and $p=0.67$, respectively).



The R-PVV/LV-ratio at US1 was significantly larger in controls compared to isolated L-CDH cases and in isolated L-CDH survivors compared to L-CDH non-survivors (p=0.001 for both). At US2 no difference in median R-PVV/LV-ratio was found between healthy controls and isolated L-CDH cases (p=0.07), nor between isolated L-CDH survivors and non-survivors (p=0.35). The R-PVV/LV-ratio at US3 was significantly larger in healthy controls compared to isolated L-CDH cases (p=0.02), but no significant difference was found between isolated L-CDH survivors and non-survivors (p=0.64) at US3.
Abbreviations US: ultrasound; US1: 19^{+0}-24^{+0} weeks' gestation; US2:), 24^{+1}-29^{+6} weeks' gestation; US3: ≥30^{+0} weeks' gestation; L-CDH: left-sided congenital diaphragmatic hernia; R-PVV: pulmonary vascular volume right lung; R-LV: lung volume right lung; GA: gestational age.

pared to healthy controls. In a multivariable logistic regression analysis, no significant association was found between the trend (level and slope) in log R-PVV or log R-PVV/LV-ratio throughout gestation and presence of isolated L-CDH (supplemental table 1). This analysis likewise revealed no association found between the level and the trend (intercept and slope) of log R-PVV, log R-LV or log R-PVV/LV-ratio throughout gestation and survival, need for treatment for PH or presence of CLD in surviving patients with an isolated L-CDH born >34 weeks' gestation (supplemental table 2).

DISCUSSION

This study presents a novel method for a reliable measurement of fetal pulmonary vasculature; i.e, by 3D-VR ultrasonography. Measurement of the R-PVV with this method showed excellent interobserver and intraobserver agreement. Fetuses with an isolated L-CDH showed less vascularization of the contralateral lung even when adjusted for fetal lung size compared to healthy fetuses. The former group also showed less growth of the R-PVV after 30 weeks' gestational age. Before 24 weeks' gestation, the R-PVV in non-surviving fetuses with isolated L-CDH was significantly lower than in survivors. The

R-PVV was not found predictive for need for treatment of PH and development of CLD in isolated L-CDH survivors.

Prenatal prediction of postnatal outcome in L-CDH patients is currently based on lung size, determined by the O/E-LHR, 3D ultrasonography of the contralateral lung, or MRI of both lungs.[10, 13] In line with a previous study,[13] a smaller contralateral lung volume in L-CDH fetuses was associated with an increased need for treatment for PH and a higher likelihood to develop CLD. These lung volume measurements, however, do not take into account the cause of postnatal PH and CLD, i.e. impaired vascular development; CDH patients show reduced branching of the small pulmonary arteries and increased medial wall thickness due to increase of muscularization.[28-33, 46-49] In our study we also found less vascularization of the contralateral lung when adjusted for fetal lung size, in fetuses with an isolated L-CDH. Like in previous studies of the pulmonary blood flow in L-CDH fetuses,[14, 50, 51] our data did not permit drawing conclusions regarding prediction of postnatal outcome. In our study, this could be due to the small sample size in the subgroup analyses, the high survival rate, and the overall moderate to mild lung hypoplasia.

In both study groups, the median R-PVV did not differ significantly between US2 and US3, even though the R-LV did increase significantly during this period. Since we found no significant difference in the quality of the volumes between US2 and US3, we hypothesize that the lack of increase in R-PVV can be attributed to the fact that from around 27 weeks of gestation the more distal part of the lung vasculature begins to develop[52] and we mainly measured the proximal vasculature of the lung in this study. This hypothesis seems to be supported by the changes in intrapulmonary artery Doppler flow patterns observed by Cruz-Martinez et al.[23] during the second half of gestation, and warrants further study.

Measurement of the R-PVV proved to be an easy and reliable assessment of the fetal pulmonary vasculature – with better interobserver and intraobserver agreement compared to previous methods described to measure vascular volumes.[50, 53] Like in previous studies, the R-PVV measured for this study included mostly the proximal vessels within the fetal lung. From the literature,[35, 54-56] however, it is known that the largest differences in pulmonary vascular development are found in the peripheral part of the lung. With use of the current ultrasound machine settings, we were not able, however, to depict small pulmonary vessels with low flow velocities. New imaging techniques that can show slow blood flow in small vessels[57, 58] might allow for a more precise assessment of the peripheral pulmonary vasculature. Comparing the performance of the different techniques with the same dataset could perhaps tell whether combined measurements – i.e., lung volumes, vascular volumes (corrected for lung size) and pulsed wave patterns – would enable a more precise prediction model for prenatal counselling. Until then, we would

recommend to include in prenatal counselling the limitations of the currently used fetal lung volume or area assessments for the prediction of outcome.

The recent fetal endoscopic tracheal occlusion (FETO)-trial in moderate L-CDH patients[59] found no significant benefit of FETO over expectant care with regard to survival and/or secondary morbidities. The authors explained this by overall increasing survival rates within the moderate L-CDH group. Still, an alternative explanation might be that an increase in lung size due to FETO does not result in improved lung vascularization or (from a developmental view) that the timing of balloon placement at 27-29 weeks gestation does not affect pulmonary (vascular) development (enough). For future studies, it would be interesting to see if there is a difference in pulmonary vascularization between fetuses with or without FETO.

In this study, significantly more high-quality 3D volumes (R-LV and R-PVV) were available for the control group than for the case group. We suggest that this could be due to more standardized planning of ultrasound examinations in control patients, resulting in a lower GA at US3 in the control group compared to the case group. In addition, in a L-CDH fetus with a smaller lung, shadow from the fetal ribs (i.e., loss of voxels for volume measurements) could have a relatively bigger impact than in a healthy control, allowing for a more extended measurement of the vascular tree in the latter. Since we studied a novel method of vasculature measurement, we concentrated on uniformity of the measurements in order to be able to evaluate the method itself. For future studies, we would suggest measurement of the total power Doppler volume instead of only the power Doppler signal connected to the main branch.

The R-PVV was measured in the BARCO I-Space system, which is special chamber enabling the use of VR. However, the relatively high cost (approximately US$500,000) and the necessity of a large separate room (40m2 or 400 square ft) makes it unsuitable for use in daily clinical practice and exclusive to well-funded hospitals.[40] Previous studies have shown that the diagnostic performance of the 3D-VR desktop version that is currently used in the outpatient clinic of our hospital, is comparable to that of the BARCO I-Space system,[60] at a considerable lower cost.[61] To enable routine use, R-PVV measurements should be validated on a 3D-VR desktop system.

CONCLUSION

From the findings of this study we conclude that the assessment by 3D-VR ultrasonography pulmonary vascular development in fetuses with an isolated L-CDH and healthy controls is feasible and reliable. Compared to healthy fetuses, a decreased vascularization of the contralateral lung is seen in fetuses with an isolated L-CDH. In the latter the

pulmonary vascular volume of the contralateral lung also shows predictive value for survival when measured <24 weeks' gestation.

In order to make these R-PVV measurements suitable for daily clinical practice, they should be validated on the desktop version of the I-SPACE. In addition, multicentre acquisition of 3D Power Doppler volumes for offline analysis in patients with L-CDH is needed – before and after FETO - to increase patient numbers for subgroup analysis. Also, future studies should include assessment of the peripheral vessels of the lungs, e.g. by use of new ultrasound techniques depicting slow blood flow.

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SUPPLEMENTAL MATERIAL

Supplemental figure 1 Inclusion flowchart.

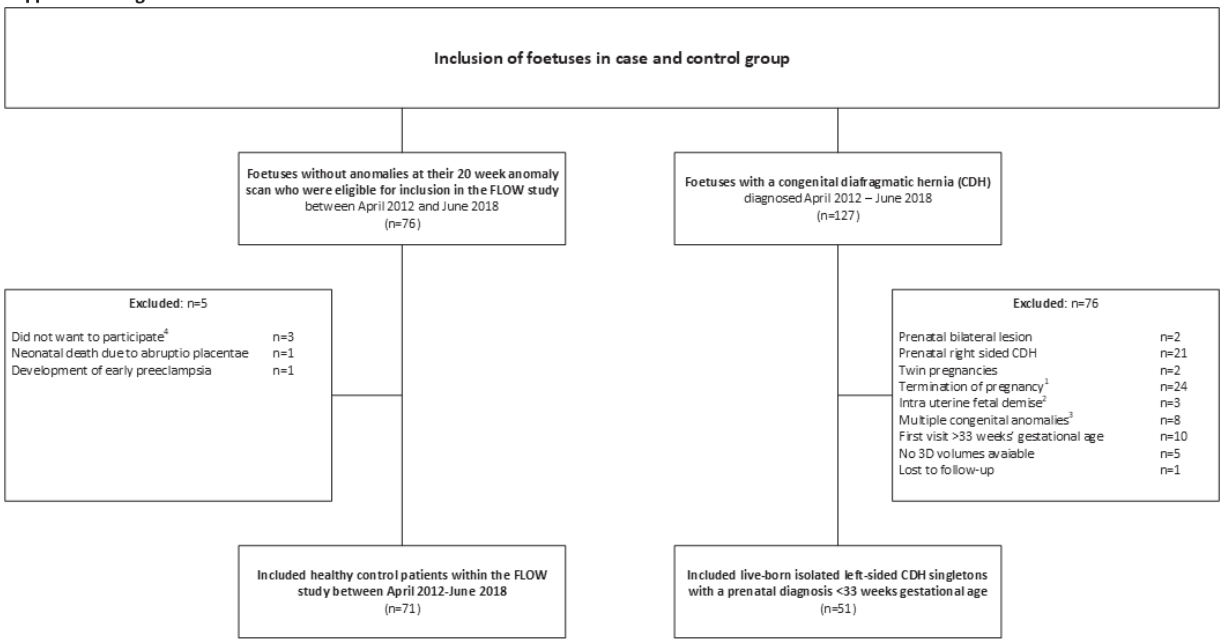

Figure 1 Inclusion Flowchart
[1] 15/24 cases showed major MCA and/or a genetic anomaly (amongst which two fetuses with a trisomy 18)
[2] 1/3 cases concerned a fetus with trisomy 18
[3] 2 fetuses showed a L-CDH with a bronchopulmonary sequestration, 4 fetuses had an additional cardiac anomaly, 1 fetus presented with an early fetal growth restriction
[4] Reasons: no means for transportation (n=1), partner of patient did not consent (n=1) and participating other scientific studies (n=1)
Abbrevations FLOW: Foetal Lung Observations and Waveforms; MCA: multiple congenital anomalies; L-CDH: left sided congenital diaphragmatic hernia; 3D: three-dimensional

Supplemental video 1 Measurement of the pulmonary vascular volume in the BARCO I-Space.
Video recording showing the offline measurement of the pulmonary vascular volume in a in the BARCO I-Space Virtual Reality system using our V-Scope software.[40] In this four-walled CAVE™-like system, the main pulmonary vascular branch at the level of the left atrium is sought out. Then by 'planting a seed'; i.e., selecting a voxel within the main pulmonary vascular branch, a semi-automatic volume measurement of all connected voxels (maximum deviation threshold) with a Doppler value meeting the pre-set threshold (120-255) was obtained. The first measured volume is of a fetus with a left-sided congenital diaphragmatic hernia at 26 weeks' gestational age, which is than later (at 31 seconds) compared to the volume in a healthy control patient at the same gestational age

Supplemental table 1 Multivariable trend analysis for pulmonary vascular volume and lung volume for prediction of the presence of an isolated L-CDH.

	Presence of a L-CDH		
	OR	**95% CI**	***p*-value**
Log R-PVV			
Intercept	0.001	0.00-0.05	**<0.001**
Slope	6.513	0.38-110.63	0.20
Log R-LV			
Intercept	0	0.00-0.00	**<0.001**
Slope	29166.89	18.33-46416785.78	**0.006**
Log R-PVV/LV-ratio			
Intercept	0.193	0.06-0.67	**0.01**
Slope	39.385	0.34-4614.93	0.13

Abbreviations L-CDH: left-sided congenital diaphragmatic hernia; OR: odds ratio; CI: confidence interval; R-LV: lung volume right lung; R-PVV: pulmonary vascular volume right lung.

Supplemental table 2 Multivariable trend analysis pulmonary vascular volume and lung volume for the prediction of survival, treatment for PH and presence of CLD in isolated L-CDH survivors born >34 weeks' gestation.

	OR	95% CI	*p*-value
Survival in L-CDH			
Log R-PVV			
Intercept	0.004	0.00-1.82	0.08
Slope	5.52	0.06-525.09	0.46
Log R-LV			
Intercept	0.001	0.00-249.09	0.29
Slope	0.005	0.00-9.14	0.17
Log R-PVV/LV-ratio			
Intercept	0.47	0.04-5.16	0.54
Slope	1420.61	0.28-7229141.37	0.10
Treatment for PH in L-CDH			
Log R-PVV			
Intercept	0.10	0.00-4.36	0.23
Slope	1.86	0.06-56.64	0.72
Log R-LV			
Intercept	0.05	0.00-479.55	0.52
Slope	0.02	0.00-6.55	0.18
Log R-PVV/LV-ratio			
Intercept	0.47	0.07-3.15	0.44
Slope	500.50	0.58-434453.08	0.07
CLD in L-CDH survivors			
Log R-PVV			
Intercept	0.74	0.01-53.67	0.89
Slope	4.61	0.12-172.21	0.41
Log R-LV			
Intercept	0.012	0.00-1357.77	0.46
Slope	0.001	0.00-3.75	0.10
Log R-PVV/LV-ratio			
Intercept	1.72	0.20-14.95	0.62
Slope	24.95	0.01-44463.13	0.40

Abbreviations L-CDH: left-sided congenital diaphragmatic hernia; OR: odds ratio; CI: confidence interval; R-LV: lung volume right lung; R-PVV: pulmonary vascular volume right lung

CHAPTER 6

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

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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.

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.

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, mea- sured 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; US 3, 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 ultra- sound 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 x width x 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 interobserver agreement calculation gave an ICC of 0.891 (95% CI, 0.751– 0.955), representing good agreement.

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).

Table 1 Pre- and postnatal characteristics of 80 infants diagnosed prenatally with congenital lung

	n	No respiratory support <24 hours n=66	n	Respiratory support <24 hours* n=14	*p* value
Prenatal characteristics					
US1: 20-24 weeks					
Gestational age (w^{+d})	60	21^{+2} (20^{+5}-22^{+0})	10	21^{+4} (20^{+6}-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: 24-30 weeks					
Gestational age (w^{+d})	46	26^{+4} (26^{+1}-27^{+2})	9	28^{+0} (26^{+4}-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: 30-36 weeks					
Gestational age (w^{+d})	66	31^{+5} (30^{+5}-32^{+2})	14	32^{+4} (31^{+6}-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 (45%)		- 8 (62%)	
Mixed		- 33 (55%)		- 2 (15%)	
Macrocystic		- 0 (0%)		- 3 (23%)	
BPS		5 (8%)		1 (7%)	
Hybrid		1 (2%)		0 (0%)	
Side of the lesion (left)	66	29 (44%)	14	8 (57%)	0.39
Multiple CVR measurements	66	63 (96%)	14	11 (79%)	0.06
CLM in regression	63		11		
Partial regression		30 (48%)		2 (18%)	0.17
Full regression		12 (19%)		4 (36%)	0.24
Postnatal characteristics					
Gestational age at delivery (w^{+d})	66	39^{+2} (38^{+4}-40^{+4})	14	39^{+1} (38^{+2}-40^{+6})	0.85
Spontaneous vaginal delivery	66	58 (88%)	14	11 (79%)	0.23
Apgar score at 5 minutes	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 (49%)	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††

	n	No respiratory support <24 hours n=66	n	Respiratory support <24 hours* n=14	*p* value
Chronic lung disease§	66	0 (0%)	14	3 (21%)	0.004††
Postnatal diagnosis	66		14		0.08
CPAM type 1		6 (9%)		5 (36%)	
CPAM type 2 ¶		23 (35%)		1 (7%)	
BPS **		14 (21%)		1 (7%)	
Hybrid		6 (9%)		2 (14%)	
CPAM type 2 and BPS		1 (2%)		0 (0%)	
CLO		12 (18%)		3 (21%)	
Bronchogenic cyst		1 (2%)		0 (0%)	
In regression		3 (5%)		2 (14%)	

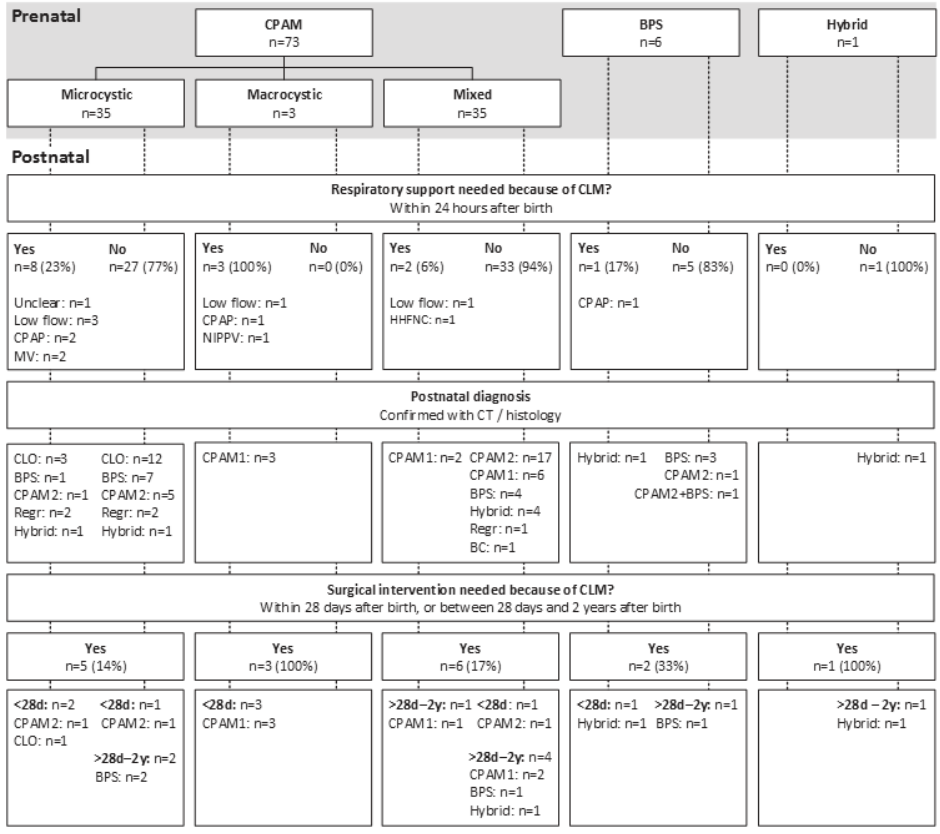
Data are presented as median (interquartile range (IQR)), n (%) or n/N (%). *Type of respiratory support: low flow supplemental oxygen (n=5; 1L, FiO2 ranged from 21% to 60%), humidified high flow nasal cannula (n=1; 4.5L, FiO2 100%), continuous positive airway pressure (n=4; positive end-expiratory pressure (PEEP) 5 or 6 cmH2O, FiO2 21% to 40%), non-invasive positive pressure ventilation (n=1; 5 above PEEP 6, FiO2 40%), mechanical ventilation (n=2; 16 or 19 above PEEP 6, FiO2 95% or 100%), unclear (n=1; required respiratory support for only a few minutes during transportation (FiO2 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 septum 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 of life[15]. ¶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);
Abbrevations CVR, CLM volume ratio; GA, gestational age; SVD, spontaneous vaginal delivery; US, ultrasound.

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.

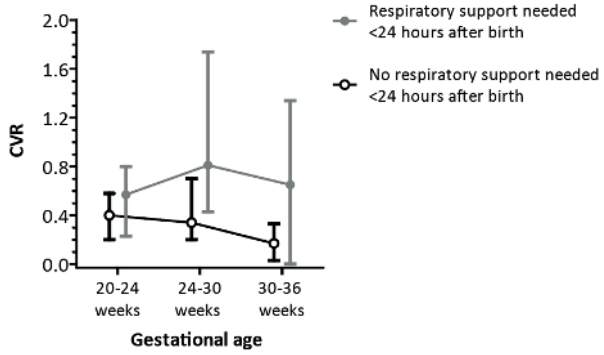
Figure 1 Flowchart presenting the need for respiratory support, postnatal diagnosis and need for surgery in 80 infants diagnosed prenatally with congenital lung malformation (CLM), stratified according to prenatal classification on prenatal ultrasound.



Abbrevations: 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.

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.

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.

Surgical intervention within 2 years after birth

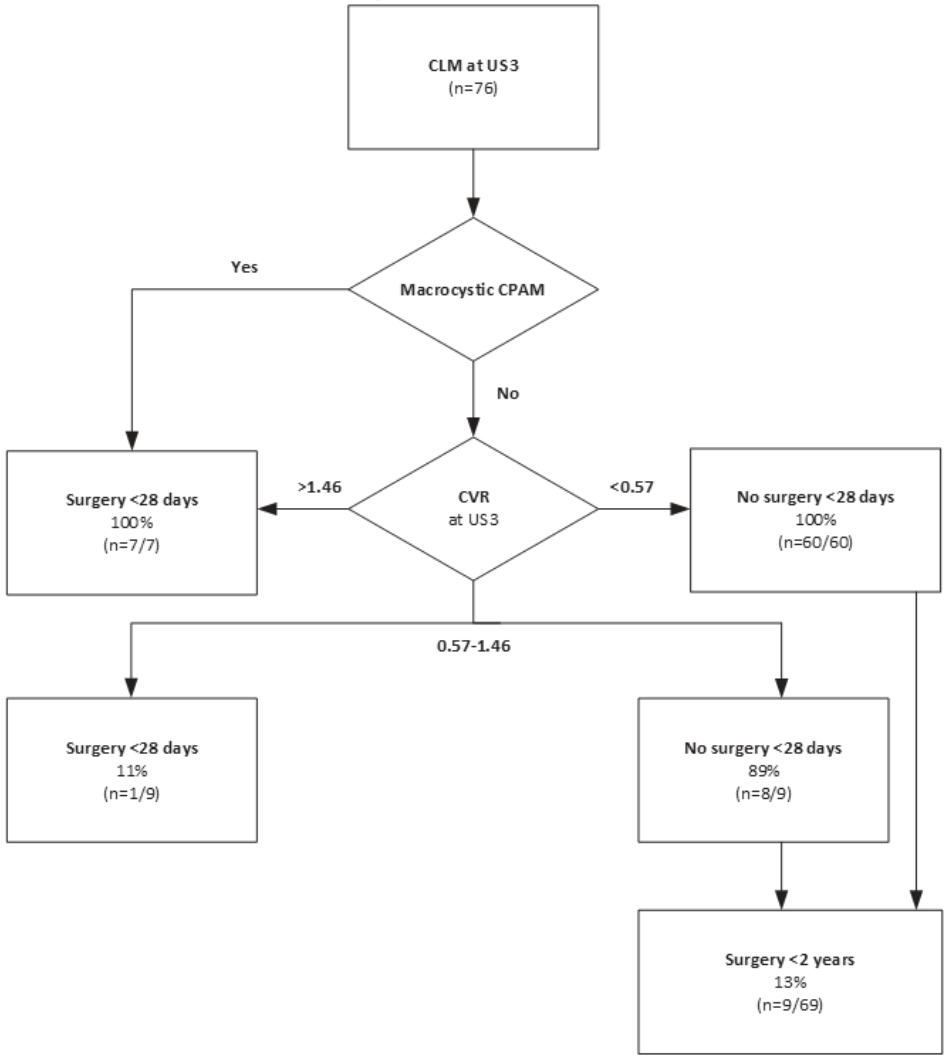
Seventeen (21%) infants required surgical intervention within 2 years after birth, eight of these requiring it within 28 days (Figure 1). Histological data were available for 16 of the 17 (94%) infants whose CLM was resected. One infant with an intralobar BPS underwent embolization of the aberrant artery 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.

Figure 3 Counseling flow chart for the need for surgery, according to prenatal type of congenital lung malformation (CLM) and CLM volume ratio (CVR) at 30^{+0} -35^{+6} weeks' gestation.



Cut-offs are based on receiver-operating-curve analyses. CPAM: congenital pulmonary airway malformation.

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, 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.

Figure 4 Our structured ultrasonography report for prenatal assessment of congenital lung malformations (CLM).

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:

$$\text{CLM Volume Ratio (CVR)} = \frac{\text{Volume CLM (AP x T x H) x 0.52}}{\text{Headcircumference (HC)}}$$

C. Border

☐ Well-defined ☐ Ill-defined

D. Vascularization

Arterial

☐ From pulmonary artery

☐ From systemic artery:

Venous

☐ Normal pulmonary

☐ Aberrant:

Remarks:

Abbrevations: AP, anteroposterior diameter; H, height; p, percentile; T, transverse diameter.

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.

ACKNOWLEDGEMENTS

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.

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 counselling 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.

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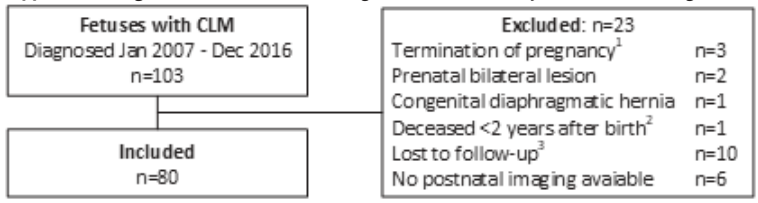
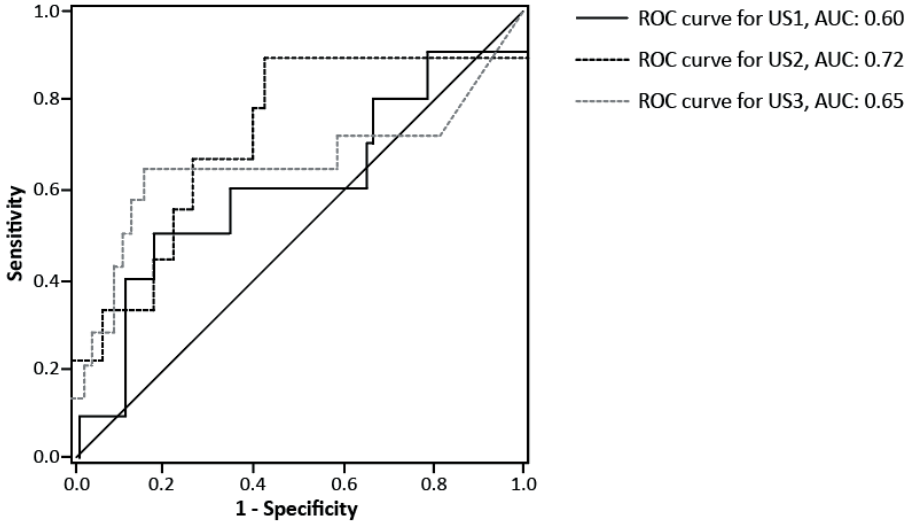
SUPPLEMENTAL MATERIAL

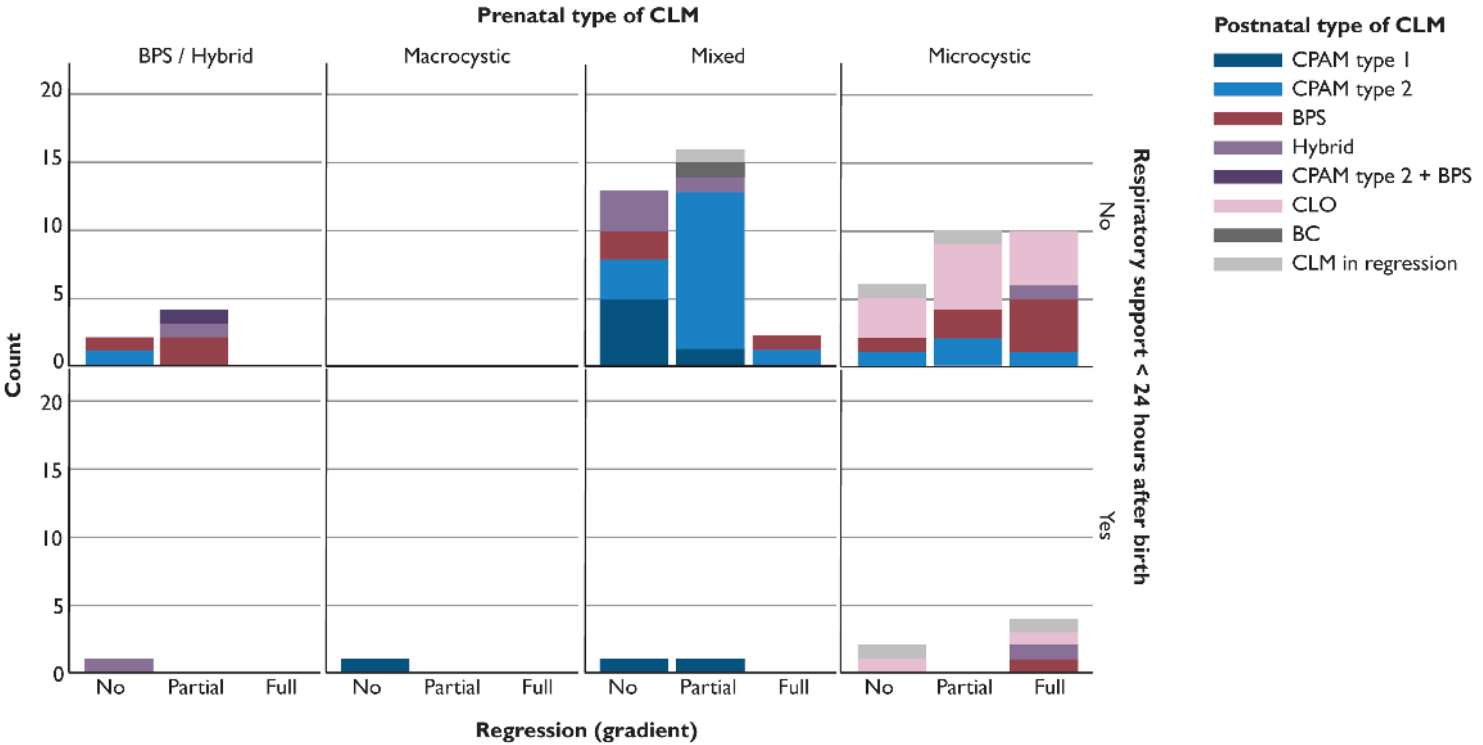
Supplemental Figure 1 Flowchart summarizing inclusion in this study of fetuses with congenital lung malformation (CLM).



Supplemental Figure 2 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.

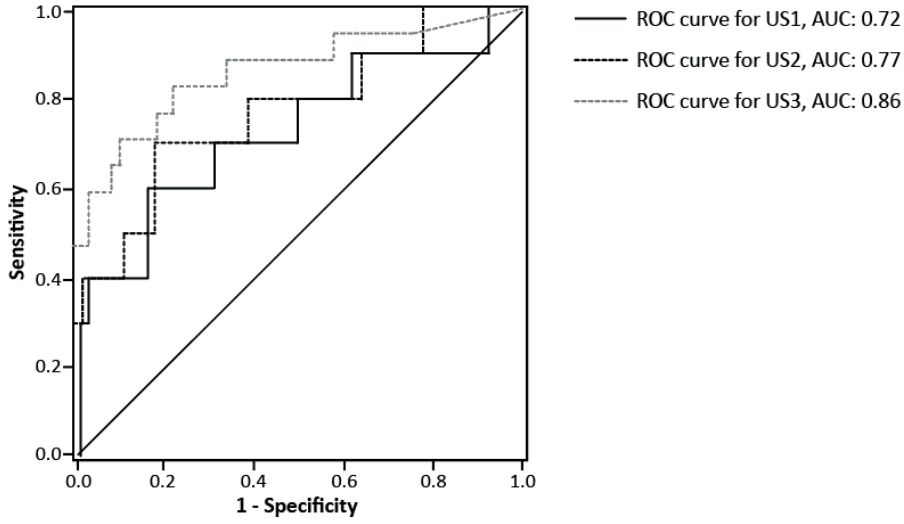


Supplemental Figure 3 Prenatal type of congenital lung malformation (CLM), postnatal diagnosis and need for respiratory support within 24 h after birth in 74 cases with multiple CLM volume ratio (CVR) measurements available.

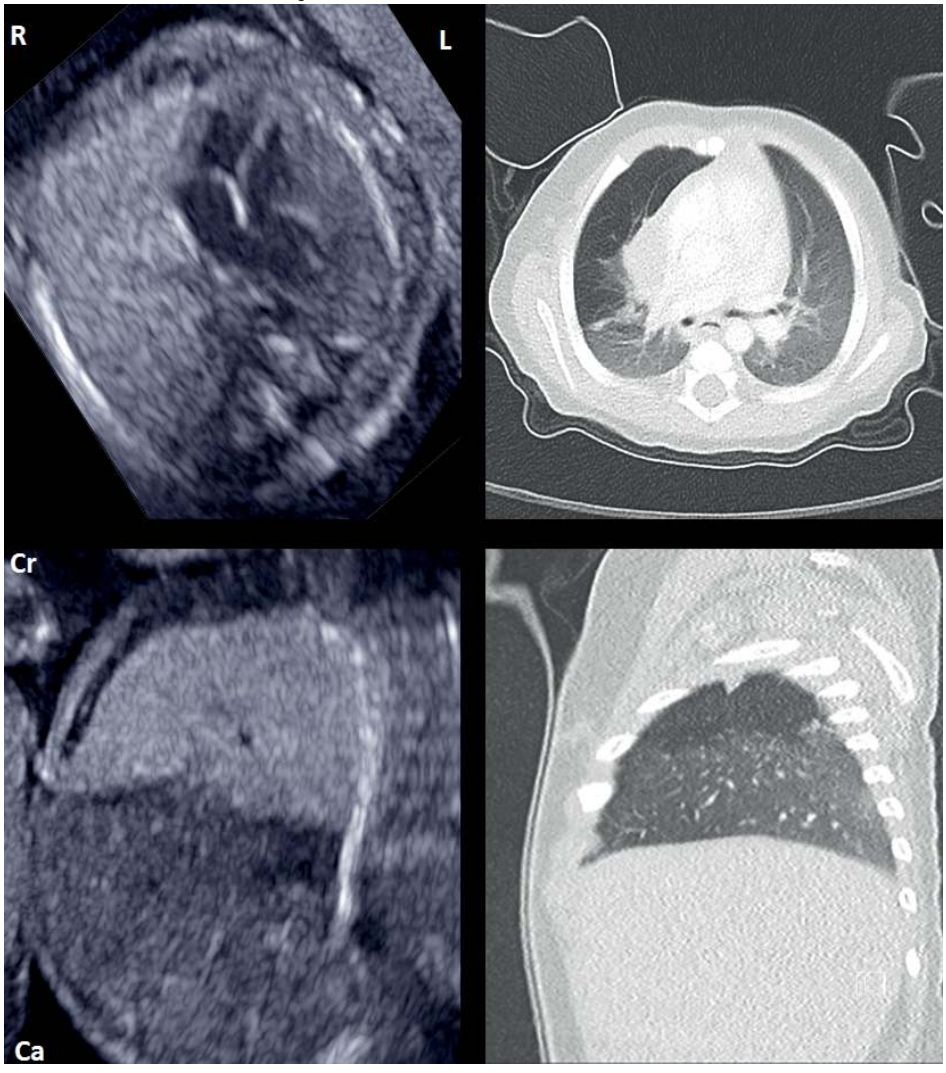


Prenatal type of CLM is shown, stratified for gradient of regression (partial: absolute decrease in lesion area and/or decrease of at least 0.1 in CVR; full: not visible on last prenatal ultrasound exam) and need for respiratory support.

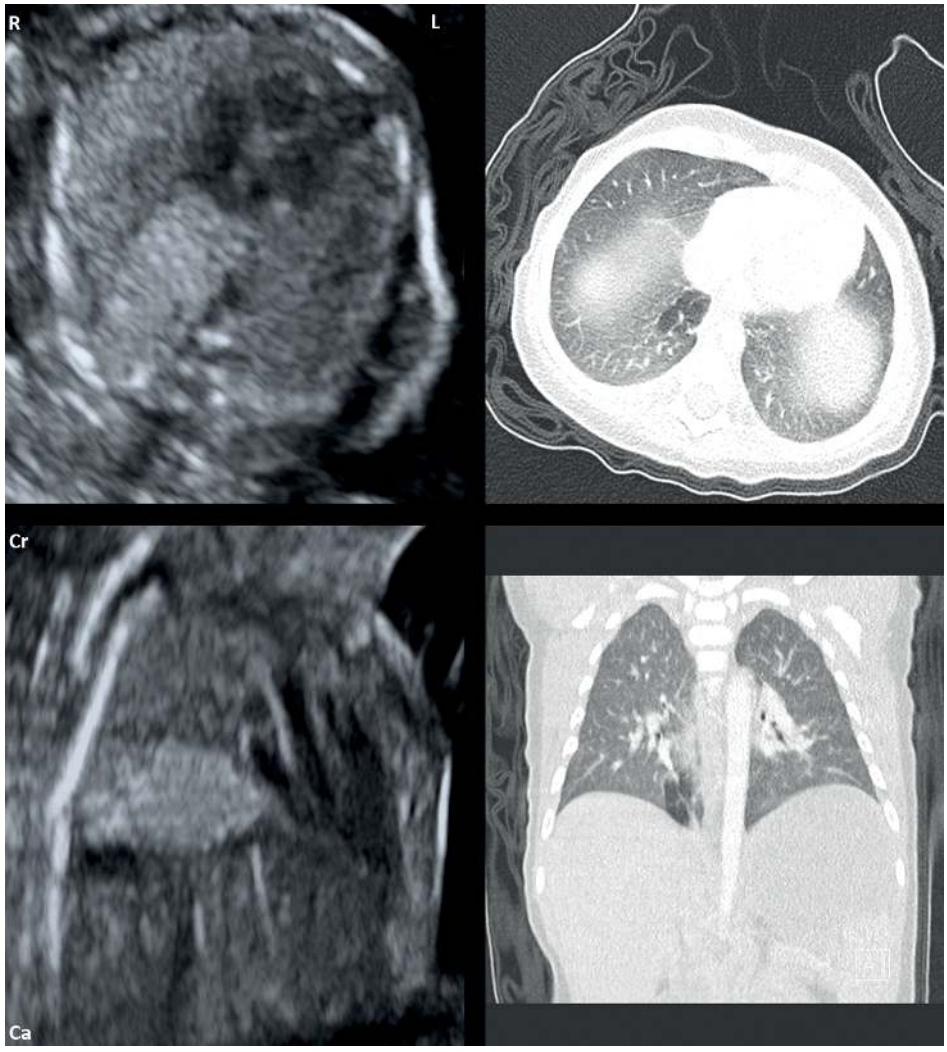
Supplemental Figure 4 Receiver-operating-characteristics-curve analysis of congenital lung malformation (CLM) volume ratio (CVR) at different gestational-age periods in prediction of the need for surgical intervention within 2 years after birth in infants diagnosed prenatally with CLM.



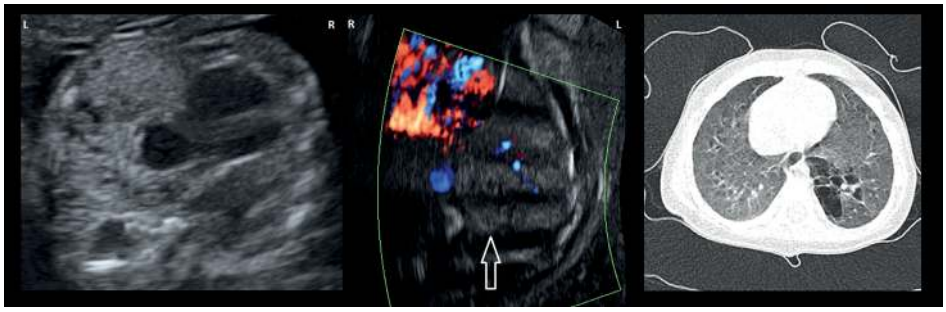
Supplemental Figure 5 Examples of prenatal appearance of congenital lung malformations (CLM) on ultrasound and corresponding postnatal appearance on computed tomography (CT) at *c*. 6 months postpartum.
The position of ultrasound images was adjusted by rotating them in order to match the orientation on the postnatal CT. Descriptions are according to the suggested structured ultrasonography report for CLM (Figure 4).
Abbrevations: BPS, bronchopulmonary sequestration; Ca, caudal; CPAM, congenital pulmonary airway malformation; Cr, cranial; CVR, CLM volume ratio; L, left; R, right; US, ultrasound.



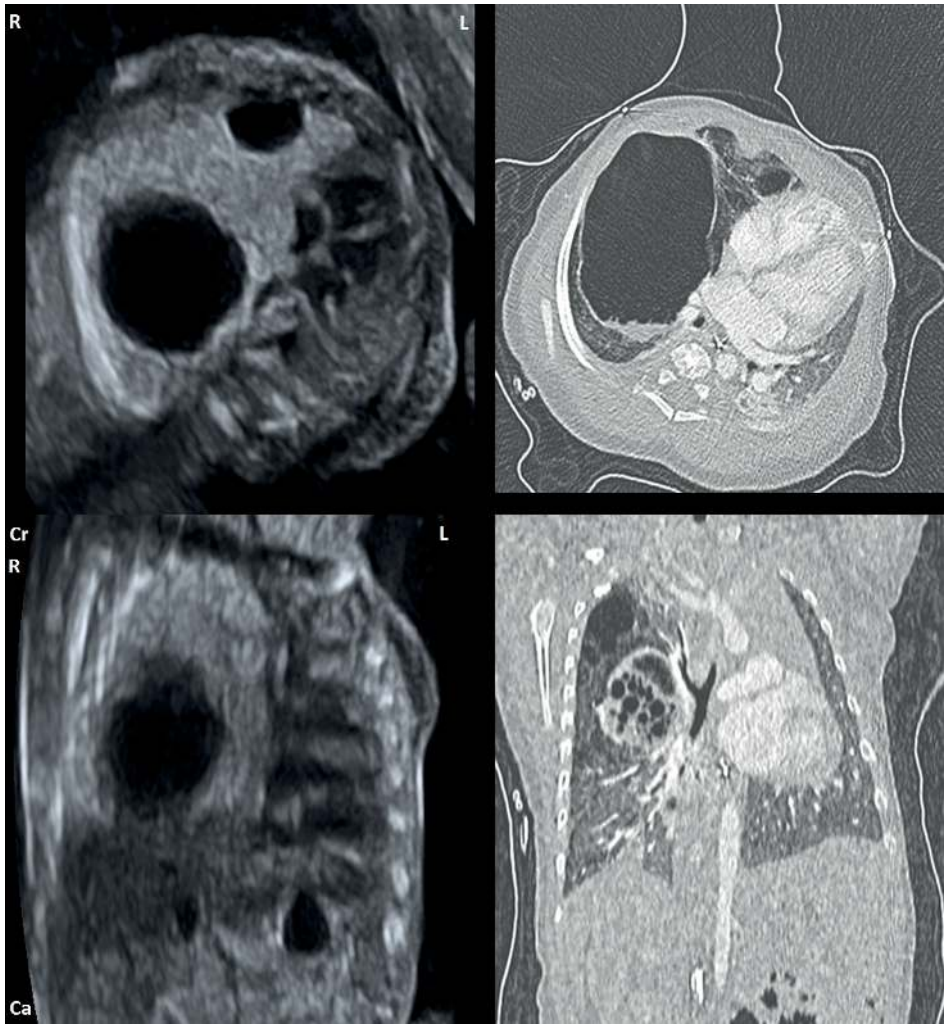
Left: Axial prenatal US image at 20 weeks' gestation showing a well-defined mixed type CPAM in the left lower lobe, presence of mediastinal shift with a CVR of 0.63. Normal pulmonary arterial and venous vascularization and no abnormalities of adjacent lung tissue.
Middle: Coronal prenatal US image at 31 weeks' gestation showing an ill-defined mixed type CPAM in the left lower lobe (indicated by the white arrow), no presence of mediastinal shift with a CVR of 0.06. Normal pulmonary arterial and venous vascularization and no abnormalities of adjacent lung tissue.
Right: Axial postnatal CT-image depicting a cluster of multiple air-filled cysts comprising up to 1/3 of the left lower lobe. Normal pulmonary arterial and venous vascularization and no abnormalities of adjacent lung tissue. Findings indicate a Congenital Pulmonary Airway Malformation type 2.



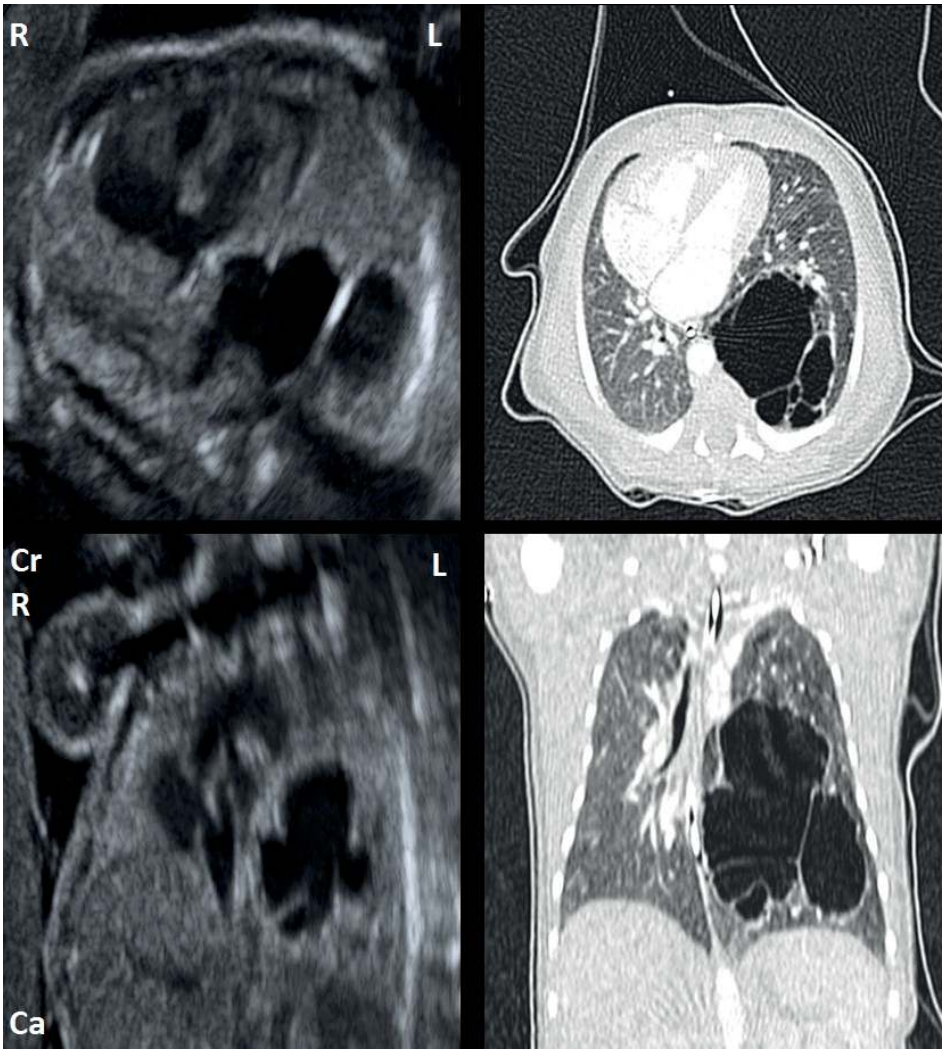
Left: Axial (upper) and sagittal (lower) prenatal US image at 21 weeks' gestation showing a well-defined microcystic CPAM in the right middle and/or upper lobe. Presence of mediastinal shift with a CVR of 0.53. Normal pulmonary arterial and venous vascularization and no abnormalities of adjacent lung tissue.
Right: Axial (upper) and sagittal (lower) postnatal CT-image depicting a hyper inflated region comprising up to 2/3 of the right upper lobe. Normal pulmonary arterial and venous vascularization and no abnormalities of adjacent lung tissue. Findings consistent with Congenital Lobar Overinflation.



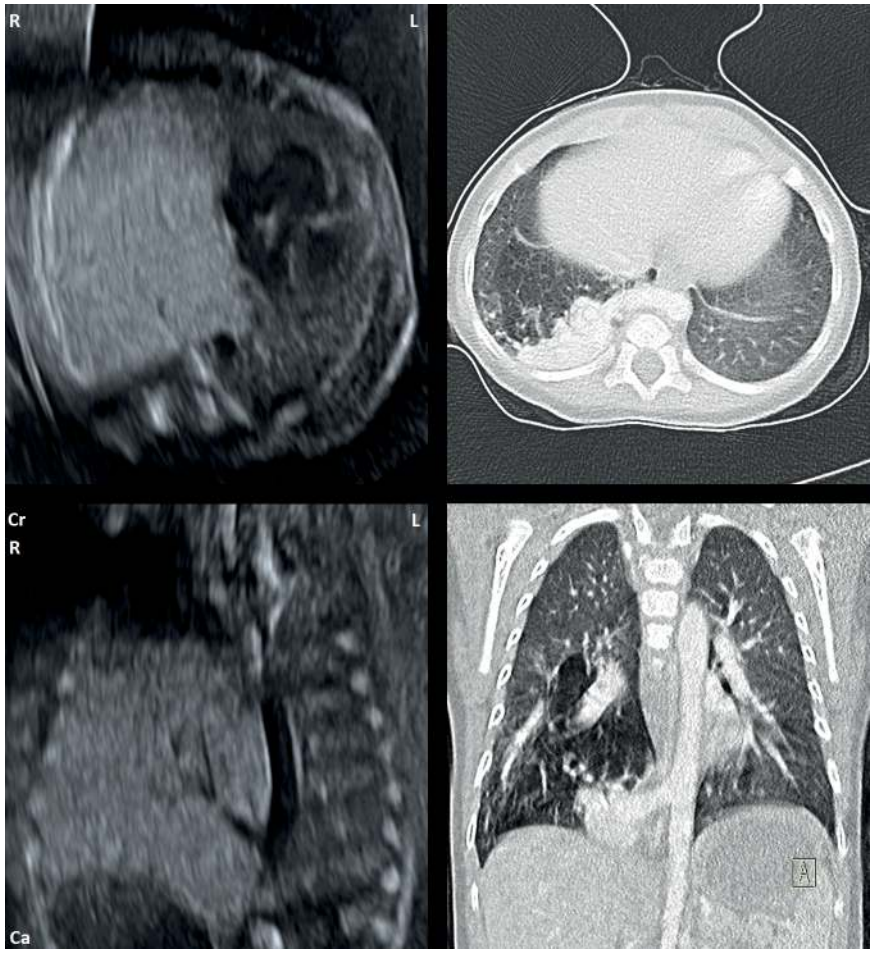
Left: Axial (upper) and coronal (lower) prenatal US image at 20 weeks' gestation showing a well-defined microcystic CPAM in the right lower lobe. No presence of mediastinal shift with a CVR of 0.08. Normal pulmonary arterial and venous vascularization and no abnormalities of adjacent lung tissue.
Right: Axial (upper) and coronal (lower) postnatal CT-image depicting a cluster of multiple air-filled cysts with a well-defined border, comprising less than 1/3 of the right lower lobe. Normal pulmonary arterial and venous vascularization and no abnormalities of adjacent lung tissue. Findings indicate a Congenital Pulmonary Airway Malformation type 2.



Left: Axial (upper) and coronal (lower) prenatal US image at 20 weeks' gestation showing a well-defined mixed type CPAM in the right middle and/or upper lobe, presence of mediastinal shift with a CVR of 0.08. Normal pulmonary arterial and venous vascularization and no abnormalities of adjacent lung tissue.
Right: Axial (upper) postnatal CT-image depicting an air-filled dominant cyst with a well-defined border, and a coronal (lower) image showing adjacent smaller cysts, comprising around 2/3 of the right upper lobe. Normal pulmonary arterial and venous vascularization and mass effect with leftward mediastinal shift. Findings indicate a Congenital Pulmonary Airway Malformation type 1.



Left: Axial (upper) and coronal (lower) prenatal US image at 22 weeks' gestation showing a well-defined macrocystic type CPAM in the left lower lobe, presence of mediastinal shift with a CVR of 0.28. Normal pulmonary arterial and venous vascularization and no abnormalities of adjacent lung tissue.
Right: Axial (upper) and coronal (lower) postnatal CT-image depicting an air-filled dominant cyst with adjacent smaller cysts, comprising the whole left lower lobe. Normal pulmonary arterial and venous vascularization, and mass effect with rightward mediastinal shift. Findings indicate a Congenital Pulmonary Airway Malformation type 1.



Left: Axial (upper) and coronal (lower) prenatal US image at 23 weeks' gestation showing a well-defined microcystic BPS in the right lower lobe, presence of mediastinal shift with a CVR of 0.99. Systemic arterial blood supply from the descending aorta, normal venous vascularization and no abnormalities of adjacent lung tissue.
Right: Axial (upper) and coronal (lower) postnatal CT-images depicting a homogeneous lesion and adjacent cluster of multiple cysts, comprising up to 2/3 of the right lower lobe. Arterial blood supply from the descending thoracic aorta by a single blood vessel, normal pulmonary venous drainage, and no abnormalities of adjacent lung tissue. Findings indicate a Hybrid BPS.

Supplemental Table 1 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.

	AUC	95% CI	*p* value	Cut-off	Sensitivity	Specificity
Respiratory support <24 hours after birth						
CVR at US1: 20-24 weeks	0.60	0.39-0.81	0.31	0.64	50%	82%
CVR at US2: 24-30 weeks	0.72	0.51-0.92	**0.04**	0.39	89%	58%
CVR at US3: 30-36 weeks	0.65	0.45-0.86	0.08	0.44	64%	84%
Surgical intervention <2 years after birth						
CVR at US1: 20-24 weeks	0.72	0.53-0.91	**0.03**	0.64	60%	83%
CVR at US2: 24-30 weeks	0.77	0.60-0.95	**0.01**	0.80	70%	82%
CVR at US3: 30-36 weeks	0.86	0.74-0.98	**<0.001**	0.46	71%	90%

Cut-offs were calculated based on the Youden's index.
Abbreviations: AUC: area under the curve; US: ultrasound.

Supplemental material Downloadable version of our ultrasonography report (figure 4) for prenatal assessment of congenital lung malformations (CLM). *Abbrevations: AP, anteroposterior diameter; H, height; p, percentile; T, transverse diameter.*

PART II

Prenatal parameters in perinatal care

CHAPTER 7

Prenatal Prediction of the Type of Omphalocele Closure by Different Medical Consultants

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ABSTRACT

Introduction

To evaluate differences between consultants of different disciplines in the prenatal prediction of the type of postnatal surgical closure of an omphalocele.

Material and Methods

Twenty-one images of prenatally detected omphaloceles prior to 24 weeks of gestation were included. A standardized form provided known prenatal information and an ultrasound image for each case. Nineteen consultants were asked to assess the probability of primary closure of an omphalocele and to state which information was the most important for their assessment.

Results

Primary closure (13/21 images) was predicted correctly in 5/13 images. The number of correct predictions per image ranged from 63 to 89%. The type of closure was predicted correctly in 7/8 images of cases which were not closed primarily, ranging from 58 to 84% correct predictions per image. There was no significant difference between consultants of different disciplines. Individual accuracy ranged from 10 to 62%. The consultants regarded omphalocele content as the most important information (34%) for counselling.

Discussion

The consultants did not differ in their prenatal judgment of the primary closure of an omphalocele. The consultants tended to be too negative in their assessment, since 75% assessed the probability of primary closure overall to be <60%, whereas 62% of the cases were primarily closed. Omphalocele content was the most important information for the consultants' judgment.

INTRODUCTION

An omphalocele is a congenital defect of the anterior abdominal wall with a birth prevalence of approximately 1:12,500.[1] Depending on the size of the defect, a variable amount of abdominal organs covered by a membrane herniates through the defect.[2] In approximately 80% of all omphaloceles, associated congenital anomalies, abnormal karyotype and/or syndromes are present. These associated anomalies, the presence of intrauterine growth retardation or premature delivery influence treatment decisions and the ultimate clinical outcome.[1, 3–10] In the pediatric surgical literature, minor and giant omphaloceles are distinguished by different therapeutic approaches. Minor omphaloceles are small defects (<5 cm at birth) with only bowel in the omphalocele, which can be closed primarily (<24 h after birth). Giant omphaloceles, larger defects (>5 cm at birth) with eviscerated liver tissue through the defect, can only be closed in a staged repair requiring multiple surgeries within the primary hospital stay or in a delayed repair with a surgical repair of the abdominal wall even at the age of 1 year after epithelialization of the membrane of the omphalocele. In both cases, the component separation technique[11] can be used to close the defect in one procedure. Both the staged and the delayed repair are associated with an increased risk of pulmonary hypoplasia, more feeding problems, multiple operations and an extended hospital stay.[12]

Prenatal prediction of postnatal prognosis is difficult for two reasons. First, inaccurate abdominal wall circum ference measurement affects the validity of fetal weight estimation and diagnosis of intrauterine growth retardation. Second, in isolated cases, the prognosis largely depends on the size of the defect and the related type of postnatal surgical closure of the defect (primary vs. delayed).[13]

Most omphaloceles are diagnosed in the late first or early second trimester of pregnancy. Following the ultrasound diagnosis, an invasive diagnostic test is offered to exclude chromosomal abnormalities. In case of normal chromosomes, advanced ultrasound examination is performed to exclude major associated abnormalities. This diagnostic period on average covers 2–4 weeks of uncertainty for the future parents. To be able to prepare themselves for a child with a major congenital anomaly, parents prefer counseling shortly following this diagnostic period.[14–16] They are counseled by both an obstetric consultant (a gynecologist or prenatal physician) and a pediatric consultant (a pediatric surgeon or pediatric intensivist). The latter informs them in depth about the postnatal outcome.[15, 17, 18] While prenatal indicators of a successful primary closure are known, so far there are no guidelines to individualize counselling about postnatal prognosis.[4, 8, 15, 19–24] Consequently, the full spectrum of postnatal morbidity is discussed.

The aim of the study was to estimate the degree of prognostic consistency among expert clinical consultants under standardized conditions and to establish which prenatal parameter influenced their prognostic judgment most. The study outcome was the assigned probability of primary surgical closure in the second trimester of pregnancy, rated on a semiquantitative scale. Judgments were obtained independently.

Materials and Methods

For this study, we selected cases diagnosed with an omphalocele in our tertiary center between 2003 and 2009. At least one complete investigation between 12 and 23 weeks of gestation, i.e. the counselling period, was required. Cases with major additional congenital anomalies influencing the type of surgical closure were not included. Cases resulting in intrauterine fetal death (IUFD), termination of pregnancy (TOP) or neonatal death (NND) were excluded as postnatal surgical closure was not performed. The type of surgical closure was documented but not revealed to the consultants. Primary closure implies closure within 24 h after birth, whereas delayed closure is defined as late or even post infancy closure after allowing the omphalocele to desiccate, contract and epithelialize with closure of the ventral hernia at a later stage. To gain insight into variations in counselling individual cases in the second trimester, we included more than one ultrasound image per case at different gestational ages (GAs) between 16 and 24 weeks and presented them as individual cases.

We presented prenatal information in a standardized way to a panel of expert clinical consultants asking for individual judgments. A standardized presentation of each case on a case form was devised (fig. 1a). This form contained a high-quality ultrasound image displaying a transverse view of the abdomen as well as the omphalocele and image-related data, i.e., omphalocele content, the diameter of the defect (in mm) and two ratios calculated from ultrasound measurements.[19, 21]

For the first ratio, the omphalocele circumference (OC) was divided by the abdominal circumference (AC; OC/AC). For the second ratio, the diameter of the defect (DD) was divided by the widest diameter of the abdomen (DA) parallel to the defect (DD/DA). The following additional prenatal data was presented: presence of (minor) additional prenatal congenital anomalies, GA and the general as well as obstetric medical history of the pregnant woman. Identical for each case, a questionnaire comprising 3 questions was devised (fig. 1b).

To test prognostic consistency among physicians under standard conditions, we selected a sample of obstetric and pediatric consultants from our tertiary center. We did not discriminate between years of working experience and age. All consultants were familiar with counselling about omphaloceles. In our hospital, newborns with major congenital

anomalies are primarily admitted to the pediatric intensive care and not to the neonatal intensive care unit. Pediatric consultants are therefore pediatric intensivists and pediatric surgeons. The consultants were blinded to each case and were unaware of the postnatal outcome and predictive value of the two calculated ratios.[19, 21]

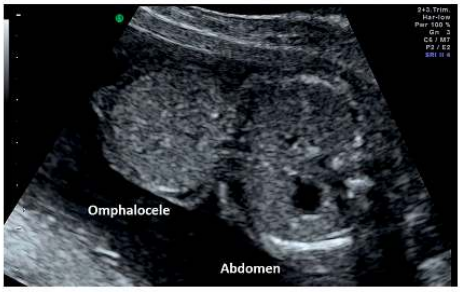
Figure 1A Example of a case form.

Patient 24 year old female

G2P1; healthy son

Isolated omphalocele

Blank medical history



Cele content **bowel and liver**

Picture at GA of **20 weeks**

Diameter defect: **20 mm**

Ratio diameter defect / diameter abdomen **0.48**

Ratio cele circumference / abdominal circumference **0.76**

Figure 1B The questionnaire, containing the same three questions per image, was given to all consultants. Identical for each image, a questionnaire comprising 3 questions was devised.

In your professional opinion, how big is the probability of a successful primary closure of an omphalocele based on this prenatal information?

- *80-100%*
- *60-80%*
- *40-60%*
- *20-40%*
- *<20%*

How would you counsel the future parents about the probability of a primary closure of the omphalocele in case of their unborn child?

- *A primary closure of the abdominal wall will most certainly succeed*
- *A primary closure of the abdominal wall will somewhat certainly succeed*
- *The probability of a successful primary closure of the abdominal wall is about the same as the probability of an unsuccessful primary closure of the abdominal wall*
- *A primary closure of the abdominal wall will somewhat certainly not succeed*
- *A primary closure of the abdominal wall will most certainly not succeed*
- *It is not possible to predict the probability of primary closure of the abdominal wall in this case*

Circle the information on the case form on which you have based your judgement about the probability of primary closure of the omphalocele

You may circle a maximum of three pieces of information

First, the outcome concerned the estimated percentage likelihood of primary closure (quantitative prediction) for each case. A 5-category response scale (probability of primary closure is 0–20, 20–40, 40–60, 60–80 or 80–100%) was offered to the consultants to facilitate their response. Second, the outcome was the verbal expression a consultant would preferably use in counselling (qualitative prediction). Six options were available, ranging from 'primary closure is almost certainly possible' to 'primary closure is almost certainly impossible'. 'Unable to predict' was also included as an option (fig. 1b). Both the quantitative category scale and the verbal expression scale were derived from discussions with experts prior to the start of the study. Finally, the consultants had to select a maximum of three items of the provided prenatal information, which, in the particular case, were most critical for their estimation. Aiming at determining the average item relevance across the consultants, the answers were recalculated into an 'information weight' as follows: with three items selected, each would be scored 0.33 (1/3), when choosing two items, each would be scored 0.50 (1/2), and if a single information determined all, the information item would be scored as 1 (3/3).

For our analysis, we reduced the quantitative outcome into three prediction categories, <40, 40–60 and >60%, and combined this prediction with the true postnatal state, which was only known to the investigators. A consultant predicted a case correctly if he/she gave an estimate of >60% chance of primary closure and the case was primary closed, or if he/she gave an estimate of <40% chance of primary closure and a delayed closure was performed. The remaining combinations were defined as incorrect or unable to predict. This decision rule is strict by intention. A particular case was considered to be correctly predicted if ≥10 of the consultants gave a correct prediction. A case was considered unable to predict if ≥10 of the consultants gave an estimate of 40–60% chance of primary closure or if none of the predictions categories included ≥10 predictions. All calculations and statistical analysis were performed using Microsoft Office Excel 2003 and SPSS statistics version 17.0. Statistical analyses included the $\chi 2$ test, Kruskal-Wallis test, Mann-Whitney U test and the Wilcoxon signed-rank test. A result was considered statistically significant at the significance level of 0.05.

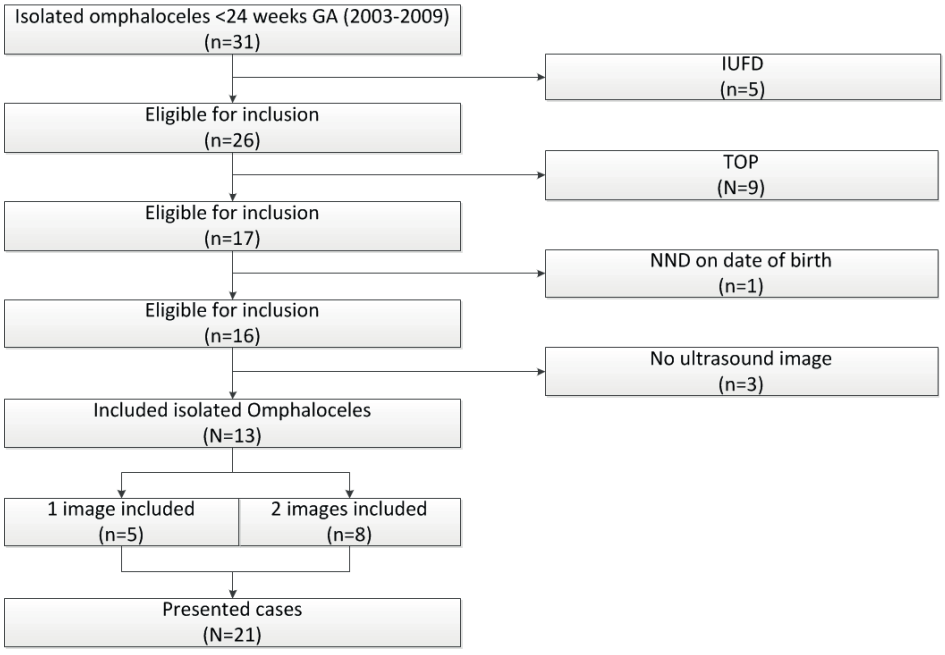
RESULTS

In total, 87 cases were diagnosed with an omphalocele in our tertiary center between 2003 and 2009. In 56 of these cases, the omphalocele was diagnosed after 24 weeks of gestation, or prenatal ultrasound and/or invasive prenatal tests revealed major associated anomalies and/or chromosomal abnormalities. Of the remaining 31 cases, 15 cases were excluded because of IUFD (n = 5), TOP (n = 9) or NND within 24 h after birth (n = 1). Three cases were excluded because the required image was unavailable due to an

incomplete patient record. The remaining 13 cases were included in the study. From 8 of these 13 cases, images of 2 examinations at different GAs were used, resulting in a total of 21 images. These 21 images were presented as separate cases in the questionnaire to the consultants and were regarded as such in the analysis (fig. 2).

Nineteen medical specialists were selected as consultants: 10 obstetric consultants (5 obstetricians and 5 prenatal medicine physicians) and 9 pediatric consultants (3 pediatric intensivists and 6 pediatric surgeons). There was no significant difference ($p = 0.11$) in the median number of years of working experience between obstetric and pediatric consultants, 8 (range 2–12) and 12 (range 2–29) years, respectively.

Figure 2 Inclusion flowchart



A summary of the clinical parameters of the 21 images is presented in table 1. Primary closure was performed in 62% (13/21) of the images, and delayed closure in 38% (8/21).

For 19 out of 21 images, 19 predictions were available. In the 2 remaining images, 1 prediction was missing, providing 18 predictions for these 2 images (image 4 and image 21). This resulted in a total of 397 out of 399 (19/21) predictions. The majority of the predictions (75%, 297/397) estimated a probability of primary closure of <60%. In 40% (118/297) of these answers, no prediction at all was given (table 2).

Table 1 Prenatal characteristics.

Case	GA (weeks)	DD (mm)	Liver in the omphalocele	OC/AC-ratio	DD/DA-ratio
1	19	8	No	0.72	0.23
2	17	16	No	0.59	0.40
3	**16**	**12**	**Yes**	**1.00**	**0.52**
4	13	4	No	0.52	0.33
5	20	35	Yes	0.81	0.70
6	**22**	**30**	**Yes**	**0.90**	**0.65**
7	19	21	No	0.53	0.60
8	20	17	No	0.53	0.37
9	16	14	Yes	0.78	0.45
10	21	21	Yes	0.59	0.46
11	22	28	No	0.56	0.42
12	**22**	**22**	**Yes**	**0.93**	**0.50**
13	12	11	Yes	0.96	0.65
14	**17**	**22**	**Yes**	**0.78**	**0.73**
15	20	20	Yes	0.76	0.48
16	**21**	**32**	**Yes**	**0.91**	**0.86**
17	**23**	**30**	**Yes**	**0.74**	**0.67**
18	15	15	Yes	0.74	0.60
19	19	17	Yes	0.66	0.53
20	**17**	**15**	**Yes**	**0.78**	**0.50**
21	**18**	**19**	**Yes**	**0.81**	**0.63**

The bold lines refer to the images with a delayed closure.
Abbrevations: DD/DA = defect diameter / diameter of the abdomen; GA = gestational age, mm = millimetre, OC/AC = omphalocele circumference / abdominal circumference.

Most (79%) qualitative answers paralleled the quantitative predictions. In 4 predictions (1%), the difference between the quantitative and qualitative estimation differed more than 20%. The qualitative assessment in comparison to the quantitative assessment was either more negative (in cases 3 and 5) or more positive (in cases 13 and 18; fig. 3).

In 38% (5/13) of the images that were primarily closed, the prediction was correct (table 2). The number of consultants who predicted correctly in these 5 images ranged from 63 to 89% (12–17/19). In the remaining 8 images, ≥10 consultants estimated the chance of primary closure to be <40% in 4 images; the other 4 images were unable to predict (<10 predictions in each category or ≥10 consultants predicted 40–60%). Of the 8 images with a delayed closure, 88% (7/8) were correctly predicted. In the remaining image, almost half (47%, 9/19) of the consultants estimated the probability of primary closure to be <40%, and 42% (8/19) of the consultants estimated the chance of primary closure to be

Table 2 Quantitative and qualitative prediction of primary closure of all assessors combined per case and per type of closure.

Cases	Closure type	Quantitative prediction			Qualitative prediction		
		<40% (n=179)	40-60% (n=118)	>60% (n=100)	Low (n=185)	Equal (n=122)	High (n=90)
1	Primary	2	5	12[a]	3	6	10[a]
2	Primary	2	4	13[a]	2	4	13[a]
3	Delayed	14[a]	3	2	14[a]	4	1
4[b]	Primary	0	5	13[a]	0	7	11[a]
5	Primary	15	3	1	17	2	0
6	Delayed	16[a]	3	0	17[a]	2	0
7	Primary	1	11	7	2	9	8
8	Primary	2	4	13[a]	3	4	12[a]
9	Primary	11	7	1	13	5	1
10	Primary	3	12	4	6	9	4
11	Primary	0	2	17[a]	1	4	14[a]
12	Delayed	14[a]	4	1	13[a]	5	1
13	Primary	14	3	2	12	6	1
14	Delayed	11[a]	8	0	13[a]	6	0
15	Primary	9	9	1	9	9	1
16	Delayed	16[a]	3	0	17[a]	2	0
17	Delayed	11[a]	7	1	10[a]	8	1
18	Primary	11	5	3	9	6	4
19	Primary	6	8	5	5	9	5
20	Delayed	9	8	2	8	9	2
21[b]	Delayed	12[a]	4	2	11[a]	6	1
Primary (n=13)		4	4	5	4	4	5
Delayed (n=8)		8	0	0	7	1	0

A single correct prediction was defined as a combination of (1) An estimate of >60% chance of primary closure or a high probability of primary closure plus a postnatal primary closure, or (2) As an estimate of <40% chance of primary closure or a low probability of primary closure plus a postnatal delayed closure.
[a]Correct prediction; [b]one missing value

between 40 and 60%. The number of the consultants who predicted correctly ranged from 58 to 84% (11–16/19) per case.

Aggregating the information weights, the type of information most vital to the estimations was the omphalocele content with 34% (fig. 4).

The information weight did not differ significantly between obstetric and pediatric consultants ($p > 0.05$). All cases ($n = 6$) without the liver present in the omphalocele were primarily closed. With regard to these cases, the estimations were more optimistic. The number of the consultants who correctly predicted primary closure in these 6

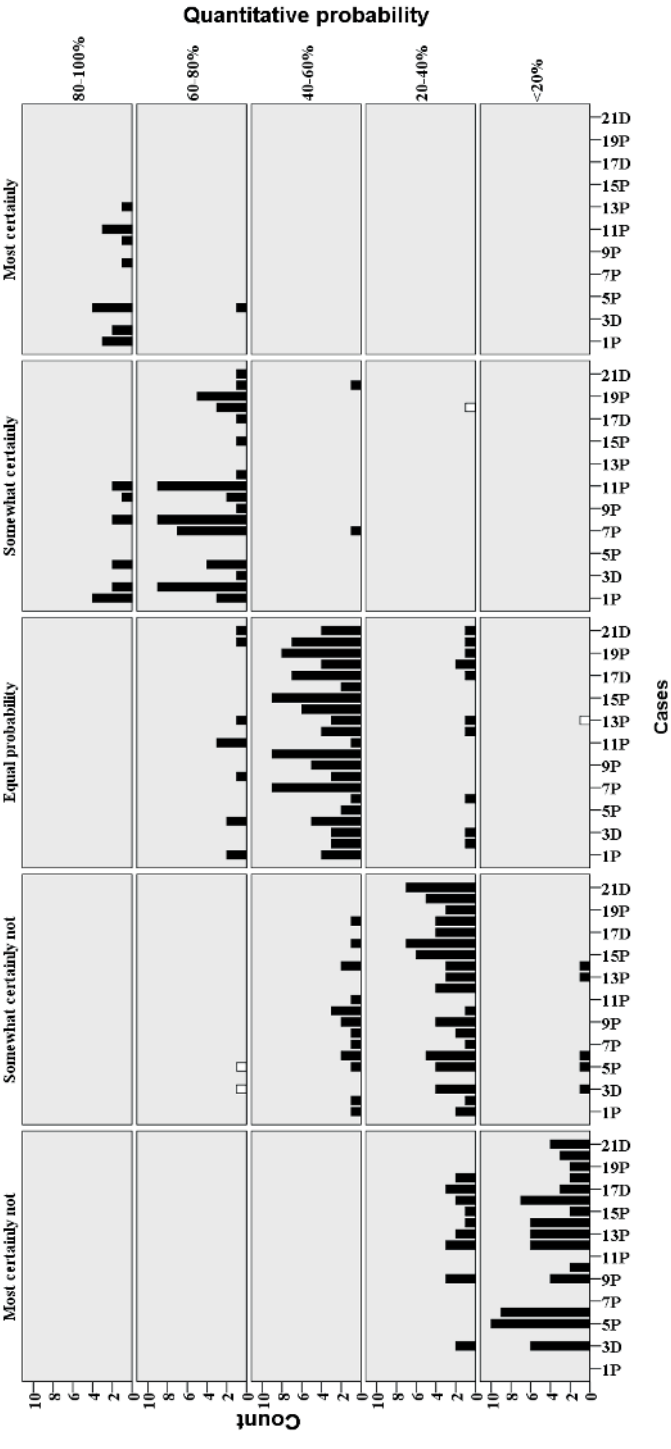
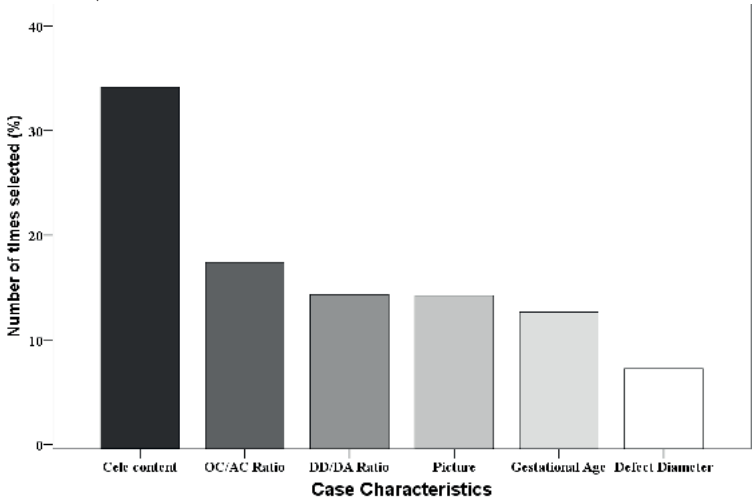


Figure 3 The quantitative estimated probability of primary closure in comparison to the estimated qualitative probability of primary closure is depicted.

The white bars are the answers in which the difference exceeded a 20% range (n = 4). 'n'P = Image number, primary closure; 'n'D = image number, delayed closure.

cases ranged from 37 to 89% (7–17/19) per case (table 3). However, in 4 of these cases, independent of being an obstetric or a pediatric consultant, 2 consultants per case did estimate the probability of primary closure to be <40%. Cases with the liver present in the omphalocele on prenatal ultrasound that were primarily closed (7/15) were either predicted incorrectly (57%, 4/7) or a prediction was not possible (43%, 3/7).

Figure 4 This bar chart depicts the chosen case characteristics for the assessment of the probability of primary closure (total = 100%).



Physicians could choose a maximum of 3 items per image.

Table 3 Quantitative predictions of the 19 assessors for the 6 cases without a liver present in the omphalocele.

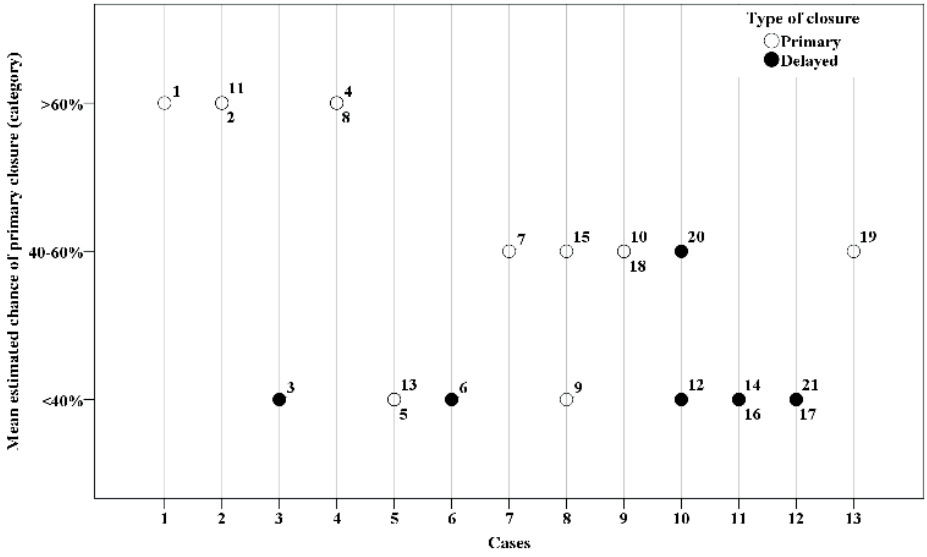
Image	Correct prediction	No prediction	Incorrect prediction
	n (%)	**n (%)**	**n (%)**
1	**12 (63.2)**	5 (26,3)	2 (10.5)
2	**13 (68.4)**	4 (21,1)	2 (10.5)
4[a]	**13 (68.4)**	5 (26,3)	0 (0)
7	7 (36.8)	**11 (57.9)**	1 (5.3)
8	**13 (68.4)**	4 (21.1)	2 (10.5)
11	**17 (89.5)**	2 (10.5)	0 (0)

A correct prediction was defined as the combination of an estimate of '>60% chance of primary closure' and postnatal primary closure. An incorrect prediction was defined as the combination of an estimate of '<40% chance of primary closure' and postnatal primary closure. The remaining combinations, i.e. all '40 – 60% chance of primary closure' answers, were defined as no prediction. The values in bold represent the majority of predictions per image. [a]one missing value.

The consultants were unaware of the fact that the 21 cases presented were actually 21 images of 13 cases at different GAs. From 8 actual cases, images of 2 examinations at different GAs were used. In 2 out of these 8 cases, the consultants' prediction at the

different GAs did not match, supporting our claim that they were unaware of the dual presentations. When the 2 predictions at the different GAs disagreed (n = 2), there was always a combination of a correct or an incorrect prediction in one with a 40–60% estimated probability of primary closure in the other (fig. 5).

Figure 5 The mean estimated chance of primary closure per actual case in the preset categories is shown.

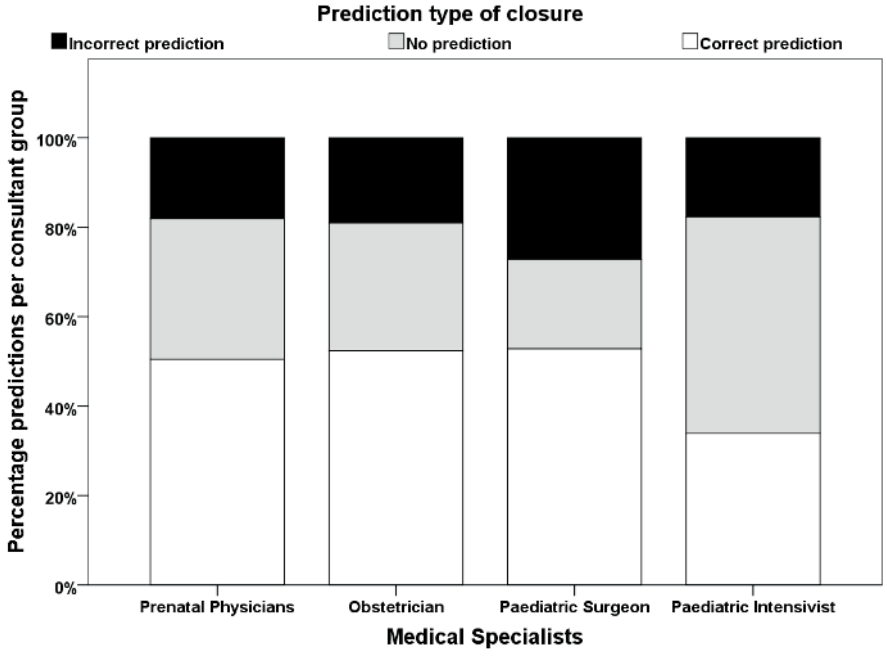


From 8 out of 13 actual cases, images of two examinations at different GAs were used. The numbers of the corresponding images as listed in table 2 are shown in the graph itself.

In cases where the experts predicted the probability of primary closure to exceed 60% (25% of the answers overall), there was a tendency for obstetric consultants to estimate this probability of primary closure more often than pediatric consultants (fig. 6).

Overall, the number of correct predictions did not differ significantly according to specialty (p = 0.30): 55% correct predictions by obstetric consultants and 45% correct predictions by pediatric consultants. Within the pediatric consultant group, the probability of delayed closure was best predicted by the pediatric surgeons. Individuals apparently randomly differed in their pessimism/optimism. The best consultants (n = 3) predicted 13/21 of the cases correctly. The number of cases predicted correctly per consultant ranged from 24 to 62% (5–13/21). The number of incorrect predictions per consultant ranged from 5 to 38% (1–8/21). According to the consultants, no prediction was possible in 5–67% (1–14/21) of the cases.

Figure 6 Prediction of the type of closure by the various consultants.



A correct prediction was defined as the combination of an estimate of >60% chance of primary closure and postnatal primary closure, or as an estimate of <40% chance of primary closure and postnatal delayed closure. An incorrect prediction was defined as the combination of an estimate of >60% chance of primary closure and postnatal delayed closure, or as an estimate of <40% chance of primary closure and postnatal primary closure. The remaining combinations, i.e., all 40–60% chance of primary closure were defined as no prediction.

DISCUSSION

This study investigated the degree of prognostic consistency among clinical expert consultants in the prediction of the type of closure of an omphalocele prenatally detected by ultrasound in the second trimester of pregnancy. We aimed at test conditions that resembled routine care. Overall, expert predictions were too negative in terms of the likelihood of primary closure of an omphalocele. Interconsultant variability in this regard was low. The consultants based their judgment on one type of prenatal information in particular, i.e., the omphalocele content.

In our tertiary center, we intend to counsel future parents in the first or second trimester of pregnancy since parents prefer counseling as early as possible in pregnancy.[14, 16] Our data suggest that GA has no influence on the prediction of the type of closure and that the prediction seems consistent per case prior to 24 weeks of gestation. In the cases (n = 2) where the estimated probabilities between the two images of one actual case did not match, the estimated probability of primary closure in one case was paired with a

40–60% estimated probability in the other. This could be explained by the fact that the 40–60% chance of primary closure or no prediction possible were the most frequent answers given in our study, i.e., 30% of all answers.

Overall, we observed that the most relevant determinant of a predicted probability of primary closure was an obstetric or a pediatric consultant, where the former counsel more often towards a primary closure (although not statistically significant). Personal experience in daily practice may explain this different tendency. Overall, the consultants are careful and do not want to be too optimistic in terms of an outcome prediction. In previous studies, a difference was found in counseling due to the difference in knowledge and years of working experience of individual medical consultants who counsel prenatal patients.[25, 26] In our study, however, adjustment for years of working experience surprisingly made no difference in the analysis.

A correct prediction was defined as the combination of an estimate of '>60% chance of primary closure' and postnatal primary closure. An incorrect prediction was defined as the combination of an estimate of '<40% chance of primary closure' and postnatal primary closure. The remaining combinations, i.e. all '40 – 60% chance of primary closure' answers, were defined as no prediction. The values in bold represent the majority of predictions per image.

In cases without the liver present in the omphalocele, the predictions were more optimistic. However, when the liver was present in the omphalocele, the consultants were not able to predict the type of postnatal surgical closure correctly, in particular in the cases that could be closed primarily. Previous studies[4, 27–29] discussed that primary closure is less likely in cases with a large defect (>5 cm postnatal) and containing a large portion of the liver. These data are based on the postnatal presentation, which is different from the prenatal environment in which the fetus is not subjected to gravity within the amniotic fluid. This does, however, confirm the negative estimated chances of primary closure by our consultants when the liver was present in the omphalocele.

From previous work, we know that an OC/AC-ratio <0.82 can be measured as a degree of visceroabdominal disproportion that is predictive of primary closure.[19] At the time of data collection for our study, the OC/AC-ratio and its relevance for the type of postnatal surgical closure was not yet published or known by the consultants.[19, 21] This study was based on 19 consultants judging 21 cases without knowledge of the OC/AC-ratio as a possible predictor for the type of closure and useful important parameter in prenatal counseling. For future studies, it would be useful to investigate if knowledge of this ratio makes consultants less negative about the probability of primary closure. From previous studies, it is known that a wide range of potential outcomes raises uncertainty in future parents.[14, 16] The question remains whether future parents would indeed prefer

case-specific counseling instead of the current general counseling. These aspects warrant further investigation, preferably in a larger study to evaluate the exact effects.

In our analysis of prognostic performance, we did not assign a different weight for a false-positive (falsely predicted primary closure) versus a false-negative (falsely predicted low probability of primary closure prediction) answer, as our focus was on overall convergence rather than best prediction. As counseling impacts prenatal and postnatal management,[30–32] differential weighting could be considered in a secondary analysis. Technically, this can be achieved in a straightforward manner.[33]

In this study, we included cases during a period of 7 years. During the study period (2003–2009), no major changes in the overall postnatal treatment modalities took place, except for an often prolonged duration of artificial ventilation to strive for a normal postnatal growth. This change may complicate the staged closure of larger defects[8, 20] but does not affect decisions with regard to the type of closure.

We can conclude that based on currently available prenatal information, obstetric as well as pediatric consultants experience a difficulty in predicting the type of omphalocele closure. They tended to be too negative, since 40% of the predicted delayed closures actually had a primary closure. Cases without eviscerated liver tissue were primarily closed, and the predictions were more positive with an average of 68% correct predictions per case. This is supported by the fact that omphalocele content was stated by all consultants as the key determinant of their judgment. The consultants can incorporate the knowledge obtained by this study in their counseling of future parents, as the position of the liver and the OC/AC-ratio seem important factors for the type of closure and related morbidity.

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CHAPTER 8

Omphalocele: from diagnosis to growth and development at 2 years of age

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ABSTRACT

Objectives

To compare the prenatal frame of reference of omphalocele (ie, survival of fetuses) with that after birth (ie, survival of liveborn neonates), and to assess physical growth and neurodevelopment in children with minor or giant omphalocele up to 2 years of age.

Design

We included fetuses and neonates diagnosed in 2000–2012. Physical growth (SD scores, SDS) and mental and motor development at 12 and 24 months were analysed using general linear models, and outcomes were compared with reference norms. Giant omphalocele was defined as defect ≥5 cm, with liver protruding.

Results

We included 145 fetuses and neonates. Of 126 (87%) who were diagnosed prenatally, 50 (40%) were liveborn and 35 (28%) survived at least 2 years. Nineteen (13%) neonates were diagnosed after birth. Of the 69 liveborn neonates, 52 (75%) survived and 42 children (81% of survivors) were followed longitudinally. At 24 months, mean (95% CI) height and weight SDS were significantly below 0 in both minor (height: −0.57 (−1.05 to –0.09); weight: −0.86 (−1.35 to –0.37)) and giant omphalocele (height: −1.32 (−2.10 to –0.54); weight: −1.58 (−2.37 to –0.79)). Mental development was comparable with reference norms in both groups. Motor function delay was found significantly more often in children with giant omphalocele (82%) than in those with minor omphalocele (21%, P=0.002).

Conclusions

The prenatal and postnatal frames of reference of omphalocele differ considerably; a multidisciplinary approach in parental counselling is recommended. As many children with giant omphalocele had delayed motor development, we recommend close monitoring of these children and early referral to physical therapy.

INTRODUCTION

Omphalocele is a midline congenital abdominal wall defect (AWD) with an estimated prevalence of 3.38 per 10 000 pregnancies.[1] It is usually defined as 'giant' if the defect is ≥5 cm at birth, with the liver (partly) protruding.[2] Otherwise, it is called 'minor'.

Nowadays, over 90% of omphaloceles are diagnosed prenatally.[3] Isolated omphalocele, which presents approximately 20%, usually has a high survival rate of 90%.4 Other fetuses, however, present with chromosomal abnormalities and/ or associated congenital anomalies (non-isolated omphalocele),[4] which lead to a high prevalence of termination of pregnancy (TOP) and intrauterine death (IUD). Therefore, we hypothesise a striking difference between the frame of reference of prenatal specialists and that of paediatric surgeons and paediatricians.

Previous research on long-term outcome mainly focused on children with giant omphalocele,[5–7] or surprisingly did not differentiate between gastroschisis and omphalocele.[8–10] We expect normal growth and development in non-syndromic children with minor omphalocele, and delayed growth and motor development in those with giant omphalocele.

The aims of our study were to (1) compare the prenatal frame of reference of omphalocele with that after birth, and (2) assess physical growth and neurodevelopment in children with minor or giant omphalocele up to 2 years of age.

METHODS

Study population

We retrospectively analysed data of all fetuses and neonates diagnosed with omphalocele between 1 January 2000 and 31 December 2012 at the Erasmus Medical Centre-Sophia Children's Hospital, Rotterdam. All parents of survivors were offered to enter their child in the longitudinal prospective follow-up programme for children with anatomical congenital anomalies treated at our hospital.[11]

Variables and definitions

Following prenatal detection of omphalocele, a prenatal specialist further examined the fetus to identify possible additional structural anomalies; karyotyping was offered in all fetuses. We classified additional anomalies by prognosis as follows: lethal (eg, trisomy 18, anencephaly), very poor (eg, congenital diaphragmatic hernia, large encephalocele) or uncertain (eg, suspected intestinal atresia, congenital heart defect). Fetuses with

isolated omphalocele were categorised according to the ratio of omphalocele circumference to abdominal circumference (OC/AC-ratio) (<0.82 or ≥0.82) at their first prenatal ultrasound.[12]

All fetuses were delivered vaginally, unless obstetric reasons required otherwise. Neonates with a birth weight <10th centile of Dutch references curves were considered small for gestational age.[13] Neonates born <37 weeks' gestation were considered preterm. Socioeconomic status scores (population mean 0, SD 1) were based on postal codes.[14, 15]

After birth, the omphalocele was defined as 'giant' if the defect diameter was ≥5 cm, with liver protruding. All neonates were screened for multiple congenital anomalies (MCA); we documented those requiring surgery or multiple follow-up visits. Chronic lung disease was diagnosed in neonates who required supplemental oxygen for at least 28 days.[16]

We documented duration of initial mechanical ventilation, time to full enteral feeding (TFEF), presence of intestinal failure (ie, TFEF ≥6 weeks) and length of initial hospital stay. If these exceeded 2 years, data were documented as 730 days. Neonatal death was defined as death during the first 28 days of life, and infant death as death between 28 days and 1 year.

Physical growth and neurodevelopment

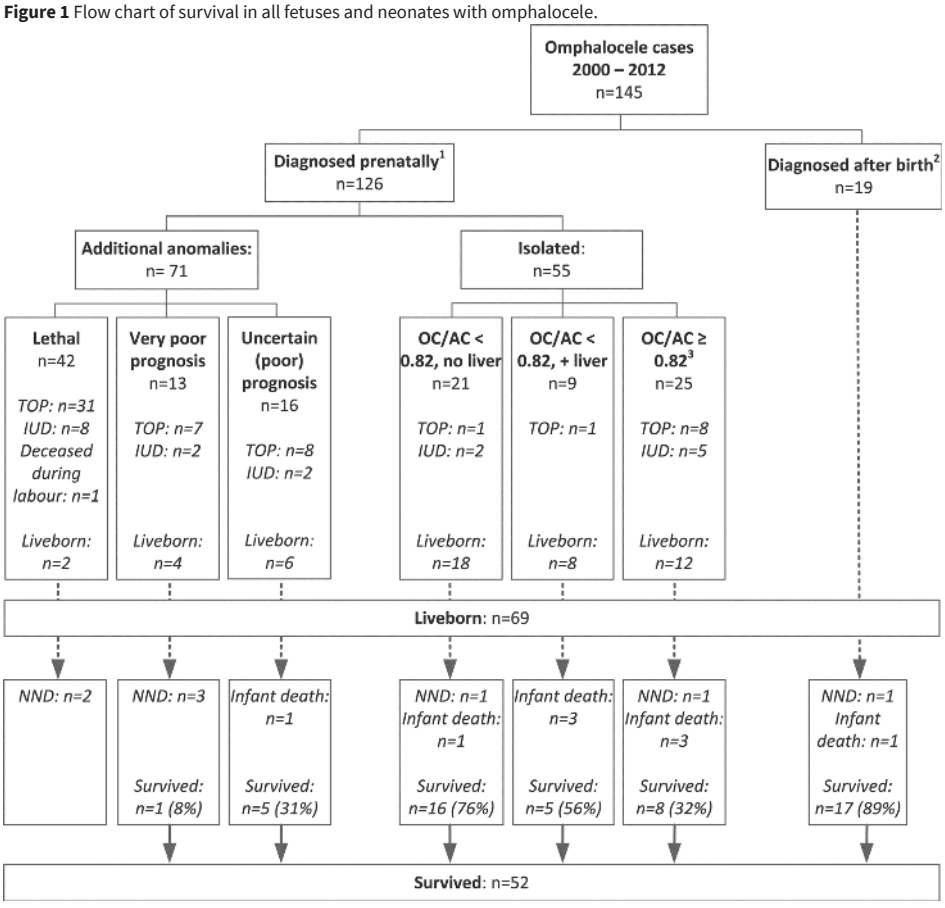
Height and weight had been measured at 12 and 24 months of age (corrected for preterm birth), and head circumference at 12 months of age. We calculated SD scores (SDS) according to Dutch reference norms; −2 to +2 SD was considered normal range.[17] Mental and motor development had been assessed at 12 and 24 months using the Bayley Developmental Scales (BOS 2–30, Dutch version)[18] and, from December 2003, Bayley Scales of Infant Development-Second Edition.[19] These scales are interchangeable[19] and provide a mental developmental index (MDI) and psychomotor developmental index (PDI) with a mean of 100 and SD of 15.[18, 19] Scores <55 are indicative of severe developmental delay; those were documented as 55. We excluded children with a confirmed syndrome influencing physical growth, neurodevelopment or both from the respective analyses.

Statistical analysis

Categorical variables are presented as number (%) and continuous variables as median (IQR). Prenatal, perinatal and postnatal characteristics of children with minor or giant omphalocele were compared using Fisher's exact tests for categorical data and Mann-Whitney tests for continuous data. We used general linear models to analyse the course of height, weight and neurodevelopment over time. These models included type of

defect (minor or giant), the time point (12 or 24 months) and their interaction term as independent variables. We used an unstructured error covariance matrix for the repeated measurements of each child to account for the within-subject correlations. The results are presented as estimated marginal means (ie, the predicted values of the dependent variable, adjusted for covariates in the model) with their 95% CIs. A two-sided P value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS V.21.0.

Figure 1 Flow chart of survival in all fetuses and neonates with omphalocele.

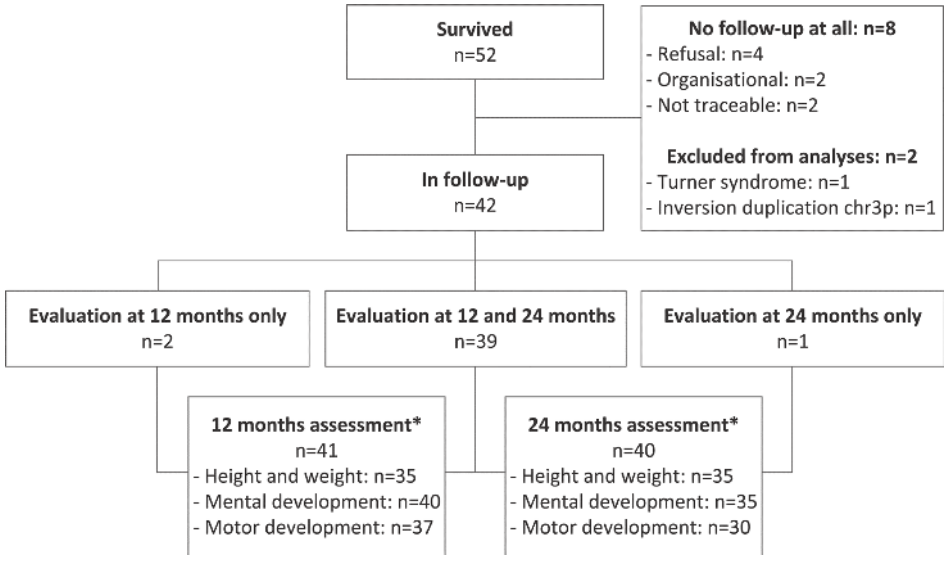


[1]2/126 were diagnosed late in pregnancy (1 at day of birth: MCA (suspected intestinal atresia); 1 at 34 weeks' gestation: isolated, but limited imaging due to severe polyhydramnios and maternal obesity); [2]1/19 prenatally diagnosed with gastroschisis instead of ruptured omphalocele; [3]including one ruptured giant omphalocele, liver was included in 22/24 fetuses (1 unknown). IUD, intrauterine death; MCA, multiple congenital anomalies; NND, neonatal death; OC:AC, omphalocele circumference:abdominal circumference; TOP, termination of pregnancy.

RESULTS

We included 145 fetuses and neonates; 126 (87%) were diagnosed prenatally, 50 (40%) of them were liveborn. Nineteen (13%) neonates were diagnosed postnatally. Of all 69 liveborn neonates, 52 (75%) survived at least 2 years (figure 1). Follow-up data of 42 (81%) children were analysed; all but 3 were seen at both time points (figure 2). Prenatal, perinatal and postnatal characteristics of children who entered our follow-up programme did not significantly differ from those who did not (data not shown).

Figure 2 Flow chart of children with omphalocele included in follow-up analyses of physical growth and neurodevelopment.



*Reasons for missing data on growth at 12 months: excluded because of Beckwith-Wiedemann syndrome (n=5) and organisational (n=1); and at 24 months: excluded because of Beckwith-Wiedemann syndrome (n=5). Reasons for missing data on development at 12 months: refusal, n=1 (both mental/motor); non-cooperative, n=1 (motor); immobilisation of legs, n=1 (motor); organisational, n=1 (motor); and at 24 months: refusal, n=1 (both mental/motor); non-cooperative, n=10 (both mental/motor, n=3; mental, n=1; motor, n=6).

Prenatal frame of reference

Overall, 50/126 (40%) fetuses diagnosed with omphalocele were liveborn and 35 (28%) survived ≥2 years. Additional structural or chromosomal anomalies were found in 71/126 (56%) fetuses. Most of these anomalies were lethal (42/71 (59%); figure 1). Two fetuses classified as having a lethal prognosis were liveborn but died shortly after birth. Thirteen fetuses had a very poor prognosis; 6/13 (46%) couples continued the pregnancy, which resulted in four live births of whom one child survived. Sixteen fetuses had an uncertain prognosis; 8/16 (50%) couples decided to continue the pregnancy; 2 fetuses died in utero and 5/6 liveborn neonates survived.

Isolated omphalocele was diagnosed in 55/126 (44%) fetuses. Thirty of them (55%) had OC/AC <0.82 and 26/30 (87%) were liveborn, compared with 12/25 (48%) fetuses with OC/ AC ≥0.82 (P=0.003). With TOPs excluded, 93% vs 71% of continuing pregnancies resulted in live birth, respectively (P=0.086). Of 38 liveborn neonates with an isolated omphalocele, 29 (76%) survived.

Postnatal frame of reference

Including the 19 (13%) neonates diagnosed after birth, 69 neonates were liveborn. Eight died within 1 week after birth, nine during infancy. Fifty-two (75%) children survived at least 2 years, and 42 children participated in our follow-up (figure 2). One child with minor omphalocele died at 3 years due to volvulus. All children with minor omphalocele underwent primary closure (table 1).

Of 11 children with giant omphalocele, 1 underwent primary closure and 10 had definitive closure at a median age of 19 months (range: 13–95). Children with giant omphalocele needed three times as many procedures under general anaesthesia as those with minor omphalocele. While more than half of the children with giant omphalocele developed chronic lung disease, none of those with minor omphalocele did. Three children with giant omphalocele needed mechanical ventilation for over 100 days; all got a tracheostomy cannula. The others breathed spontaneously within 1 week. The median TFEF was less than 1 week in neonates with minor omphalocele. TFEF was three times longer in those with giant omphalocele; almost one-third developed intestinal failure. Children with giant omphalocele stayed seven times longer in hospital than those with minor omphalocele (table 1).

Physical growth and neurodevelopment

Height and weight SDS are shown in figure 3.

The general linear model analysis showed no significant differences over time. At 12 months, the estimated marginal mean height SDS was significantly below 0 in children with giant omphalocele (−1.24 (95% CI −2.01 to −0.46)); weight SDS fell significantly below 0 both in children with minor (−0.61 (−1.04 to –0.18)) and in those with giant omphalocele (−1.49 (–2.20 to –0.78)). At 24 months, height and weight SDS were significantly below 0 in both children with minor omphalocele (height: −0.57 (−1.05 to –0.09); weight: −0.86 (–1.35 to –0.37)) and in those with giant omphalocele (height: −1.32 (−2.10 to –0.54); weight: −1.58 (–2.37 to –0.79)). Head circumference SDS was measured in 23 children with minor omphalocele (median (IQR): −0.56 (−0.89 to 0.42)) and in 6 with giant omphalocele (−0.22 (−1.18 to –0.05)), with no statistically significant difference between these groups (P=0.854).

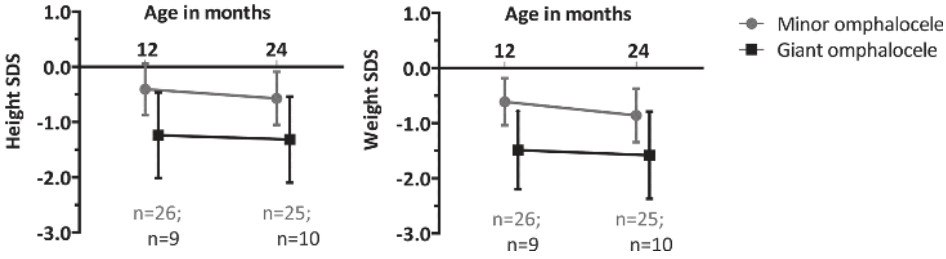
Table 1 Prenatal, perinatal and postnatal characteristics of children on follow-up (n=42).

	Minor omphalocele n=31	Giant omphalocele n=11	P value
Maternal age (years)*	31 (28–35)	31 (29–33)	0.890
Male sex	15 (48%)	4 (36%)	0.726
Multiple pregnancy	3 (10%)	0 (0%)	0.554
Socioeconomic status score at birth	0.08 (−0.53 to 0.88)	0.06 (−0.95 to 0.53)	0.463
Low status score (<−1)	8 (26%)	2 (18%)	1.000
Prenatal Characteristics			
Prenatal diagnosis	18 (58%)	10 (91%)	0.067
Gestational age (weeks) at diagnosis	22.9 (19.5–30.4)	21.2 (15.6–33.4)	0.654
OC/AC ≥0.82 at diagnosis	0 (0%)[b]	8 (73%)	<0.001
Liver protruding at diagnosis	4 (22%)	9 (90%)	0.001
Perinatal characteristics			
Caesarean section	8 (26%)	6 (55%)	0.136
Gestational age at birth (weeks)	38.9 (38.0–39.9)	38.4 (37.0–38.9)	0.163
Preterm birth	3 (10%)	2 (18%)	0.593
Birth weight (g)	3180 (2500–3640)	2750 (2140–3430)	0.124
Small for gestational age	6 (19%)	3 (27%)	0.676
Apgar score at 5 min*	10 (9–10)	9 (8–9)	0.043
Apgar score <7 at 5 min*	0 (0%)	1 (9%)	0.282
Postnatal characteristics			
Ruptured omphalocele	5 (16%)	3 (27%)	0.412
Content of omphalocele‡			
Liver	5 (16%)	11 (100%)	<0.001
Stomach	0 (0%)	3 (27%)	0.014
Bladder	0 (0%)	1 (9%)	0.262
Multiple congenital anomalies§	11 (35%)	3 (27%)	0.723
Primary closure	31 (100%)	1 (9%)¶	<0.001
Number of procedures under general anaesthesia**	1 (1–2)	3 (2–5)	0.003
Duration of initial mechanical ventilation	0 (0–1)	3 (0–119)	0.062
Chronic lung disease	0 (0%)	6 (55%)	<0.001
Time to full enteral feeding (days)	6 (3–9)	20 (13–49)	<0.001
Intestinal failure[bb]	2 (6%)	3 (27%)	0.103
Length of initial hospital stay (days)	7 (5–13)	50 (23–108)	<0.001
Paediatric physiotherapy			
At 12 months of age	4 (13%)‡‡	6 (55%)	0.013
At 24 months of age	2 (7%)§§	2 (18%)	0.300

Data presented as n (%) or median (IQR). *Unknown in n=3 minor omphalocele. [b]Unknown in n=4 prenatally diagnosed minor omphalocele. ‡Percentages do not necessarily add up to 100, as multiple organs can be herniated. §Minor omphalocele: cryptorchidism (n=1), cryptorchidism+renarcuatus (n=1), Beckwith-Wiedemann syndrome (n=4), enlarged monokidney (n=1), intestinal atresia (n=2), intestinal atresia+microcolon (n=1) and ileal cyst (n=1); giant omphalocele: Beckwith-Wi-

edemann syndrome (n=1), aortic stenosis (n=1) and cryptorchidism+epiglottic dysfunction (n=1). ¶Ruptured omphalocele. **Unknown in n=1 minor omphalocele. [bb]Time to full enteral feeding: 49–>730 days. Minor omphalocele: intestinal atresia (n=1) and intestinal atresia+microcolon (n=1); giant omphalocele: respiratory insufficiency due to sepsis, therefore nil per os (n=1), and intestinal passage problems (n=2). ‡‡Unknown in n=1 (no follow-up at 12 months). §§Unknown in n=2 (no follow-up at 24 months). OC/AC, omphalocele circumference/abdominal circumference

Figure 3 Height and weight SD scores (SDS) of children with minor or giant omphalocele.



Symbols represent estimated marginal means with 95% CIs, based on a general linear model that includes age, type of omphalocele and their interaction term as explanatory variables. At 12 months, height SDS was <−2 in 1/26 (4%) children with minor and in 2/9 (22%) children with giant omphalocele. Weight SDS was <−2 in 3/26 (12%) children with minor and in 4/9 (44%) children with giant omphalocele. At 24 months, height SDS was <−2 in 2/25 (8%) children with minor and in 3/10 (30%) children with giant omphalocele. Weight SDS was <−2 in 4/25 (16%) children with minor and in 4/10 (40%) children with giant omphalocele.

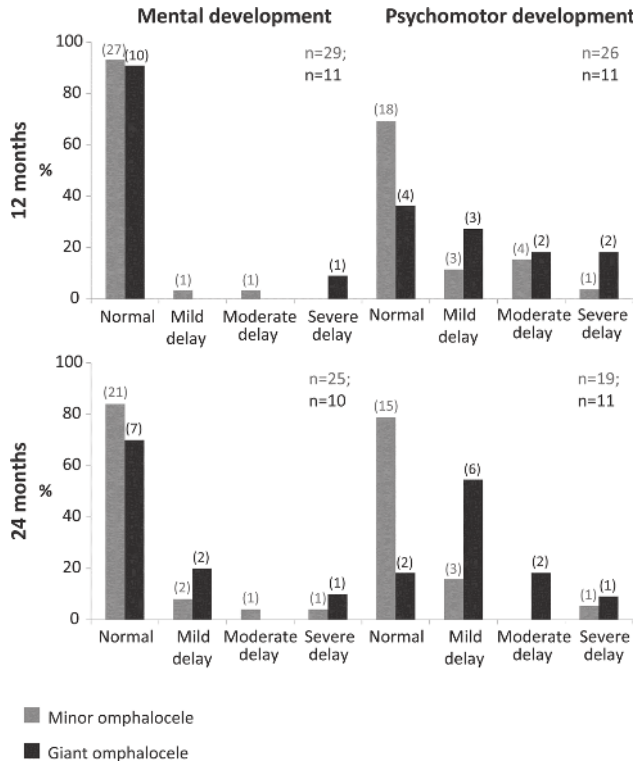
The estimated marginal mean MDI was comparable with reference norms at both time points in children with minor omphalocele (12 months: 106 (100–112); 24 months: 100 (93–108)) and in those with giant omphalocele (12 months: 97 (87–107); 24 months: 98 (86–110)) and did not differ between these groups. The mean PDI in children with minor omphalocele was significantly below 100 but within the normal range of 85–115, both at 12 months (89 (82–95)) and 24 months (93 (87–99)). PDI in those with giant omphalocele was significantly below normal at both time points (12 months: 75 (65–86); 24 months: 77 (69–86)); overall, children with giant omphalocele scored 15 (5–26) points less than those with minor omphalocele. At 24 months, motor developmental delay occurred significantly more often in children with giant omphalocele (82%) than in those with minor omphalocele (21%, P=0.002) (figure 4).

At 12 months, four (13%) children with minor and six (55%) with giant omphalocele received physiotherapy at home. This was continued up to at least 24 months in two (7%) children with minor and two (18%) with giant omphalocele.

DISCUSSION

We evaluated the course of omphalocele from diagnosis to growth and development at 2 years of age. As we hypothesised, the prenatal frame of reference was considerably worse than that after birth; additional structural or chromosomal anomalies—mainly

Figure 4 Proportions of children with minor or giant omphalocele with normal or delayed mental (left panel) and motor (right panel) at 12 and 24 months of follow-up.



Mild delay: developmental index: 70–84; moderate delay: 55–69; severe delay: <55. Numbers of children are shown in brackets.

lethal—were found in more than half of the fetuses. Physical growth at 2 years mainly fell within normal range. Mental development was generally normal. Motor development was delayed in over 80% of children with giant omphalocele.

The 2-year survival rate in liveborn neonates was 75%, which is in concordance with previous literature.[4, 20] The 2-year survival rate in prenatally diagnosed omphalocele was almost three times as low, causing a considerable difference between prenatal and postnatal frames of reference of this anomaly. The low survival rate in prenatally diagnosed omphalocele was mainly determined by the high prevalence of additional anomalies and concomitantly high rate of TOP. In addition, IUD and neonatal death occurred frequently in this group, which confirms previous literature.[21–23]

The OC/AC-ratio is intended to provide individualised counselling by predicting type of closure.[12] In our study, many parents of fetuses with an isolated omphalocele and OC/AC

≥0.82 opted for TOP. In the continuing pregnancies, IUD occurred in 29%. In fetuses with OC/AC <0.82, the rates of TOP and IUD were much lower. Earlier studies on omphalocele ratios only included liveborn neonates[12, 24-26] or were unable to distinguish between isolated and non-isolated omphalocele due to small sample sizes.[27] Our finding that the OC/AC-ratio may predict survival requires further research.

This study emphasises the importance of a multidisciplinary approach in parental counselling; paediatric surgeons and paediatricians may be more optimistic about survival rates than obstetricians and prenatal specialists. Moreover, inclusion criteria in studies on survival rates in omphalocele should be considered accurately; those including only prenatally diagnosed children are more likely to report lower survival rates than those including all children with omphalocele.

Previous studies on physical growth in children with AWD—not distinguishing between gastroschisis and omphalocele—reported suboptimal growth in infancy[10, 11] and normal[28] or suboptimal[9] growth in childhood. Henrich and coworkers[29] reported weight <p3 in 3/15 (20%) children with omphalocele aged 1–10 years, and height <p3 in two (13%) children. These proportions are similar to our results in 2-year-olds and higher than those in the reference population (ie, 2.3%, based on a standard normal distribution). Although their height and weight fell within the normal range at both time points, children with omphalocele seem to be at greater risk of failure to thrive. Our data did not allow for conclusions regarding determinants of poor growth. We assume that several aspects play a role, including neonatal surgery, work of breathing, prolonged hospitalisation and impaired mother–child interaction. We recommend close monitoring of growth, and early nutritional intervention if necessary.

Neurodevelopment has previously been studied in cohorts combining different types of non-cardiac anatomical anomalies[8, 30, 31] or AWD,[9–11] and in cohorts limited to giant omphalocele.[5–7] Similar to our results, Burnett and coworkers[32] reported motor function delay in 2-year-old children with omphalocele. Studies that did not differentiate between non-cardiac anatomical anomalies reported high prevalence of neurodevelopmental problems.[8, 30, 31] In contrast, studies that evaluated children with AWD showed normal neurodevelopment in infancy[10, 11] and normal motor development in childhood.[9] Note, however, that gastroschisis and omphalocele are two different entities; the prenatal and postnatal outcomes of children with omphalocele included in the present study differ much from those in children with gastroschisis in our previous study.[33]

Parental counselling should stress the importance of the difference between giant and minor omphalocele, as we found that giant omphalocele carried a greater risk of motor developmental delay. A previous study reported both mental and motor developmental delay in more than half of 31 children with giant omphalocele aged 6–35 months.[6] We

suspect the higher proportion of mental developmental delay could be explained by the inclusion of children with major MCA and rare syndromes in that study.[6]

We assume that in many children with giant omphalocele, the ventral hernia and altered trunk stability — due to abnormal development of the anterior abdominal muscles — contribute to impaired motor development in infancy, with a catch-up effect in childhood. A previous study reported normal motor function in children with giant omphalocele aged 3.5–12 years.[5] Nevertheless, monitoring of motor development in children with giant omphalocele with timely interventions if needed may be helpful. Moreover, parents should be encouraged to stimulate physical activity and should be counselled on leisure and sport participation of their children.

Strengths of our study are the data collection from a longitudinal prospective follow-up programme of mostly prenatally diagnosed children; the high proportion (81%) of children that entered this programme; the relatively large sample size for such a rare disease; and the use of standardised assessments both prenatally and during follow-up. Several limitations need to be addressed. First, the sample size was too small to study determinants of neurodevelopmental delay. Second, we compared height SDS with reference norms rather than with target height SDS, as parental height was often missing.

In conclusion, the prenatal frame of reference of omphalocele differs considerably from the frame of reference after birth, and a multidisciplinary approach in parental counselling is recommended. As 2-year-old children with giant omphalocele often had delayed motor development, we recommend timely referral to a paediatric physical therapist and prolonged follow-up, at least until these children have reached school age.

ACKNOWLEDGEMENTS

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What is already known on this topic?

- Fetuses and neonates with an isolated omphalocele usually have a good prognosis.
- Longitudinal data on growth and neurodevelopment in children with minor and giant omphalocele are scarce.

Wat this study adds?

- The prenatal and postnatal frames of reference of omphalocele differ considerably; a multidisciplinary approach in parental counselling is recommended.
- Two-year-old children with minor and giant omphalocele have similar growth and mental development; those with giant omphalocele are more likely to have motor delay.

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CHAPTER 9

Routine Intubation in Newborns with Congenital Diaphragmatic Hernia Reconsidering the Paradigm

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Congenital diaphragmatic hernia (CDH) is a rare developmental defect of the diaphragm and lungs, resulting in pulmonary hypoplasia and pulmonary hypertension (PH). With improved prenatal diagnostics, lung hypoplasia severity in CDH can be classified more accurately.[1,2] Infants with isolated left-sided CDH, observed-to-expected lung-to-head ratio (O/E LHR) $50%, and intraabdominal liver position are categorized as "mild lung hypoplasia" because their survival rate exceeds 95%.[1,3] All international guidelines advise routine intubation at birth for neonates with CDH to establish adequate oxygenation and cardiovascular stability.[4–7] However, in mild CDH, this potentially results in overtreatment and disturbance of physiologic perinatal transition.[8] Our aim with this study was to evaluate a spontaneous breathing approach (SBA) in the treatment algorithm of infants with mild CDH.

METHODS

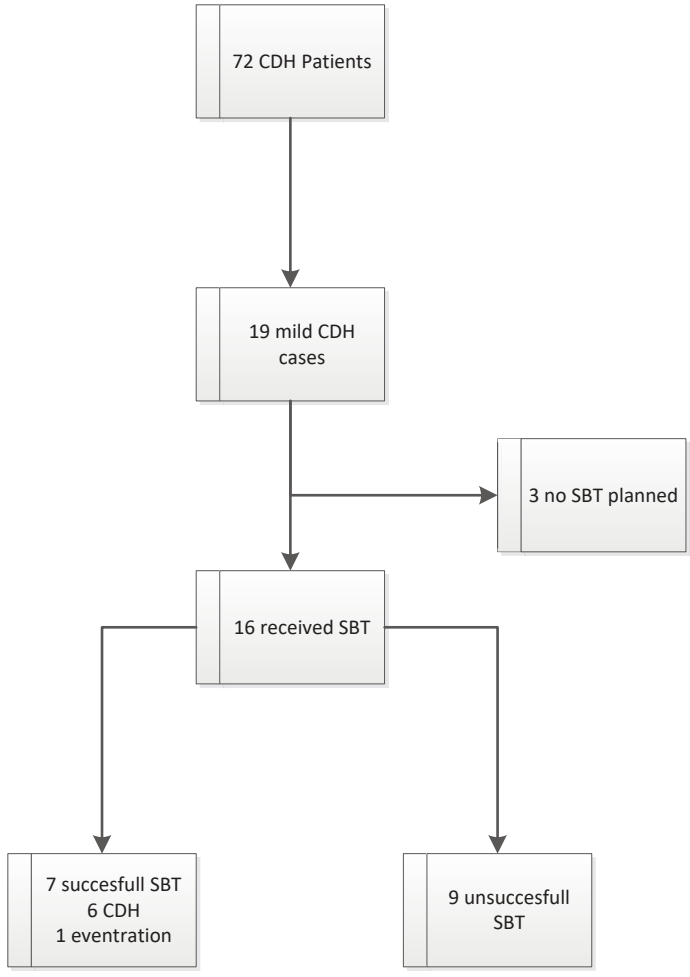
After study approval by the local institutional review board (MEC2019-714) and waived informed consent, we performed a retrospective study in newborns with CDH born at Erasmus University Medical Center Rotterdam, a national and level 3 referral center with extracorporeal membrane oxygenation.

Our local protocol is based on the CDH EURO Consortium guidelines. Accordingly, we modified our protocol in December 2014, allowing planned SBA in patients with mild CDH born >35 weeks' gestation.[4] We used the O/E LHR measured between 24 and 38 weeks' gestational age.[1] Congenital anomalies were defined as anatomic anomalies on prenatal ultrasound or genetic mutations (microarray). We included all patients with mild CDH born between December 2014 and July 2019. The SBA was classified as failed if the infant required intubation any time before elective intubation for surgery. Surgery was planned electively with an experienced CDH operating team.

In our center, a perinatal treatment plan is made for all patients with CDH in a multidisciplinary team meeting at ~32 weeks' gestation, attended by obstetricians, fetal medicine specialists, neonatologists, pediatric intensivists, and surgeons. The treatment strategies are subsequently discussed with the parents, including an SBA if applicable. Postnatal resuscitation is executed according to CDH guidelines.[4] The newborn is positioned on the resuscitation table and a Replogle tube (10F catheter) is inserted for continuous stomach decompression. In the case of planned SBA, the infant is supported with oxygen if necessary (Neopuff infant T-piece resuscitator; Fisher & Paykel Healthcare, Ltd, Auckland, New Zealand), aiming for preductal saturations 0.85%.[4] Continuous positive airway pressure is allowed. The infant is intubated if insufflation breaths or ventilation

are needed because positive pressure ventilation via mask increases the air in the digestive tract, subsequently compressing the lungs, resulting in hypoxia and PH.

Figure 1 Patient flowchart.



Flowchart of patient selection for the case series.

RESULTS

During the study period, 71 newborns with CDH were treated in our referral center, and 18 (25%) fulfilled the SBA criteria. However, in 3 patients, SBA was not prenatally planned and thus not performed (Fig 1). SBA was successful in 6 of 15 patients (40%); 3 required continuous positive airway pressure for several minutes, and 5 were transferred to the

unit with binasal cannulae (Intersurgical, Inc, Syracuse, NY) with 1 to 2 L flow and 30% to 40% of inspired oxygen. All were electively intubated for surgery. In total, 9 of 15 patients required intubation after birth (7 at birth and 2 several hours after birth). Only 1 patient (O/E LHR 57%) developed PH and was treated with inhaled nitric oxide for 4 days and oxygen supplement therapy for 28 days.

Apart from the anticipated difference in ventilation days and duration of oxygen therapy, there were no clinical differences between patients with successful and failed SBA (Table 1). The overall survival was 100%.

Table 1 Patients with and without successful SBA.

	Successful SBA (*n* = 6)	Failed SBA (*n* = 9)	*P*
Male sex, %	50	78	—
Birth weight, kg, median (IQR)	2.78 (2.38–3.22)	3.0 (2.85–3.20)	.24
Apgar score 1 min, median (IQR)	7.5 (5.8–8)	6.5 (4.3–7.8)	.41
Apgar score 5 min, median (IQR)	8 (8–9.3)	7 (7–8.8)	.18
Gestational age at birth, wk, median (IQR)	37.8 (37.0–38.5)	38.3 (37.9–38.6)	.37
O/E LHR, %, median (IQR)	66 (49.8–82.3)	55 (52–64.5)	.56
Peak ventilator pressure,[a] cm H_2O, median (IQR)	23.5 (21.5–27)	23 (19.5–25)	.37
VIS score,[a] median (IQR)	0 (0–18.8)	4.6 (0–15.5)	.57
Days on ventilator, median (IQR)	1 (1–2.5)	7 (4–10)	<.05
Day of surgery, median (IQR)	3 (2–4)	3 (2–5)	.90
Defect type, *n* (%)			.89
A	0 (0)	2 (22)	—
B	2 (33)	5 (56)	—
C	1 (17)	0 (0)	—
D	0 (0)	0 (0)	—
Missing	3 (50)	2 (22)	—
Patch repair, *n* (%)	2 (33)	5 (56)	.53
Days on ventilator after surgery, median (IQR)	1 (1–2.5)	4 (2–5.5)	.05
Total oxygen therapy, d, median (IQR)	4.5 (2.5–7)	15 (5–17)	<.05
Discharge from ICU in d, median (IQR)	6 (5–10.75)	18 (7.5–25)	<.05
Discharge from the hospital in d, median (IQR)	18 (9–31.5)	28 (13.5–45)	.44
Medical support at discharge,[b] *n* (%)			
None	4 (66)	4 (44)	.7
G-tube feeding	2 (33)	5 (56)	—

[a]Recorded continuously during ICU admission. [b]Defined as ventilatory, oxygen, pharmaceutical, G-tube feeding.
Abbrevations: G-tube: nasogastric tube; VIS: vasoactive inotropic support; —: not applicable.

DISCUSSION

In the group of patients with mild CDH, a prenatally planned SBA is feasible. We consider it safe, and it avoids overtreatment with potential adverse side effects. Although numbers are low, and data are collected retrospectively in a single center, this suggests that individualized care in patients with CDH should be considered. By allowing SBA, iatrogenic complications due to prompt intubation and ventilation could be minimized. In addition, stress, pain, and the need for sedation is reduced in these infants; consequently, postnatal parent-infant interaction is improved. Delayed intubation did not seem to negatively affect outcomes. However, a larger prospective trial is needed to ensure that SBA is safe. Furthermore, we believe that this approach should only be done in expertise centers that have a multidisciplinary team of specialists caring for infants with CDH.

ABBREVATIONS

CDH: congenital diaphragmatic hernia
IQR: interquartile range
O/E LHR: observed-to-expected lung-to-head ratio
PH: pulmonary hypertension
SBA: spontaneous breathing approach

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PART III

Discussion and Summary

CHAPTER 10

General Discussion

GENERAL DISCUSSION

Foetuses with a congenital diaphragmatic hernia (CDH), congenital lung malformation (CLM) or giant omphalocele (GO) are at risk of impaired pulmonary and/or pulmonary vascular development and pulmonary hypoplasia.[1] Consequently, they are also at risk of developing respiratory morbidities such as pulmonary hypertension (PH) of variable duration and/or chronic lung disease (CLD) in the long term. As the postnatal survival rates of affected infants are increasing, these morbidities on the short and long term are becoming more important to include in prenatal counselling.[2, 3]

Previous studies have shown that the changes in the pulmonary vasculature leading to postnatal PH and sometimes CLD – i.e. reduced branching of the small pulmonary arteries and increased medial wall thickness due to increased muscularization[4-9] – are already present in the foetal period.[10-12] Review of the literature regarding the assessment of pulmonary development by prenatal ultrasound indicated that previous studies have concentrated on the predictive value of 2D and 3D measurement of diameters of the pulmonary artery, lung area or lung volumeas markers for postnatal outcome.[13-20] A few papers addressed functional assessment of the lung by measurement of Doppler flow velocities in de pulmonary arteries and veins during the second and third trimester of pregnancy.[20-23] Even fewer papers aimed to measure the amount of blood flow through the foetal lung, and even then they concentrated on the foetus with a congenital anomaly.[24, 25] Still much is unknown about normal and abnormal intrauterine pulmonary development. It remains a challenge to predict postnatal lung 'function' from prenatal parameters. These parameters are measured in a still highly immature fluid filled lung in the second and/or third trimester of pregnancy when only a very small part of cardiac output passes through the lungs. This in contrast to an aerated and perfused lung after birth.

Prenatal ultrasound is a well-established imaging tool for daily clinical practice since it is safe in pregnancy, easily accessible and low in cost.[26] Different health professionals worldwide – e.g., foetal medicine specialists, obstetricians, radiologists, ultra-sonographers and paediatricians – perform prenatal ultrasound examinations, representing different perceptions of the images acquired during the assessment. The actual challenge lies in uniform structured assessment, interpretation and documentation of foetal parameters, as well as standardized prenatal counselling of the future parents. Several studies that assessed feedback on prenatal counselling from future parents whose unborn child appeared to have congenital anomaly on prenatal ultrasound reported that individualized, multidisciplinary, uniform counselling,[27-29] written or visual illustrations[27, 30] and frequent follow-up visits[30] were of high importance. Lalor et al. reported that education on prenatal counselling for healthcare professionals is important as well,[31] especially

since parents have reported that compassion from the side of the caregiver is of major importance in counselling – independent of the choice they will make.[3]

The studies presented in this thesis evaluated the potential of currently used and new prenatal ultrasound parameters throughout gestation for the prediction of postnatal (pulmonary) outcome, and for their usefulness for counselling and for perinatal and postnatal management, especially regarding infants at risk for the development of chronic lung disease (CLD).

Congenital lung malformations

From a morphological point of view, lung development can be divided into five stages: embryonic (4-7 weeks), pseudoglandular (5-17 weeks), canalicular (16-26 weeks), saccular (24-term) and alveolar (36 weeks-21 years after birth).[32] During the embryonic stage the major airways, pleura and extrapulmonary and lobar arteries are formed. In the following foetal stages these primary trachea and lungs are further developed by a complex mechanism of branching; 1) formation of the bronchial tree (i.e., bronchi, bronchioles and respiratory bronchioles) and pre-acinar and intra-acinar arteries develop during the pseudoglandular stage, 2) the most distal airway branches and alveolar ducts develop during the canalicular and 3) the saccular stage when expansion of airspaces and formation of alveolar duct arteries takes place. Septation of the immature alveoli occurs after birth during the alveolar stage, at which also microvascular maturation occurs and alveolar capillaries are formed.[32] Congenital lung malformations (CLM) result from abnormal branching during morphogenesis of the foetal lung. Different types of CLM are thought to develop during separate stages of lung development, arising from tracheal, bronchial, bronchiolar or alveolar tissue. As a result , pathologically, five types (type 0-4) of congenital pulmonary airway malformations (CPAM) can be identified.[33] Types 1 and 2 are most frequently found and originate from the proximal bronchioles (type 1) or distal bronchioles (type 2). This might explain why CLMs commonly are visible by ultrasound from 17-18 weeks gestational age (GA) onwards, and why they show signs of regression after 28 weeks' gestation. Prenatal 'regression' of these lesions could be hypothesized to proceed as follows: the part of the lung that shows abnormal development does not grow after the pseudoglandular stage, whereas the other, healthy, parts grow accelerated during the canalicular and saccular stages of lung development, and mask the CLM on prenatal ultrasound. In foetuses with a CLM, our results showed that neither prenatal regression nor growth of the CLM is correlated with the need for respiratory support within 24 hours after birth or the need for surgery. In many cases, however, the postnatal CT scan revealed a CLM that was not visible on prenatal ultrasound, and could be symptomatic within 24 hours after birth. Even today, there is no consensus on the optimal approach (resection or 'wait and see') of an asymptomatic CLM. We therefore

recommend delivery of these foetuses in a paediatric surgical expertise centre with an admission for 24 hours observation in the maternity ward. We found that only a persistent cardiac mediastinal shift between 20 and 30 weeks' gestation was associated with the need for postnatal surgery (Chapter 6). Correspondingly, Shulman et al.[34] reported that the angle of cardio mediastinal shift was of predictive value for adverse perinatal outcome. Ongoing multicentre research is needed to investigate if and how perinatal management can be further individualized based on prenatal parameters (e.g., by setting cutoff values of CLM volume ratio, type of CLM, and/or presence of temporary or persistent mediastinal shift).

For small CLMs, limited to 1-2 segments, lung-sparing surgery such as segmentectomy appears to be preferable over a lobectomy, since it preserves normal healthy lung parenchyma, and is associated with shorter length of stay and fewer postoperative complications.[35-37] As these lung segments are not visible on prenatal ultrasound, prenatal prediction about the actual size and location of the CLM has until now not been possible. For prenatal counselling about postnatal management (such as prediction of need for surgical intervention), it is important to see whether we can determine to how many lung segments, and which, the CLM is limited. To this aim, we would suggest assessment of the number of arterial branches arising from the main left and right pulmonary arteries.

Nevertheless, in the environment with high intrapulmonary vascular resistance, it is difficult to assess these pulmonary blood vessels with slow blood flow in close proximity to the foetal heart by use of prenatal ultrasound. Next generation ultrasound machines, however, offer a feature to depict blood flow in the smaller vessels.[38, 39] In addition to clarifying which lung segment or segments are affected, this feature possibly provides for visualizing branching patterns of the pulmonary vasculature in foetuses at risk for pulmonary hypoplasia.

Lessons learned

Overall, the prenatal appearance of a congenital lung malformation (CLM) does not coincide with the postnatal type. Further insight into the development and appearance of the different types of CLM improves prenatal counselling.

Prenatal microcystic CLMs appear to be congenital lobar overinflation in 40% of the cases.

Neonates with a prenatally identified macrocystic CLM need respiratory support within 24 hours after birth and require a surgical resection.

Persistent mediastinal shift in the third trimester of pregnancy is associated with greater need for postnatal surgical intervention.

More standardized description of the prenatal and postnatal appearances of a CLM results in a better comparison between patient subgroups.

All foetuses with a prenatal diagnoses of a CLM should be delivered in a hospital with specialized pediatric surgical care and admitted for at least 24 hours observation.

Whether the term born neonate needs to be admitted at the maternity ward or the neonatal intensive unit depends on the prenatal parameters at 30 weeks' gestation: a neonate with a small CLM, no persistent mediastinal shift and/or systemic arterial blood flow evident at 30 weeks gestation, and who shows a good transition at birth can be admitted to the maternity ward for 24 hours observation.

Goals for the future

To achieve more individualized perinatal planning of foetuses with a prenatally detected CLM, based on ultrasound parameters.

To acquire knowledge about the pulmonary vasculature in foetuses with a CLM, since a detailed assessment of the pulmonary vasculature could predict need for surgical resection.

Left-sided congenital diaphragmatic hernia

Currently, the prediction of postnatal outcome in foetuses with a left-sided CDH (L-CDH) is based on the observed-versus-expected lung-to-head ratio (O/E LHR)[13] of the contralateral lung and position of the liver (up or down).[40] Previous studies have debated whether or not the O/E LHR is independent of GA.[13, 41] We found that, although absolute values of the O/E LHR tend to differ throughout gestation, about 75% of foetuses remain in the same CDH severity group[42] during their foetal life (Chapter 4). For this study, we

evaluated the usefulness of the O/E LHR in an era of standardized neonatal treatment[43] and demonstrated that it is still valid for prediction of the degree of pulmonary hypoplasia. In addition, we have shown that it is associated with the postnatal defect size and the development of CLD in L-CDH survivors. From previous studies, we know that the postnatal defect size is correlated with survival and length of stay.[44, 45] This makes defect size a notable outcome parameter, also for future studies, when it comes to predicting short-term and long-term postnatal morbidity.

Recently, the outcomes of the foetal endoscopic tracheal occlusion (FETO)-trials in moderate and severe L-CDH patients were published.[46, 47] In the trial in severe L-CDH patients, the survival rate after FETO was higher than that after expectant management. The trial performed in moderate L-CDH patients showed no significant benefit of FETO versus expectant care with regard to survival and secondary co-morbidities such as need for oxygen at discharge. The lack of benefit might be ascribed to high survival rates within the moderate L-CDH group as a result of e.g. standardized neonatal management due to postnatal guidelines of the CDH-EURO consortium. Other hypotheses are that an increase in lung size due to FETO does not result in improved vascularization, and that timing of balloon placement (27-29 weeks gestation) does not influence morphological changes in pulmonary vascular development. Animal studies have shown fewer branches in the peripheral pulmonary arteries and veins of foetuses with a CDH.[48-51] These findings help us understand the importance of assessment of the pulmonary vascular development for prediction of postnatal outcome. The study presented in Chapter 5 demonstrated that volume measurements of the pulmonary vasculature are reliable and reproducible, and were significantly different between foetuses with a CDH and healthy controls. Since we aimed to develop novel, reliable, investigator-independent methods of assessment of the pulmonary vasculature, we used uniform pre-set settings for the Power Doppler on the ultrasound machine and restricted the measurements to all Power Doppler voxels of one lung adjacent to the proximal pulmonary tree. Thus, we did neither assess vascular volume of the peripheral part of the lungs, nor the Doppler flow patterns and vascular branching yet. In the future, we would like to measure all Power Doppler voxels within the acquired volume and to assess patterns in vascular branching. In foetuses undergoing FETO, we intend to measure the vascular volume before and after balloon placement, in order to detect whether foetal therapy changes the pulmonary vascular structure and to see whether this assessment could help in patient selection.

Our above-mentioned study revealed a significant difference in pulmonary vascular volume between isolated CDH survivors and non-survivors, but not for the need of treatment of PH and the development of CLD. The latter may be due to high survival rates within our isolated L-CDH cohort and an overall moderate to mild lung hypoplasia, but also due to the small subgroup sample sizes. According to international criteria, PH

is defined as a pulmonary wedge pressure above 20 mmHg proven by invasive cardiac catherisation, at least in adults. This information is often not available in these neonates, as cardiac catherization is seldom performed in view of the high risk. Therefore, in daily practice PH is diagnosed by cardiac ultrasound showing signs of septal deviation, left to right shunting or tricuspid regurgitation.[52] Not all neonates with a PH diagnosis on echocardiography in the first 24-48 hours after birth show clinical symptoms of PH and require treatment. When counselling future parents, the need for treatment rather than the diagnosis without clinical consequence is more relevant in our opinion; we therefore chose the need for treatment as an outcome measure in our study. This choice has probably resulted in a smaller number of patients meeting this outcome measure; a larger sample size might be required to reach statistical significance.

In the study presented in Chapter 5, we measured the PVV of the right lung (PVVR) in the BARCO I-Space system, which requires the availability of a large separate room (40m^2 or 400 sqft) and a fairly high budget of approximately US$ 500,000.[53] In order to make the measurement suitable for use in daily clinical practice worldwide – and not exclusively for well-funded hospitals and high-income countries – we plan to validate these PVV-measurements on the 3D virtual reality (VR) desktop system currently used at our outpatient clinic.[54]

Several studies reported that L-CDH foetuses show smaller left ventricle dimensions and dysfunction of the left ventricle after birth.[55-58] These abnormalities are thought to be caused not only by 'compression' by abdominal organs, but also by a decrease in pre-load as a result of increased blood flow through the ductus venosus and the right ventricle.[59, 60] Hypoplasia and diastolic dysfunction of the left ventricle after birth have been associated with a lesser response to current treatment modalities (sildenafil and nitric oxide) in L-CDH foetuses with PH.[56, 61] Dhillon et al.[62] evaluated left-sided heart dimensions in foetuses undergoing FETO and in L-CDH severity-matched controls, and found that increased lung growth after FETO was not associated with an increase in left-sided cardiac structures. We suggest that this may indicate that left ventricular size is an independent predictor for postnatal outcome. Until now, prenatal cardiac assessment for prediction of PH has not been proven possible, and comparison between prenatal and postnatal populations, and also within patient populations, is hampered by differences in performed measurements.[55-60, 63-66] There is a need for multicentre studies with uniform measurement of cardiac structures, both structural as well as functional, since the values of cardiac parameters could be of predictive value for postnatal outcomes such as the need for treatment of PH.

In the study presented in Chapter 9, we evaluated a spontaneous breathing approach after birth in neonates with a L-CDH based on prenatal ultrasound parameters (i.e.,

O/E LHR (>50%) and an abdominal liver position), which appeared feasible. For future development of prenatal prediction and/or treatment algorithms, we suggest the use of outcome parameters applied in daily clinical practice (e.g. need for treatment, long-term morbidities), which are relevant for future parents and for the daily management of the neonate. As the newly emerging ultrasound techniques, such as 3D, 4D and 3D-VR are not yet applicable in daily practice and not widely accessible, the combined use of flow patterns of the pulmonary arteries and veins[21, 67] and foetal cardiac parameters should be assessed for improved prenatal prediction and perinatal and postnatal treatment algorithms with and without prenatal volume measurements.

Lessons learned

The observed-versus-expected lung-to-head-ratio (O/E-LHR) predicts the degree of pulmonary hypoplasia, the postnatal defect size, the presence of chronic lung disease, and the chance of survival.

Based on the O/E-LHR and the prenatal liver position, 75% of foetuses with a CDH remain in the same pulmonary hypoplasia severity group throughout gestation.

The pulmonary vascular volume of the contralateral lung in isolated L-CDH can be reliably measured by 3D-VR ultrasound and shows predictive value for survival <24 weeks' gestation.

Prediction of postnatal outcome in the very diverse group of foetuses with a moderate L-CDH remains challenging.

Prenatal counselling should include possible limitations of the stand alone prenatal lung volume and area measurements.

The presence of pulmonary hypertension (PH) on prenatal echocardiography leads to an overestimation of neonates needing treatment for PH – and is therefore less suitable for prenatal counselling.

In foetuses with an O/E-LHR >50% and liver down, a spontaneous breathing approach instead of immediate intubation after birth seems feasible.

Goals for the future

Validate the PVV measurements on the desktop version of the I-SPACE, in order to make them suitable for daily clinical practice.

Multicentre acquisition of 3D Power Doppler volumes in patients with L-CDH for offline analysis to increase patient numbers for subgroup analysis based on foetal therapy options and postnatal outcome.

Further assessment of the 3D analysis of the peripheral vessels of the lungs to evaluate the predictive value for postnatal outcome; e.g. by use of new ultrasound techniques depicting slow blood flow.

To standardize cardiac measurements in L-CDH patients for multicentre analysis of the predictive value of left ventricular dimensions and/or contractility for postnatal outcome.

Assessment of the predictive value of prenatal parameters for clinically relevant outcome parameters (e.g., need for treatment for PH, long-term morbidities) and treatment protocols in order to improve prenatal counselling and perinatal care.

Development of prenatal and perinatal prediction algorithms based on 2D parameters with and without 3D ultrasound and MRI parameters, making it useful in all centres for perinatal care.

Omphalocele

Previous studies have reported that, apart from the variable amount of pulmonary hypoplasia, PH can be present in foetuses with a giant omphalocele (GO).[68-71] This is a significant morbidity in GO patients and it would be valuable if GO and the need for PH treatment could be predicted. The occurrence of GO in live-born neonates is rare,[16] which implicates that uniform multicentre studies are needed to achieve enough power for a statistical analysis. The omphalocele circumference/abdominal circumference (OC/AC)-ratio predicts survival and type of surgical closure based on decreasing cut-offs throughout gestation (Chapters 2 and 3): in foetuses with a GO (or OC/AC-ratio 0.63-0.69), closure is more often delayed. A delayed – or staged – closure carries a higher risk of prolonged hospital stay, feeding problems, development of PH and/or CLD, and a lower chance of survival.[68, 72-74] By predicting the type of surgical closure, an indirect estimate could be made on the probability of the above-mentioned risks (Chapter 8).

In addition, a smaller OC/AC-ratio was more often seen in neonates with chromosomal or syndromal anomalies, and in one third of the prenatally assumed isolated cases, associated structural anomalies were detected after birth (Chapter 3). From previous

studies, it is known that associated anomalies influence postnatal treatment possibilities.[74, 75] Prenatal counselling should include the association between omphalocele size and syndromal anomalies as well as the fact that around 30% of associated anomalies are not detected prenatally.

In Chapter 7, we established that medical specialists – both obstetric and paediatric consultants – base their prenatal counselling in most cases on prenatal ultrasound images. Obstetric specialists tended to be more optimistic regarding postnatal outcomes and the possibility of primary closure of an abdominal wall defect than the paediatric specialists. This discrepancy could be related to the difference in the patient populations seen prenatally and postnatally (Chapter 8). In line with previous studies,[76, 77] we recommend multidisciplinary management for foetuses with GO too, so as to reduce variability in prenatal counselling and to improve their perinatal care.

Lessons learned

A small omphalocele circumference/abdominal circumference (OC/AC)-ratio is associated with more chromosomal and/or syndromal anomalies, and predicts primary closure of the abdominal wall defect.

The OC/AC-ratio can reliably predict type of closure <24 weeks' gestation, as well as per trimester of pregnancy with decreasing cut-offs throughout gestation.

In about a third of the prenatally assumed isolated omphalocele cases, associated structural anomalies are detected after birth.

In all omphalocele cases without liver protruding, the defect was primarily closed.

Multidisciplinary prenatal counselling ensures future parents of consistent information with regard to prenatal and perinatal management as well as short-term and long-term postnatal outcome.

Goal for the future

Assessment of the pulmonary vasculature in foetuses with a giant omphalocele to improve prediction of pulmonary hypertension in these neonates.

Conclusion and recommendations

Differences in pulmonary vascular development between patients can be reliably established by prenatal 2D, 3D and 3D-VR ultrasound, but prenatal ultrasound cannot fully predict postnatal outcomes within patient subgroups. The most important problems that cannot be resolved are the sudden change of pulmonary vascular flow after umbilical cord clamping and the prediction of the pulmonary vascular response, both from a functional and a morphological point of view. Future imaging modalities, such as depicting vessels with slow flow, could improve these measurements and add to prenatal prediction algorithms. By assessment of prenatal parameters throughout gestation, insight into physiological and pathophysiological foetal pulmonary and pulmonary vascular development can be expanded. Expecting parents can then be informed about the value of various measurements made at different time points during gestation. In our studies we have assessed different prenatal parameters in different patient populations throughout gestation, and found that prenatal counselling based on these parameters (e.g. regression of a CLM >27 weeks GA, or development of foetal hydrops) has to be adapted throughout gestation. Preferably, expecting parents are counselled before 24 weeks' gestation, which is the legal term for termination of pregnancy in the Netherlands. However, if it turns out that a better prediction is possible ≥24 weeks GA, one could wonder whether this strict legal term should be adhered to with regard to foetuses with severe abnormalities. Moreover, uncertainty about postnatal outcome <24 weeks could possibly lead to unnecessary terminations of pregnancy.

We have shown the importance of a multidisciplinary approach for the detection and counselling of surgical congenital anomalies. Paediatric specialists regularly consult a different patient population than foetal medicine specialists do. The potential outcome should be assessed from both perspectives to get a full understanding of the patient population. Multidisciplinary collaboration increases uniformity in prenatal counselling and perinatal management, and ensures ongoing clinical research to further develop models for prenatal prediction in order to improve care for these patients.

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CHAPTER 11

Summary | Samenvatting

SUMMARY

Foetuses with a congenital diaphragmatic hernia (CDH), congenital lung malformation (CLM) or giant omphalocele (GO) are at risk of impaired pulmonary vascular development and pulmonary hypoplasia. If impairments occur, they are also at risk of developing respiratory morbidities such as pulmonary hypertension (PH) of variable duration and/or chronic lung disease (CLD). This thesis describes the study of foetal ultrasound parameters for prediction of postnatal outcome in these patients with a congenital anatomical malformation. The described studies were conducted to improve the prenatal prediction of perinatal and postnatal outcomes, and to provide tools for a more patient-specific counselling. The introduction to this thesis, which is in two parts, is described in **Chapter 1.**

The thesis consists of two parts. **Part I** focuses on the usefulness of prenatal ultrasound parameters for the prediction of postnatal survival, treatment and morbidities. In **part II**, the use of these ultrasound predictors by different medical specialists is discussed.

PART I Prenatal prediction of postnatal outcome

Chapter 2 describes the validation of the defect diameter/abdominal diameter (DD/DA)-ratio and the omphalocele circumference/abdominal circumference (OC/AC)-ratio for the prediction of postnatal surgical closure in 24 foetuses with an isolated omphalocele prior to 24 weeks' gestational age. Primary closure was possible in all cases (n=11) without liver protruding through the abdominal wall defect. The OC/AC-ratio better predicted type of postnatal surgical closure than did the DD/DA-ratio; an OC/AC-ratio >0.82 predicted delayed closure. The OC/AC-ratio was then validated throughout gestation in 63 foetuses with an omphalocele (**Chapter 3).** We concluded that the optimal cut-off values for prediction of postnatal surgical closure decreased with increasing gestational age (GA) from 0.69 to 0.63; an association between the trend of the OC/AC-ratio and surgical closure was not found. For the prediction of survival, the OC/AC-ratio is of predictive value from 17 weeks onwards. In the survivors, the OC/AC-ratio declined more steeply between the first and the beginning of second trimester than in the non-survivors. Ninety-seven percent of the infants who underwent primary closure of the defect survived. All non-survivors developed CLD, and 89% of them showed herniation of the liver. A counselling flowchart regarding type of closure and corresponding survival based on the OC/AC-ratio and presence of liver herniation is presented in this chapter. The OC/AC-ratio in foetuses with an omphalocele as part of a syndrome or chromosomal abnormality overall was significantly smaller than that in foetuses with an isolated omphalocele. In the former group, there were fewer cases of liver herniation. Intrauterine death or neonatal death could not be predicted from the OC/AC-ratio.

Chapter 4 describes a multicentre study we conducted to validate for survival the observed-versus-expected lung-to-head (O/E LHR)-ratio in isolated left-sided CDH patients, and to establish the presence of CLD in survivors since the introduction of standardized neonatal treatment in the EURO consortium. We found that the first measured O/E LHR-ratio predicts a patient's survival, the postnatal defect size and development of CLD. In addition, for almost 80% of patients, the category for prediction of severity of pulmonary hypoplasia remained stable from 20 weeks' gestation onwards. Since the O/E LHR is an indirect method of assessing lung functionality, we started the FLOW (Foetal Lung Observations and ultrasound Waveforms) study to analyse the development of the pulmonary vasculature by use of ultrasound. The results of the pulmonary vascular volume measurements by use of 3D virtual reality ultrasound are described in **Chapter 5**. The contralateral pulmonary vascular volume (PVV) in foetuses with left sided CDH (L-CDH, n=51) was significantly smaller than that in healthy controls (n=72), even when correcting for lung size by dividing the PVV by the lung volume (LV). Both the interrater and intrarater variability of the measurement of the PVV were very low. Regarding the group of neonates with L-CDH born >34 weeks GA, the PVV <24 weeks' gestation in non-survivors was smaller than that in survivors.

In foetuses with a CLM, we aimed to predict the postnatal outcome in mostly conservatively managed neonates. Results of this study are presented in **Chapter 6**. Fourteen of the 48 neonates (18%) required respiratory support within 24 hours after birth, seven (15%) needed a surgical intervention within 28 days after birth due to respiratory problems, and another nine (19%) needed surgery within two years after birth. We found that prenatal regression of a CLM does not rule out respiratory problems within the first 24 hours after birth; the CLM volume ratio (CVR) >30 weeks' gestation was not predictive for the need for respiratory support. A high CVR (>0.46 after 30 weeks GA) and a persistent mediastinal shift from 20 weeks onwards are associated with a higher probability of need for surgical intervention. No concordance was found between prenatal appearance (microcystic/macrocystic/mixed) and postnatal type of CLM. Yet, all neonates with a prenatal macrocystic congenital pulmonary airway malformation (CPAM) needed respiratory support after birth and a surgical resection within 28 days after birth. In almost 40% of those with a microcystic CPAM, a postnatal diagnosis of congenital lobar overinflation was made. Because the descriptions of the prenatal appearance of a CLM differed between ultrasonographers, we devised a standardized ultrasonography report for assessment of a CLM. Since need for respiratory support within 24 hours after birth cannot be excluded based on prenatal parameters, we recommend a delivery in centres with surgical expertise and at least 24 hours' observation.

PART II Prenatal parameters in perinatal care

Chapter 7 presents the results of an assessment of differences between medical specialists (obstetricians, foetal medicine specialists, paediatric intensivists and paediatric surgeons) regarding the prediction of the probability of primary closure of an omphalocele based on maternal obstetric and medical history, gestational age, prenatal ultrasound image, contents of the omphalocele, defect size in millimetres and the DD/DA-ratio and OC/AC-ratio. In most cases, the specialists based their predictions on the omphalocele content, followed by the OC/AC-ratio; a novel unpublished ratio at the time the questionnaire was filled out. The inter-consultant variability in the assessment of the likelihood of primary closure was low. Although obstetric consultants tended to be more inclined to counsel higher likelihood of primary closure compared to paediatric consultants, the overall tendency was to be more negative towards chances of primary closure. After publication of the predictive value of the OC/AC-ratio (Chapter 2) and assessment of the differences between medical specialists, we aimed to compare the prenatal frame of reference of an omphalocele with the one after birth up to 2 years of age. This study is discussed in **Chapter 8**. The prenatal characteristics of a retrospective cohort from 2000 through 2012, included 70 continuing omphalocele cases out of 126 prenatal diagnoses. An intrauterine foetal demise occurred in 20 (16%) cases, resulting in 50 (40%) live born infants, of whom 35 (28%) survived ≥2 years. In isolated cases with an OC/AC-ratio ≥0.82, the survival rates were lower than in foetuses with an OC/AC-ratio <0.82 – in concordance with the research described in Chapter 3. In 19 cases, the omphalocele was diagnosed after birth; thus there were 69 live born postnatal cases, with a survival rate of 45% (n=32). This finding warrants careful review of the criteria for patient inclusion in papers reporting survival rates. Since we aim to counsel future parents also on the postnatal morbidity, we assessed length of stay (LOS), development of CLD, physical growth and neurodevelopment in survivors with an omphalocele. The infants with a giant omphalocele had a seven times longer LOS than those with a minor omphalocele, more than half of these children developed CLD, and over 80% developed a delay in motor development. There was no significant difference in growth parameters and mental development between the groups at the age of 2 years.

Application of the prenatal O/E LHR in the postnatal management of L-CDH foetuses is discussed in **Chapter 9**. Current CDH guidelines recommend postnatal resuscitation in all neonates with a L-CDH. In our tertiary referral centre we opted for a spontaneous breathing approach for foetuses with a L-CDH and an O/E LHR >50% and intra-abdominal position of the liver. This approach was successful in six out of the fifteen included infants. Nine of the infants required intubation at birth, and two others for several hours after birth. Delayed intubation did not seem to negatively affect outcome.

Chapter 10 concludes with the general discussion reflecting on the combined results presented in this thesis. It offers a broader perspective, relates findings to perspectives for use in daily practice and offers suggestions for future studies. **Chapter 11** provides an English and Dutch summary of this thesis.

SAMENVATTING

Ongeboren kinderen met een congenitale hernia diafragmatica (CDH: congenital diafragmatic hernia), een congenitale longafwijking (CLM: congenital lung malformation) of een 'giant' omphalocele (GO) lopen het risico op een gestoorde ontwikkeling van de long(vascularisatie). Daarmee kunnen op de lange termijn ook ademhalingsaandoeningen zoals pulmonale hypertensie (PH) en/of chronische longziekte (CLD: chronic lung disease) ontstaan. Dit proefschrift beschrijft onderzoek naar prenatale echoscopische parameters voor het voorspellen van postnatale uitkomsten van deze kinderen. Het onderzoek had als doel om de prenatale voorspelling van de perinatale en postnatale uitkomst te verbeteren en om instrumenten aan te reiken voor een meer patiënt-specifieke counseling. De inleiding tot dit proefschrift in twee delen wordt beschreven in **Hoofdstuk 1**.

Deel I richt zich op de bruikbaarheid van prenatale echoscopische parameters voor het voorspellen van de postnatale overlevingskans, de nodige behandeling en eventuele bijkomende (respiratoire) aandoeningen. In **deel II** wordt het gebruik van deze echoscopische parameters door verschillende medisch specialisten bij het voorspellen van deze aspecten besproken.

DEEL I Prenatale voorspelling van postnatale uitkomst

In **Hoofdstuk 2** wordt de voorspellende waarde van de defectdiameter/buikdiameter (DD/DA)-ratio en de omphalocele omtrek/abdominale omtrek (OC/AC)-ratio voor het type chirurgische sluiting van de buikwand beschreven bij 24 foetussen met een geïsoleerde omphalocele met een zwangerschapsduur <24 weken. Een primaire sluiting is mogelijk in alle gevallen waarin geen lever aanwezig is in de cele. De OC/AC-ratio heeft een betere voorspellende waarde hiervoor dan de DD/DA-ratio; een OC/AC-ratio >0.82 voorspelt een secundaire sluiting. De OC/AC-ratio werd vervolgens in **Hoofdstuk 3** gevalideerd gedurende de gehele zwangerschap in alle 63 foetussen met een omphalocele. We concludeerden dat de optimale afkapwaarden voor het voorspellen van het type chirurgische sluiting afnemen met de toenemende zwangerschapsduur van 0,69 tot 0,63, maar er werd geen associatie gevonden tussen de trend van de OC/AC-ratio en het type chirurgische sluiting. Voor het voorspellen van overleving is de OC/AC-ratio van voorspellende waarde vanaf 17 weken; en bij overlevenden vonden we een sterkere daling in OC/AC-ratio tussen het eerste trimester en het begin van het tweede trimester in vergelijking met niet-overlevenden. Een primaire sluiting van het defect was geassocieerd met een overlevingspercentage van 97%. Alle niet-overlevenden ontwikkelden CLD, en 89% van hen vertoonde een herniatie van de lever. In dit hoofdstuk wordt een stroomschema voor counseling gepresenteerd met betrekking tot het type sluiting en de

bijbehorende overleving op basis van de OC/AC-ratio en de aanwezigheid van herniatie van de lever. De OC/AC-ratio in foetussen met een omphalocele als onderdeel van een syndroom of chromosomale afwijking is over het algemeen significant kleiner dan in foetussen met een geïsoleerde omphalocele; de eerstgenoemden vertonen ook minder herniatie van de lever. Op basis van de OC/AC-ratio kon het optreden van intra-uteriene sterfte of neonatale sterfte niet worden voorspeld.

Hoofdstuk 4 beschrijft een multicenterstudie ter validering van de voorspellende waarde voor overleving van de observed-versus-expected lung-to-head (O/E LHR)-ratio bij patiënten met een geïsoleerde linkszijdige CDH (L-CDH), sinds de introductie van gestandaardiseerde neonatale behandeling in het EURO-consortium. Een tweede doel was het onderzoek naar de voorspellende waarde van de O/E-LHR voor de aanwezigheid van CLD bij overlevenden. Het bleek dat de eerste gemeten O/E LHR zowel de overlevingskans als ook de postnatale defectgrootte en ontwikkeling van CLD bij een patiënt met een geïsoleerde L-CDH voorspelt. Voor bijna 80% van de patiënten bleef de categorie voor het voorspellen van de ernst van pulmonale hypoplasie stabiel vanaf 20 weken zwangerschap. Omdat de O/E LHR een indirecte methode is om de longfunctionaliteit te beoordelen, zijn we de FLOW (Foetale Long OntWikkeling) studie gestart om de ontwikkeling van de longvascularisatie te analyseren met behulp van echografisch onderzoek. De resultaten van de volumemetingen van de longvaten met behulp van 3D virtual reality echografie zijn beschreven in **Hoofdstuk 5**. De foetussen met een L-CDH (n= 51) hadden een significant kleiner contralateraal longvaatvolume dan de gezonde controles (n=72), zelfs na correctie voor de grootte van het longvolume. Zowel de interbeoordelaarsvariabiliteit als de intrabeoordelaarsvariabiliteit voor het meten van de PVV was zeer laag. Binnen de groep neonaten met L-CDH geboren na 34 weken zwangerschapsduur was het longvaatvolume gemeten vóór 24 weken zwangerschapsduur bij de niet-overlevenden significant kleiner dan bij de overlevenden.

De resultaten van een studie naar de postnatale uitkomst bij 48 voornamelijk conservatief behandelde neonaten met CLM worden gepresenteerd in **Hoofdstuk 6**. Veertien van hen (18%) hadden ademhalingsondersteuning nodig binnen 24 uur na de geboorte zeven (15%) hadden binnen 28 dagen na de geboorte een chirurgische ingreep nodig vanwege ademhalingsproblemen, en nog eens negen (19%) moesten na deze 28 dagen – maar binnen twee jaar – worden geopereerd. Een prenatale afname van de grootte van een CLM bleek ademhalingsproblemen binnen de eerste 24 uur na de geboorte niet uit te sluiten; de CLM-volumeratio (CVR) na 30 weken zwangerschapsduur was niet voorspellend voor de behoefte aan ademhalingsondersteuning. Een hoge CVR (>0.46 na 30 weken zwangerschapsduur) en een aanhoudende mediastinale shift vanaf 20 weken bleken geassocieerd met een verhoogde kans op een noodzakelijke chirurgische ingreep. Er werd geen overeenstemming gevonden tussen de prenatale verschijnings-

vorm (microcysteus/macrocysteus/gemengd) en het postnatale type CLM. Toch hadden alle pasgeborenen met een prenatale macrocysteuze verschijningsvorm ademhalingsondersteuning nodig direct na de geboorte en een chirurgische resectie binnen 28 dagen. Bij een microcysteuze verschijningsvorm werd in bijna 40% van de gevallen een postnatale diagnose congenitale lobaire overinflatie (CLO) vastgesteld. Aangezien de beschrijving van de prenatale kenmerken van een CLM verschilde tussen echoscopisten hebben we een gestandaardiseerd echografierapport ontwikkeld voor de beoordeling van een CLM. Aangezien de behoefte aan ademhalingsondersteuning binnen 24 uur na de geboorte niet kan worden uitgesloten op basis van prenatale parameters, raden we een bevalling aan in een centrum met chirurgische expertise en opname voor minimaal 24 uur observatie.

DEEL II Prenatale paremeters gebruikt in perinataal beleid

In **Hoofdstuk 7** worden de resultaten gepresenteerd van een onderzoek naar de verschillen tussen medisch specialisten (gynaecologen, foetale geneeskunde specialisten, kinderintensivisten en kinderchirurgen) bij het voorspellen van de kans op een primaire chirurgische sluiting van een omphalocele op basis van de maternale obstetrische en medische voorgeschiedenis, zwangerschapsduur, prenataal echobeeld, inhoud van de omphalocele, defectgrootte in millimeters en de DD/DA-ratio en OC/AC-ratio. In de meeste gevallen koos men de inhoud van omphalocele om de voorspelling op te baseren, gevolgd door de OC/AC-ratio; een ratio die bij het invullen van de vragenlijst nog niet gepubliceerd was en/of bekend was bij de medisch specialisten. De variabiliteit tussen de specialisten in de beoordeling van de waarschijnlijkheid van een primaire sluiting was laag. En hoewel prenatale specialisten meer geneigd waren om een hogere kans op primaire sluiting in te schatten vergeleken met de postnatale specialisten, zagen we een algemene tendens om negatiever te zijn ten aanzien van de kans op primaire sluiting. Na publicatie van de voorspellende waarde van de OC/AC-ratio (**Hoofdstuk 2**) en beoordeling van de verschillen tussen medisch specialisten wilden we het prenatale referentiekader van een omphalocele vergelijken met dat na de geboorte tot 2 jaar. Deze studie wordt besproken in **Hoofdstuk 8**. Het ging hierbij om een retrospectief cohort van 2000 tot en met 2012 van 70 doorgaande zwangerschappen met een omphalocele van in totaal 126 prenatale diagnoses. Een intra-uteriene vruchtdood trad op bij 20 (16%) foetussen; en 50 (40%) foetussen waren dus levend geboren. Hiervan overleefden er 35 (28%) ≥2 jaar. Bij geïsoleerde gevallen met een OC/AC-ratio ≥0.82 was het overlevingspercentage lager dan dat bij foetussen met een OC/AC-ratio <0.82. Dit is in overeenstemming met het onderzoek beschreven in hoofdstuk 3. In 19 casus werd de omphalocele gediagnosticeerd na de geboorte; in totaal ging het dus om 69 levendgeborenen met een overlevingspercentage van 45% (n=32). Dit rechtvaardigt een zorgvuldige beoordeling van de criteria voor inclusie van patiënten in wetenschappelijke artikelen die over-

levingspercentages rapporteren. Omdat we toekomstige ouders ook willen adviseren over de kans op bijkomende aandoeningen na de geboorte, hebben we de opnameduur, het ontstaan van CLD, de fysieke groei en de neurologische ontwikkeling bij overlevende kinderen met een omphalocele beoordeeld. We ontdekten dat de opnameduur van kinderen met een 'giant' omphalocele zeven keer langer was in vergelijking met kinderen met een kleine omphalocele. In meer dan de helft van alle gevallen was CLD ontstaan, en meer dan tachtig procent ontwikkelde een achterstand in de motorische ontwikkeling. Op 2-jarige leeftijd werd geen significant verschil gevonden in groeiparameters en mentale ontwikkeling tussen kinderen met een 'giant' omphalocele en kinderen met een kleine omphalocele.

De toepassing van de prenatale O/E LHR in het perinataal beleid voor L-CDH-foetussen wordt besproken in **Hoofdstuk 9**. Volgens de huidige CDH-richtlijnen wordt postnatale intubatie uitgevoerd bij alle pasgeborenen met een L-CDH. In ons tertiair verwijscentrum hebben we gekozen we voor een 'spontane ademhalingsaanpak 'wanneer de O/E LHR groter is dan 50% en de lever in intra-abdominale positie is. Deze aanpak was succesvol bij bijna de helft (zes van de vijftien) van de geïncludeerde neonaten. Negen van alle vijftien neonaten moesten toch bij de geboorte worden geïntubeerd en nog twee anderen enkele uren na de geboorte. Uitstel van intubatie lijkt de uitkomst niet negatief te beïnvloeden.

Hoofdstuk 10 wordt afgesloten met de algemene discussie, die ingaat op de gecombineerde resultaten die in dit proefschrift worden gepresenteerd. Deze biedt een breder perspectief, relateert bevindingen aan mogelijkheden voor gebruik in de dagelijkse praktijk en biedt suggesties voor toekomstig onderzoek. **Hoofdstuk 11** geeft een Engelse en Nederlandse samenvatting van dit proefschrift.

PART IV

APPENDICES

List of publications
About the author
PhD portfolio
Dankwoord

LIST OF PUBLICATIONS

Erwin Brosens, **Nina C J Peters**, Kim S Van Weelden, et al. Unravelling the genetics of Congenital Diaphragmatic Hernia: an ongoing challenge. Front Pediatr. 2022 Feb 3;9;800915.

Nina C.J. Peters, Titia E. Cohen-Overbeek, Katinka Weller et al. Measurement of pulmonary vascular volume by use of 3D-VR in foetuses with left sided congenitale diaphragmatic hernia and healthy controls. *In submission*

Kevin P Cinca, Catherine A de Planque, **Nina CJ Peters**, et al. Prenatal ultrasound parameters of twins with sagittal suture craniosynostosis question mechanical constraint as the leading cause. J Craniofac Surg. *Accepted for publication*

Katinka Weller, **Nina C.J. Peters**, Joost van Rosmalen, et al. Prenatal stomach position and volume in relation to postnatal outcomes in left-sided congenital diaphragmatic hernia. Prenat Diagn. 2022 Mar;42(3):338-347.

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Bazelmans M, **Peters NC**, Koning AH, et al. Power Doppler rendering of fetal bilateral accessory renal arteries in virtual reality. Ultrasound Obstet Gynaecol. 2014; 44(3):375-6.

Prick BW, Steegers EAP, Jansen AJG, Hop WCJ, Essink-Bot ML, **Peters NCJ**, et al. Well being of Obstetric patients on Minimal Blood transfusions (WOMB trial). BMC Pregnancy and Childbirth. 2010, 10:83.

Brusse IA, **Peters NCJ**, Steegers E.A.P, et al. Electroencephalogram during normotensive and hypertensive pregnancy: a systematic review. Obstet Gynecol Surv. 2010 Dec; 65(12):794-803.

Peters NCJ, Duvekot JJ. Carbetocin for the prevention of postpartum hemorrhage: a systematic review. Obstet Gynecol Surv. 2009 Feb; 64(2):129-35.

ABOUT THE AUTHOR

Nina Catharina Josephina Peters was born on October 25th 1984 in Maastricht. She attended the Montessori College Maastricht, where she completed her atheneum in 2003. In the same year she commenced medical school at the Erasmus University Medical Centre in Rotterdam. During her research internship in 2007 on the use of carbetocin to prevent primary postpartum haemorrhage under supervision of dr. Hans Duvekot and on the Electro-encephalogram (EEG) during pregnancy under supervision of dr. Ingrid Brussé, her enthusiasm for research and obstetrics and foetal medicine was sparked. After graduation from medical school in 2010, she started working at the department of Obstetrics and Gynaecology, subdivision Obstetrics and Foetal Medicine. A year later she began her PhD project on prenatal prediction of postnatal outcome in foetuses at risk for development of chronic lung disease (prof. dr. Eric Steegers and prof. dr. Dick Tibboel (promotores) and dr. Titia Cohen-Overbeek and dr. Alex Eggink (co-promotores)). After her dissertation she will continue working as a senior foetal medicine specialist at the Erasmus University Medical Centre in Rotterdam. Nina Peters lives in Rotterdam with Wan Zheng Chiu and together they have two daughters, Noa (2015) and Milu (2018).

PHD PORTFOLIO

	Year	Workload (ECTS)
General courses		
Short introduction course on statistics & survival analysis for MDs	2010	0.5
Basic Introduction course on SPSS	2011	0.3
Biomedical English Writing and Communication	2012	4.0
Systematic literature search in PubMed and other Databases	2013	2.0
CPO short course "Methodologie voor Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen"	2013	1.0
BROK (Basiscursus Regelgeving Klinisch Onderzoek)	2014	1.5
Research Integrity course	2014	0.3
Specific courses (e.g. Research school, Medical Training)		
Theoretical course ultrasound examination – Hogeschool Rotterdam	2010	1.0
DIN (Digitale individuele Nascholing) – Stichting Prenatale Screening	2010	0.3
Educational day on clinical genetics for residents Gynaecology	2010	0.5
SEO (Structureel Echoscopisch Onderzoek) masterclass	2010	0.3
Congenital anomalies and fetal echocardiography – ISUOG London	2010	0.6
Introduction to clinical research – NIHES winter programme	2012	0.9
Biostatistics for clinicians – NIHES winter programme	2012	1.0
Regression analysis for clinicians – NIHES winter programme	2012	1.9
Survival analysis for clinicians – NIHES winter programme	2012	1.9
Neurosonography – UMC Utrecht	2012	0.6
Longterm outcome congenital malformations – ESPNIC	2013	0.3
CDH (Congenital Diafragmatic Hernia) Workshop – Sophia Children's Hospital	2013	0.2
Open clinica introduction – Erasmus MC	2014	0.2
DIN 2.0 (Digitale individuele Nascholing) – Stichting Prenatale Screening Zuidwest Nederland (SPSZN)	2016	0.3
Seminars and workshops		
Symposium Paediatric cardiology – Erasmus MC	2010	0.2
Symposium Trisomie 13/18	2011	0.2
Symposium Prenatal screening and diagnostics – Reinier de Graaf Gasthuis Delft	2011	0.2
Symposium Prenatal screening	2011	0.2
Symposium "Early Pregnancy" – Erasmus MC	2013	0.2
Symposium "Spina Bifida" – Sophia Children's Hospital	2014	0.2
Reference meeting of the Department of Plastic Surgery of the Sophia Children's Hospital	2020	0.1
(Inter)national conferences		
ISUOG World Congress Ultrasound in Obstetrics and Gynecology: 2 oral presentations	2011	1.0
ISUOG World Congress Ultrasound in Obstetrics and Gynecology: 1 poster	2012	1.0

	Year	Workload (ECTS)
ESPNIC Annual Meeting of the European Society of Paediatric and Neonatal Intensive Care: 2 posters	2013	1.0
ISUOG World Congress Ultrasound in Obstetrics and Gynecology: 1 oral presentation	2014	1.0
DOHaD World Congress International Society for Developmental Origins of Health and Disease: 1 poster	2017	1.0
ISPD International Conference on Prenatal Diagnosis and Therapy: 2 posters	2018	1.0
ISUOG World Congress Ultrasound in Obstetrics and Gynecology: 3 oral presentations	2019	1.0
Teaching		
Prenatal screening for medical students	2010-2021	3.0
SEO (Structureel Echoscopisch Onderzoek) masterclass hands-on	2013-2022	2.0
Foetal spine for medical students	2013-2020	2.0
Supervising medical student	2013-2014	2.0
3D ultrasound for physicians of the department of Obstetrics and Prenatal Medicine at the Erasmus University Medical Center	2014	0.2
Ultrasound diagnosis of a CCAM for the regional Case conference of the SPSZN ("Stichting Prenatale Screening Zuid-west Nederland")	2014	0.2
Supervising research master medical student (21 weeks)	2014	1.0
Prenatal Diagnosis of lung hypoplasia for the International Society for Ultrasound in Obstetrics and Gynecology in London: Neck and Thorax	2014	1.0
Prenatal anomalies of the head/neck for medical students of the minor 'From head to hands' Erasmus MC	2015	0.2
Prenatal Diagnosis of thoracic anomalies for obstetricians of the GUO (geavanceerd ultrageluidsonderzoek) course Erasmus MC	2016	0.2
Prenatal Diagnosis of thoracic anomalies for gynaecologists in training	2016	0.1
Prenatal Diagnosis of spine anomalies for obstetricians of the GUO (geavanceerd ultrageluidsonderzoek) course Erasmus MC	2017	0.2
Prenatal anomalies of the head/neck for medical students of the minor 'From head to hands' Erasmus MC	2017	0.2
Prenatal Diagnosis of thoracic anomalies for obstetricians, neonatologists and clinical geneticists of the GUO (geavanceerd ultrageluidsonderzoek) course Erasmus MC	2018	0.2
3D imaging techniques for obstetricians, neonatologists and clinical geneticists of the GUO (geavanceerd ultrageluidsonderzoek) course Erasmus MC	2019	0.2
Lecture on multidisciplinary review of congenital anomalies (prenatal ultrasound and pathology) for medical students	2019	0.2
Workshop Prenatal Counselling for medical students of the minor 'Kinderwens' Erasmus MC	2019	0.2
Prenatal anomalies of the head/neck for medical students of the minor 'From head to hands' Erasmus MC	2019	0.2
Lecture on prenatal diagnostics of fetal pulmonary abnormalities at the Pediatric Thoracic Symposium Paola Pediatric Hospital in Antwerp	2019	0.2

	Year	Workload (ECTS)
Prenatal Diagnosis of thoracic anomalies for obstetricians, neonatologists and clinical geneticists of the GUO (geavanceerd ultrageluidsonderzoek) course Erasmus MC	2020	0.2
Prenatal anomalies of the head/neck for medical students of the minor 'From head to hands' Erasmus MC	2020	0.2
Workshop Prenatal Counselling for medical students of the minor 'Kinderwens' Erasmus MC	2020	0.2
SEO Masterclass theoretic lecture (2 presentations)	2020	0.2
Lecture on prenatal diagnosis of craniosynostosis at the IGO-Doelen congress in Rotterdam	2021	0.2
Lecture 'Knobology – advanced' – BEN (Beroepsvereniging Echoscopisten Nederland)	2021	0.2
Other		
Research meeting Obstetrics (weekly)	2010-2021	5.0
Outpatient clinic meeting Prenatal Medicine (weekly)	2010-2021	5.0
Multidisciplinary meeting Obstetrics and Pediatrics (weekly)	2010-2021	5.0
Fetal pathology meeting (monthly)	2010-2021	2.0
WFE/WPDT meeting: oral presentation	2012	0.2
Abdominal wall defects patient day: oral presentation	2011	0.2
Research meeting Paediatric Surgery and Intensive Care: oral presentation	2011	0.2
KGKC meeting: oral presentation	2013	0.2
Wladimiroff researchday	2013-2014	0.4
WFE/WPDT meeting: oral presentation (2015)	2015	0.2
VISUOG – Visual encyclopedia for medical professionals and patients: chapter about omphaloceles	2019	0.2
Lecture on prenatal diagnosis in left sided congenital diaphragmatic hernia at the Grand Round of the Sophia's Children's Hospital	2020	0.2
ECTS = European Credit Transfer and Accumulation System 1 ECTS represents 28 hours		61.2

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