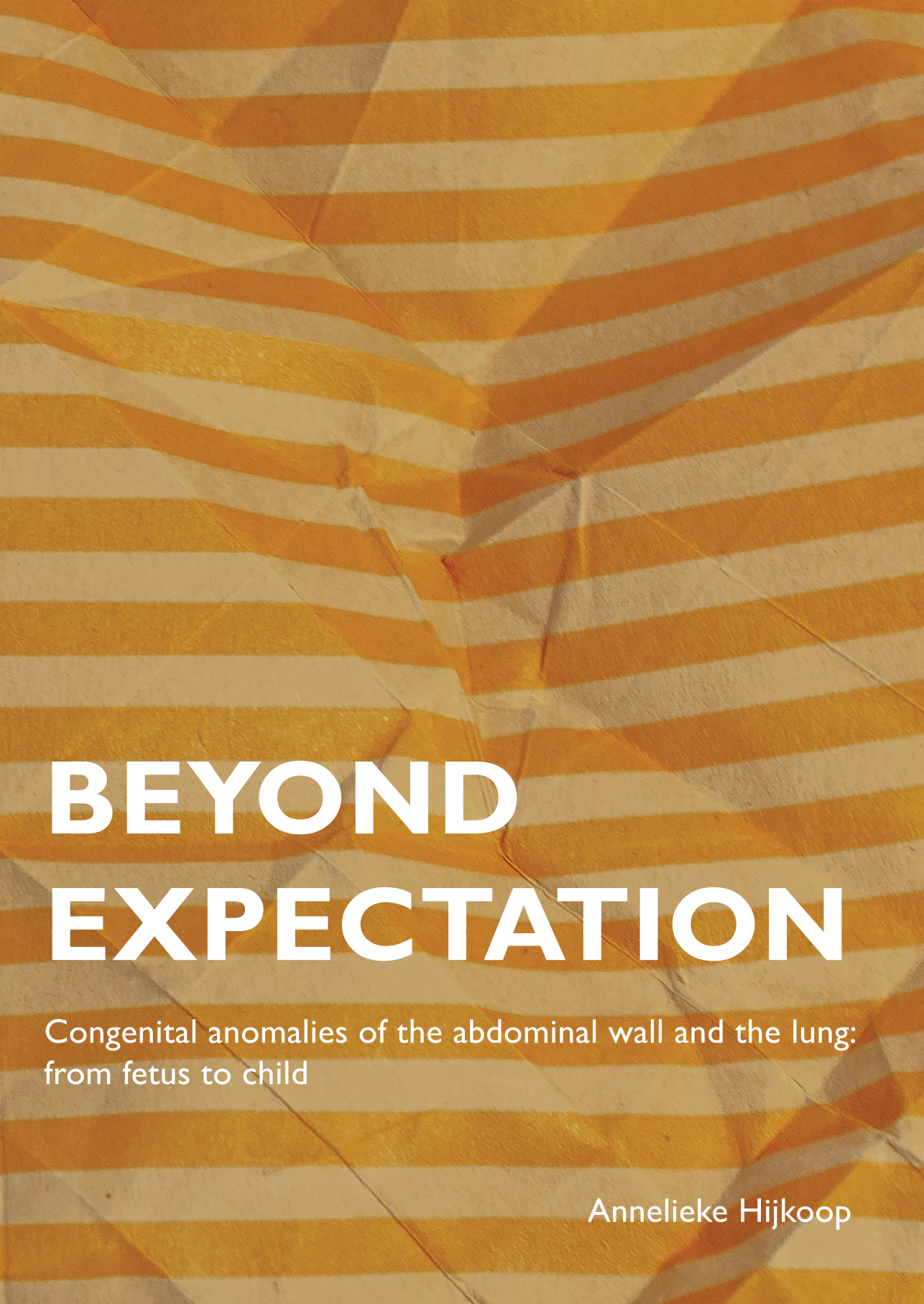

BEYOND EXPECTATION

Congenital anomalies of the abdominal wall and the lung: from fetus to child

Annelieke Hijkoop

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Beyond Expectation

Congenital anomalies of the abdominal wall and the lung:
from fetus to child

Voorbij verwachting

Aangeboren afwijkingen van de buikwand en de long:
van foetus tot kind

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INTRODUCTION



1

General introduction

Major structural or genetic congenital anomalies affect approximately 3% of births in Europe.[1] Since the introduction of prenatal screening methods such as the 20-week fetal anomaly scan (the Netherlands, 2007), 40% of major structural congenital anomalies are detected prenatally.[2] This offers the possibility of early parental counseling and of optimizing postnatal care, provided that sufficient information is available on the implications of the fetal anomaly on survival, hospital outcome, and long-term consequences.

As of yet, limited data are available on the long-term outcome of children with either an abdominal wall defect (AWD; i.e. gastroschisis or omphalocele) or a congenital lung malformation (CLM). The prenatal detection rates of these anomalies are high; approximately 90% of AWD are diagnosed prenatally,[2] and previous research reported a three-fold increase in prenatally detected CLM between 1994 and 2012.[3-5] In the past, the follow-up of these children after birth was characterized by a monodisciplinary approach, and research focused on survival rates and surgical outcome. As medical possibilities and survival rates have improved, the focus of research is shifting towards the long-term implications.

Twenty years ago, a longitudinal multidisciplinary follow-up program was initiated at the Erasmus MC-Sophia Children's Hospital as standard of care for children with structural congenital anomalies; in particular for those with any of the surgical index diagnoses as described by Ravitch.[6, 7] Data from this prospective follow-up program have been collected, and analyzed in numerous papers published by our group.[6, 8-15] The long-term outcomes of children with AWD or CLM have not yet been described.

When counseling expectant parents, it is important to know how to interpret certain prenatal characteristics. Adequate parental counseling should also include expectations of the child's long-term outcome. Many surviving infants with AWD or CLM experience feeding difficulties, respiratory problems and infections, which put them at risk for long-term impairments.

General key questions

- Can we identify prenatal characteristics that contribute to the prediction of postnatal morbidity?
- What kind of long-term morbidity is seen in these children?

Gastroschisis

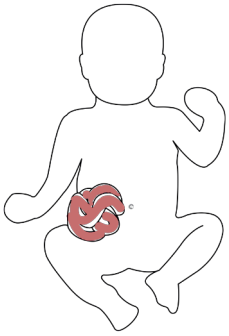

Figure 1 Gastroschisis

The term *gastroschisis* was introduced by the Italian pathologist Cesare Taruffi in 1894 to describe all types of congenital AWD.[16] The currently used classifications of gastroschisis and omphalocele were established by Thomas Moore and George Stokes in 1953, on the basis of the location of the umbilical cord, the presence or absence of a covering membrane, and the appearance of eviscerated intestines.[17]

Gastroschisis is a congenital AWD, usually located on the right side of the umbilical cord. Abdominal organs herniate through the defect, and are – in contrast with omphalocele – not covered by a membrane (figure 1). Gastroschisis occurs in approximately 2.6 per 10 000 births.[1] It is associated with accumulation of a variety of maternal stressor exposures, including young maternal age, smoking, alcohol use, illicit drug use, infections, and use of several medications.[18] The mothers typically have a lower body mass index,[19] and are more likely to be nulliparous.[20]

Infants with gastroschisis require surgery shortly after birth, by means of primary closure if possible, or by secondary closure (e.g. by placing a silastic silo to allow gradual reduction into the abdominal cavity prior to definite closure).[21] Although survival rates are now over 90%,[22] children with gastroschisis are at high risk of morbidity – especially when additional intestinal defects are diagnosed. Gastroschisis complicated by intestinal atresia, necrosis, perforation or volvulus is therefore called 'complex gastroschisis'; this occurs in approximately 17% of cases.[23, 24] It often takes longer than usual to establish full enteral feeding in these children, they are more likely to develop complications such as sepsis, intestinal failure and parenteral nutrition-related cholestasis, and need to stay longer in hospital.[23-25]

Prenatal prediction of complex gastroschisis

If the presence of complex gastroschisis could be predicted prenatally, parental counselling would be more complete. Unfortunately, it is difficult to distinguish simple from complex gastroschisis on prenatal ultrasound. The association between two-dimensional (2D) prenatal ultrasound findings (such as bowel and stomach dilatation) and complex gastroschisis has been investigated in a number of retrospective studies, which showed conflicting results.[26] Three-dimensional (3D) ultrasound has been proposed to be superior to 2D ultrasound in fetal imaging.[27, 28] The fetal stomach volume could perhaps be measured more accurately using 3D ultrasound, and thus facilitate predicting complex gastroschisis. To date there are no studies, however, to support this hypothesis.

Long-term outcome

In addition to the high risk of morbidity in early life, many neonates with gastroschisis are born small for gestational age[29, 30] or preterm.[22] These characteristics give reason for concern regarding these children's long-term outcome, such as physical growth, mental development, and motor function. Unfortunately, relevant information in the literature is scarce.

The two studies on physical growth that took into account the type of gastroschisis (i.e. simple or complex) found that children with complex gastroschisis had lower weight than those with simple gastroschisis at the ages of 12 months[31] and 5-17 years.[32] Studies comparing mental development and motor function between infants with simple and complex gastroschisis are still lacking.

Outcomes of children born with gastroschisis at school age (i.e. 4-17 years) vary between studies. Most studies reported normal health status.[33-35] Other results were contradictory: some studies showed normal intelligence,[36-38] motor function[39, 40] or behavior,[38, 41] whereas others found intellectual delay,[41] problems regarding motor skills,[41] or behavioral problems.[36, 37]

Specific key questions

- Can we identify prenatal 2D or 3D ultrasound markers of complex gastroschisis? (**chapters 2 and 3**)
- How do infants with either simple or complex gastroschisis grow up in terms of physical growth, mental development, and motor development? (**chapter 3**)
- How do parents rate their child's motor function, cognition, health status, quality of life and behavior at school age? (**chapter 4**)

Omphalocele

Omphalocele is a midline congenital AWD; abdominal organs protrude through the opening into the umbilical cord, and are covered by a membrane (figure 2). Omphalocele occurs in approximately 3.4 per 10 000 births.[1] It is associated with either young or advanced maternal age (i.e. <20 or >34 years),[42] and several maternal stressor exposures, including smoking,[43] use of

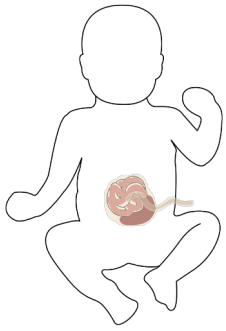

Figure 2 Omphalocele

alcohol,[43] and use of several medications.[44, 45] Other than in the case of gastroschisis, women who are pregnant with a fetus with omphalocele are more likely to be obese,[19, 46] and to be pregnant with multiple fetuses.[42, 47]

Prenatal and postnatal frames of reference

Survival rates up to 90% have been reported for live-born infants with isolated omphalocele.[42] However, approximately 75-80% of fetuses with omphalocele present with chromosomal abnormalities and/or additional congenital anomalies.[42, 48] This leads to a high prevalence of termination of pregnancy and intrauterine death. The frame of reference of prenatal specialists could therefore be different from that of pediatric surgeons and pediatricians.

Prenatal prediction of the type of surgical closure

After birth, an omphalocele is usually defined as giant if the defect is ≥5cm at primary evaluation, with the liver (partly) protruding.[49] Otherwise, it is called minor omphalocele. Minor omphaloceles can usually be closed primarily, within 48 hours after birth. In contrast, closure of giant omphaloceles is usually delayed in view of the visceroabdominal disproportion. In the Erasmus MC-Sophia Children's hospital, most children with a giant omphalocele are treated conservatively; this implies that after epithelialization of the omphalocele, the abdominal wall is reconstructed using the component separation technique by Ramirez.[50, 51] This is usually planned before 12 months postnatal age.[50]

Several prenatal ultrasound parameters have shown to be predictive of the type of surgical closure (i.e. primary or delayed); these include the ratio between omphalocele diameter (OD) and abdominal circumference (AC; OD/AC-ratio),[52, 53] and the ratio between omphalocele circumference (OC) and AC (OC/AC-ratio).[54, 55] Three of these studies found an optimal cut-off of 0.26 (when calculating OD/AC)[52, 53] or 0.82 (0.26*π; when calculating OC/AC).[54] These studies had only one measurement per fetus available,[53] however, or included only fetuses with an isolated omphalocele.[52, 54] It is yet unclear whether the OC/AC-ratio throughout gestation is a valid predictor of type of surgical closure in all fetuses with an omphalocele, including non-isolated ones.

Long-term outcome

In addition to the need for surgery in early life, complications such as respiratory failure or feeding difficulties could negatively affect the long-term outcomes.[56] Previous research on outcome in infants with omphalocele mainly focused on those with giant omphalocele,[56-58] or did not distinguish between different types of non-cardiac structural anomalies.[59-61] Information on outcomes beyond the age of five years is limited.[40, 57, 62]

Specific key questions

- How does the prenatal frame of reference differ from that after birth? (**chapter 6**)
- Can we prenatally predict the type of surgical closure in fetuses with either isolated or non-isolated omphalocele? (**chapter 5**)
- How do infants with either minor or giant omphalocele grow up in terms of physical growth, mental development, and motor development? (**chapter 6**)
- How do parents rate their child's motor function, cognition, health status, quality of life and behavior at school age? (**chapter 7**)

Congenital lung malformations

CLM are a heterogeneous group of malformations, including congenital pulmonary airway malformation (CPAM; figure 3), bronchopulmonary sequestration (BPS), congenital lobar emphysema (CLE), bronchogenic cysts (BC), and hybrid forms of these lesions.[63]

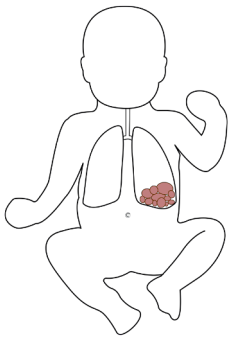

Figure 3 Congenital pulmonary airway malformation

As a result of routine fetal anomaly scanning and improved ultrasound technology, CLM are increasingly being detected prenatally.[3] The current estimated incidence is 4.2 per 10 000 births.[3]

Prenatal ultrasound evaluation of CLM focuses on the location, size, appearance of the cysts (i.e. microcystic, macrocystic, or mixed), and on the presence or absence of systemic blood supply, hydrops, and mediastinal shift. Correctly diagnosing the specific type of CLM is challenging, as fetal lungs are not aerated yet, and because different CLM can look similar on prenatal ultrasound. In addition, the postnatal classification of CLM differs from the prenatal classification; after birth, CPAMs are classified into Stocker type 0 to 4,[64] rather than being grouped into microcystic, macrocystic or mixed. Only few studies have recently studied the concordance between prenatal appearance and postnatal type of CLM.[65-67]

Prenatal prediction of adverse postnatal outcome

Prenatal prediction of the need for respiratory support and the need for surgery would not only be useful in parental counseling, but also for delivery planning and appropriate follow-up. After birth, the majority of neonates with CLM remain asymptomatic, whereas some require immediate respiratory support and intensive care admission. Others present with recurrent lower respiratory tract infections later in childhood. Those children who develop symptoms, either directly after birth or later in life, undergo surgical resection.

Previous studies have sought to identify prenatal predictors of adverse postnatal outcome, including the CPAM volume ratio (CVR). The volume of the CLM is calculated using the formula for the volume of an ellipse (length x weight x height x 0.52); to normalize for gestational age, the calculated volume is divided by the head circumference: length x weight x height x 0.52 / head circumference = CVR.[68] The CVR, which was originally developed to predict fetal hydrops,[68] has proven to be predictive of several adverse perinatal outcomes, including respiratory distress,[69] need for intensive care admission,[70] and need for early surgical resection.[71, 72] Most studies calculated a cut-off for the maximum CVR measured at any time during pregnancy,[69, 71, 72] or for the CVR at initial evaluation with a large range in gestational age.[72, 73] Neither of these cut-offs is helpful in the parental counseling at the 20-week fetal anomaly scan. The study that calculated multiple cut-offs during pregnancy for predicting the need for intensive care admission, suggested a cut-off of 0.5 for a CVR measured before 24 weeks' gestation.[70] Optimal cut-offs for the CVR measured around 20 weeks' gestation, for predicting respiratory distress or the need for surgical resection, are not well established yet.

Controversies and long-term outcome

Although the management of children with symptomatic CLM is straightforward, there is ongoing debate regarding the need for and the most accurate timing of surgery in asymptomatic children.[74] Those who support elective surgical resection of asymptomatic CLM worry mostly about pulmonary infections and malignant development. Others advocate observational management, considering that the possible benefits of elective surgical resection may not outweigh the risk of postoperative complications and the adverse effects of anesthesia on children's brain development.[74, 75]

The literature on pulmonary outcome in children with CLM is scarce. A previous study at our center showed that approximately one third of them suffered from airflow obstruction in the first year after birth, with no significant difference between those

managed surgically or observationally.[76] Data on long-term outcome are also scarce, especially in those with asymptomatic CLM.[77-79]

Specific key questions

- How does the prenatal appearance of CLM correspond with that after birth? (**chapter 8**)
- Can we prenatally predict the need for postnatal respiratory support and/or surgical intervention? (**chapter 8**)
- How do these children, either managed observationally or surgically, grow up in terms of physical growth, lung function, and exercise tolerance? (**chapter 9**)

Aims and outline of this thesis

The studies presented in this thesis were performed with the aim to improve the knowledge on prenatal characteristics and long-term outcome of gastroschisis, omphalocele, and CLM, with the ultimate goal to optimize parental counselling and postnatal follow-up.

In **chapter 10**, the study results are discussed and put into perspective, and suggestions for future research are described. The results of all studies are summarized in English (**chapter 11**) and in Dutch (**chapter 12**).

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GASTROSCHISIS



2

Using three-dimensional ultrasound in predicting complex gastroschisis: a longitudinal, prospective, multicenter cohort study

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Abstract

Objective

To determine whether complex gastroschisis (i.e. intestinal atresia, perforation, necrosis or volvulus) can prenatally be distinguished from simple gastroschisis by fetal stomach volume and stomach-bladder distance, using three-dimensional (3D) ultrasound.

Methods

This multicenter prospective cohort study was conducted in the Netherlands between 2010-2015. Of seven university medical centers, we included the four centers that performed longitudinal 3D ultrasound measurements at a regular basis. We calculated stomach volumes (n=223) using Sonography-based Automated Volume Count. The shortest stomach-bladder distance (n=241) was determined using multiplanar visualization of the volume datasets. We used linear mixed modelling to evaluate the effect of gestational age and type of gastroschisis (simple or complex) on fetal stomach volume and stomach-bladder distance.

Results

We included 79 affected fetuses. Sixty-six (84%) had been assessed with 3D ultrasound at least once; 64 of these 66 were live-born, nine (14%) had complex gastroschisis. With advancing gestational age, stomach volume significantly increased, and stomach-bladder distance decreased (both $p<0.001$). The developmental changes did not differ significantly between fetuses with simple and complex gastroschisis, neither for fetal stomach volume ($p=0.85$), nor for stomach bladder distance ($p=0.78$).

Conclusion

Fetal stomach volume and stomach-bladder distance, measured during pregnancy using 3D ultrasonography, do not predict complex gastroschisis.

Introduction

Gastroschisis is an abdominal wall defect that is diagnosed prenatally in over 90% of the cases, usually before 23 weeks' gestation.[1] In countries that offer routine ultrasound scans at 11-14 weeks' gestation, gastroschisis is usually diagnosed in the first trimester.[2] This allows for early parental counselling and adjustment of obstetric management.

Seventeen percent of all neonates with gastroschisis are diagnosed with additional intestinal defects at birth, i.e. intestinal atresia, perforation, necrosis or volvulus (defined as complex gastroschisis).[3, 4] Infants with complex gastroschisis have a higher risk of morbidity than those with simple gastroschisis; they often experience prolonged time to full enteral feeding (TFEF), more complications, and prolonged length of hospital stay (LOS).[3-6]

Prenatal detection or prediction of complex gastroschisis would lead to more complete parental counselling. The association between two-dimensional (2D) prenatal ultrasound findings (e.g. bowel dilatation, stomach dilatation, or amniotic fluid index) and complex gastroschisis has been investigated in a number of studies, which showed conflicting results.[7] Intra-abdominal bowel dilatation has been associated with intestinal atresia, but its positive predictive value is debatable.[8] Fetal stomach dilatation has been associated with neonatal death, but not with complex gastroschisis.[8] However, volume calculation using 2D ultrasound measurements assumes certain geometric characteristics and regular contours of the stomach, which may not be accurate. Three-dimensional (3D) ultrasound might be more accurate in measuring fetal stomach volume and thus predicting complex gastroschisis, but to date there are no studies to support this hypothesis.

One study used magnetic resonance imaging (MRI) to describe fetal development in case of gastroschisis.[9] Extensive contact was seen between the stomach and urinary bladder in all but the youngest third trimester fetus who presented with simple gastroschisis at birth. In contrast, those fetuses presenting with intestinal stenosis had not shown any stomach-bladder contact, as their abdominal cavity was filled with dilated bowel loops.[9] Therefore, stomach-bladder distance might be a reflection of intra-abdominal bowel dilatation (IABD), and may predict complex gastroschisis.

The primary aim of this study was to define whether fetal stomach volume, measured longitudinally using 3D ultrasound, can predict complex gastroschisis. In addition, we aimed to evaluate the value of stomach-bladder distance in predicting complex gastroschisis in 3D ultrasound volumes.

Methods

Between June, 2010 and April, 2015, we performed a prospective, longitudinal, multicenter cohort study at seven university medical centers with a prenatal and a pediatric surgery department in The Netherlands. The centers that performed longitudinal 3D ultrasound measurements on fetuses with gastroschisis at a regular basis (i.e. if ≥50% of included fetuses had ≥1 assessment) were included. Fetuses were eligible for inclusion if gastroschisis without any extra-gastrointestinal anomaly was confirmed by prenatal ultrasound. Neonates who presented with unexpected additional extra-gastrointestinal anomalies at birth were excluded post-hoc. This study was approved by the Medical Ethical Review Board of University Medical Center Utrecht. Parents gave written informed consent.

Ultrasound examinations

Advanced ultrasound examinations were planned at 20, 24, 28, 30, 32, 34, 35 and 36 weeks' gestation for longitudinal measurements. 2D ultrasound measures are described elsewhere (i.e. fetal biometry, amniotic fluid index, pulsatility indices of the umbilical and superior mesenteric artery, and bowel diameter measurements.[10] 3D volumes of the fetal abdomen were obtained if logistically possible (settings: coronal or sagittal plane; sectional planes with speckle reduction imaging (SRI) and X-beam activated; quality: high). The volume sample box was adjusted to include the entire fetal abdomen, but as narrow as possible to shorten the acquisition time. The acquisition of the volume was repeated if movement artifacts were detected. All examinations were performed by three to five trained ultrasonographers per center, using a General Electric Voluson 730 or E8 (General Electric Healthcare, London) ultrasound machine, with a 4-8 MHz transabdominal transducer.

To calculate fetal stomach volumes, we used the Sonography-based Automated Volume Count (SonoAVC) method.[11] Each volume was analyzed using 4D View V14 Ext. 4. After uploading the volume dataset, we used multiplanar visualization and positioned the reference point in the center of the stomach in all three planes. We started volume analysis and selected the smallest box possible (figure 1). After activating SonoAVC general, stomach volumes were calculated by right clicking inside the stomach walls (figure 1). If necessary, we used the edit mode to cut or merge contours. Volume datasets were excluded if they did not include the stomach, or if insufficient image quality or presence of debris hampered SonoAVC to calculate a volume.

To measure the shortest stomach-bladder distance, from outer wall to outer wall, we used the multiplanar visualization of the volume datasets (figure 2). Volume datasets were excluded from analysis if they did not include the stomach or bladder, or if image

quality was insufficient for stomach-bladder distance calculation. All volumes were analyzed by one investigator (AH), who was blinded to the type of gastroschisis.

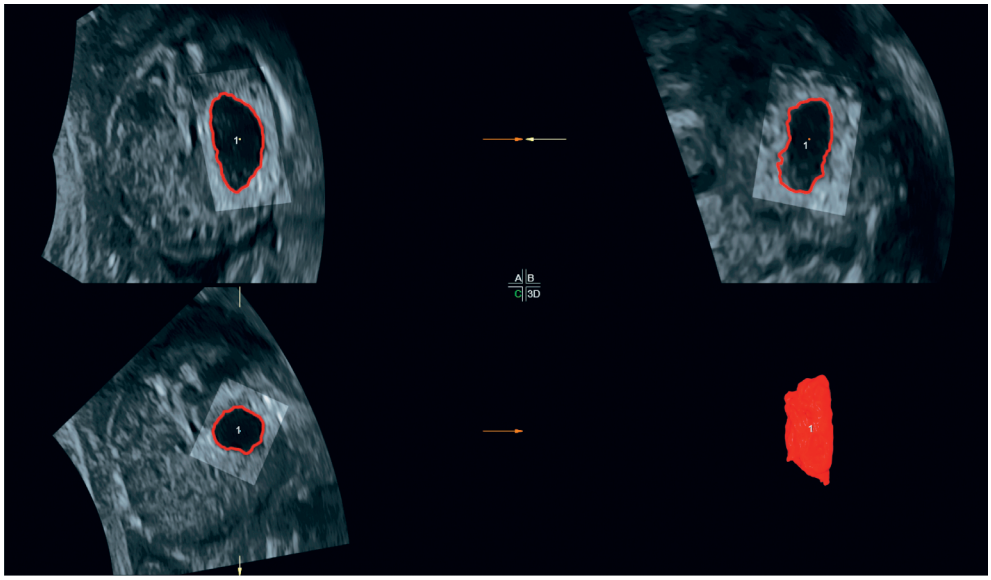

Figure 1 Fetal stomach volume at 21 weeks' gestation, measured using Sonography-based Automated Volume Count (SonoAVC)

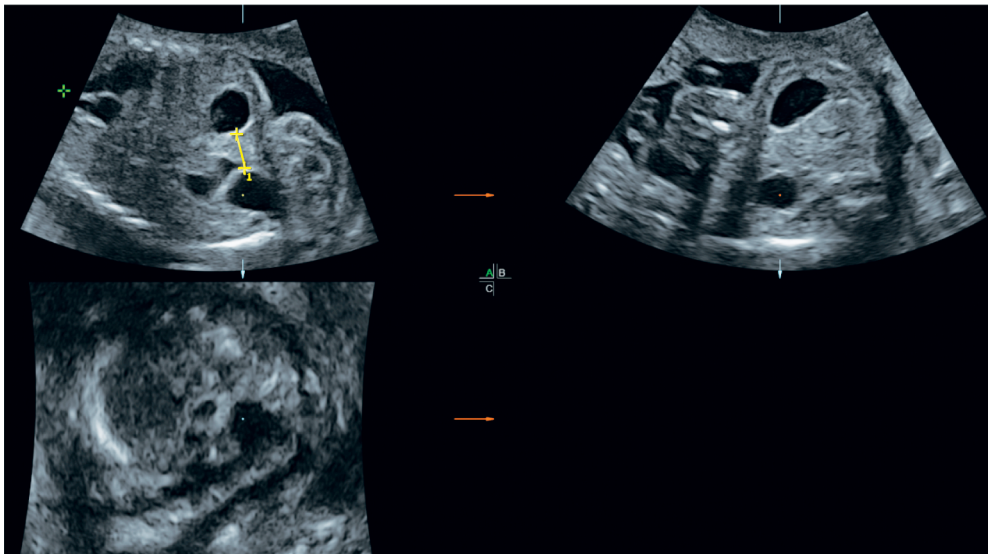

Figure 2 Fetal stomach-bladder distance at 24 weeks' gestation (yellow markers and line), measured in multiplanar visualization

Variables and definitions

We documented maternal, perinatal and postnatal characteristics of infants with simple and complex gastroschisis. Complex gastroschisis was defined as gastroschisis complicated by intestinal atresia, volvulus, perforation and/or necrosis at primary evaluation at birth. Neonates were classified as small for gestational age (SGA) if their birth weight was below the 10th percentile according to Dutch reference curves.[12] If infants needed parenteral nutrition for over 2 years, TFEF was documented as 730 days. Data of deceased infants were excluded from TFEF and LOS analyses.

Statistical analysis

Categorical variables were presented as number (%) and continuous variables as median (interquartile range, IQR). We compared maternal, perinatal and postnatal characteristics between infants with simple and complex gastroschisis using the chi-square tests or Fisher's exact tests (in case of expected counts <5) for categorical data, and the Mann-Whitney U test for continuous data. A two-sided *p* value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS V.21.0.

Intra- and inter-observer reliability and agreement

A random subset of 30 stomach volumes was analyzed twice by one investigator (AH) to determine intra-observer agreement. The same subset was analyzed by a second independent investigator (MA) to determine inter-observer agreement. A different subset, also consisting of 30 volumes, was used to determine intra- and inter-observer agreement of stomach-bladder distance measurements. We constructed Bland-Altman plots using the absolute difference between measurements against their mean. The intra- and inter-observer reliability was estimated by calculating the 95% limits of agreement.[13] In addition, intra- and inter-observer agreement scores were assessed by calculating the intraclass correlation coefficient (ICC) with 95% confidence interval (CI).

Longitudinal 3D ultrasound measurements

Non-normally distributed data were natural log (ln) transformed. If the fetal stomach was adjacent to the bladder (value zero), stomach-bladder distance was registered as 0.01 cm. We used linear mixed modelling to evaluate the effects of gestational age (GA), type of gastroschisis (simple or complex), and their interaction on the developmental courses of fetal stomach volume and stomach-bladder distance. Mixed-effects models allow for intra-fetal correlation of repeated measurements, make use of the exact age at measurement, and account for a dissimilar number of measurements on each fetus. Such models also allow for individual variation in growth trajectories, as random effects permit variability in intercept and slope between subjects. We explored linear and quadratic terms of GA that were included as both fixed and random effects. Type of

gastroschisis was included as a main effect and also as an interaction with the GA terms. Model estimates are presented as mean and 95% CI.

Results

During the study period, 131 fetuses were diagnosed with gastroschisis in The Netherlands. Twenty-seven (21%) fetuses were excluded: one pregnancy resulted in intra-uterine demise (IUD) before 20 weeks' gestation, 12 couples opted for termination of the pregnancy, and 14 couples did not want to participate in this study (figure 3). In addition, three out of seven university medical centers did not perform longitudinal 3D ultrasound measurements on a regular basis; fetuses from these three centers (n=25) were excluded. No statistically significant differences in maternal, perinatal or postnatal characteristics were found between infants who were included in our study and those who were excluded, apart from the proportion of neonates delivered by cesarean section which was almost four times higher in the included neonates (p=0.023, supplemental table 1).

The remaining four centers included 79 fetuses, of which 66 (84%) had been assessed with 3D ultrasound at least once. Two (3%) of these pregnancies resulted in IUD at 28 and 33 weeks' gestation, respectively, and 9 of the remaining 64 (14%) live-born neonates were diagnosed with complex gastroschisis.

A total of 312 3D ultrasound examinations were performed (figure 3): 275 in 55 fetuses with simple gastroschisis (mean (range) per fetus: 5 (1-11)), and 37 in 9 fetuses with complex gastroschisis (mean (range) per fetus: 4 (1-7)). Eighty-nine stomach volumes of 45 fetuses and 71 stomach-bladder distances of 42 fetuses were excluded from analysis (e.g. due to insufficient quality). In the 89 volume datasets that were excluded from analysis of stomach volume, the proportion of volumes derived from fetuses with complex gastroschisis (20/89, 22%) was significantly higher than that in the total number of volumes available (37/312, 12%) (p=0.011).

We included a total of 223 stomach volume calculations: 206 of 52 fetuses with simple gastroschisis (mean (range) per fetus: 4 (1-9)), and 17 of 8 fetuses with complex gastroschisis (mean (range) per fetus: 2 (1-5)). We included a total of 241 stomach-bladder distances: 216 of 53 fetuses with simple gastroschisis (mean (range) per fetus: 4 (1-9)), and 25 of 7 fetuses with complex gastroschisis (mean (range) per fetus: 4 (1-8)). Eight fetuses had only one stomach volume calculation available, and for 3 fetuses only one stomach-bladder distance could be calculated.

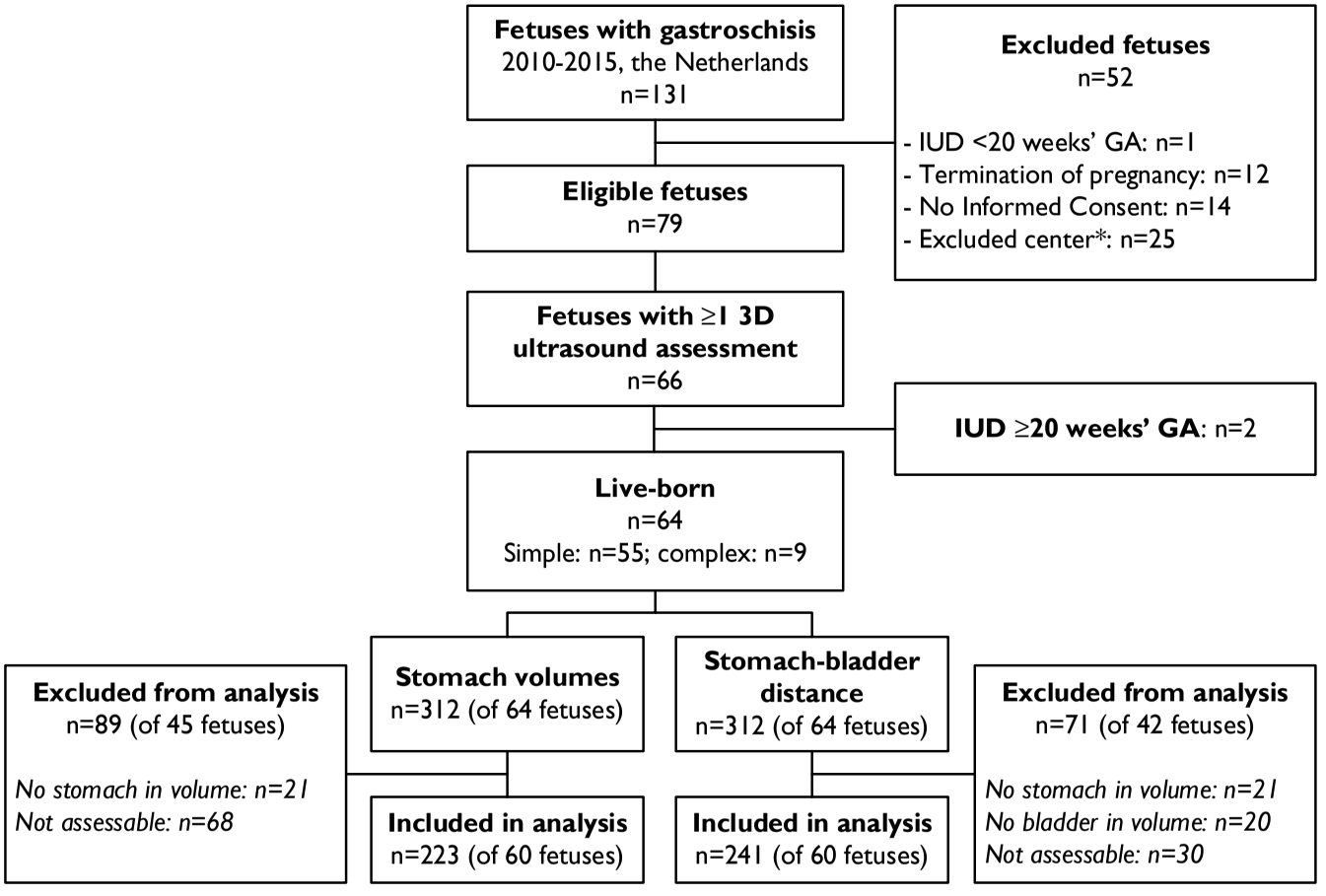

Figure 3 Flow chart of fetuses with gastroschisis included in analyses of stomach volume and stomach-bladder distance

*Centers were excluded if <50% of included fetuses had ≥1 assessment. IUD: intra-uterine demise; GA: gestational age.

Intra- and inter-observer reliability and agreement

We found a high degree of intra-observer reliability for both stomach volume (ICC: 0.997, 95% CI: 0.988-0.999) and stomach-bladder distance calculations (ICC: 0.931, 95% CI: 0.861-0.966). The same was true for inter-observer reliability (ICC: 0.981, 95% CI: 0.955-0.991 for stomach volume, and ICC: 0.962, 95% CI: 0.950-0.992 for stomach-bladder distance calculations). Bland-Altman plots showed good intra- and inter-observer agreement for both stomach volume and for stomach-bladder distance calculations (mean intra-observer and inter-observer differences with 95% limits of agreement are shown in supplemental figure 1).

Maternal, perinatal and postnatal characteristics

Neonates with complex gastroschisis were born 1.5 weeks earlier than those with simple gastroschisis, but this difference did not reach statistical significance. Infants with complex gastroschisis were over three times more likely to develop cholestatic jaundice than those with simple gastroschisis (table 1). In addition, wound infections were over six times more prevalent in the complex gastroschisis group. Median TFEF was more than six months in infants with complex gastroschisis, compared to less than one month in infants with simple gastroschisis. Median LOS was four months in infants with complex gastroschisis, and one month in those with simple gastroschisis. One infant with complex gastroschisis died of sepsis at 8 months of age.

Table 1 Maternal, perinatal and postnatal characteristics of included live-born infants (n=64, from 4 centers) with simple or complex gastroschisis

	n	**Simple gastroschisis** n=55 (86%)	n	**Complex gastroschisis** [A] n=9 (14%)	***p* value**
Number of 3D assessments	55	5 (4-7)	9	4 (2-6)	0.30
Maternal characteristics					
Age (years)	54	25 (22-30)	9	24 (22-29)	0.54
Primigravid	55	31 (56%)	9	4 (44%)	0.72
Smoking	49	17 (35%)	8	3 (38%)	1.00
Recreational drug use [B]	50	6 (12%)	8	2 (25%)	0.30
Perinatal characteristics					
Gestational age at birth (weeks)	55	36.9 (35.7-37.4)	9	35.4 (33.5-37.0)	0.06
Spontaneous onset of delivery	55	13 (24%)	9	4 (44%)	0.23
Cesarean section	55	16 (29%)	9	4 (44%)	0.44
Birth weight (grams)	55	2565 (2230-2775)	9	2220 (1840-2800)	0.23
Birth weight <p10	55	8 (15%)	9	3 (33%)	0.18
Male gender	55	25 (45%)	9	5 (56%)	0.72
Apgar at 5 min <7	54	3 (6%)	9	1 (11%)	0.47

Table 1 (*continued*)

	n	Simple gastroschisis n=55 (86%)	n	Complex gastroschisis [A] n=9 (14%)	*p* value
Postnatal characteristics					
Primary closure	55	34 (62%)	9	5 (56%)	0.73
Complications [C]	55	28 (51%)	9	8 (89%)	0.07
- Necrotizing enterocolitis		0 (0%)		1 (11%)	0.14
- Cholestatic jaundice		13 (24%)		7 (78%)	0.003
- Line sepsis		18 (33%)		5 (56%)	0.26
- Wound infection		3 (5%)		3 (33%)	0.03
Mortality	55	0 (0%)	9	1 (11%)	0.14
Time to full enteral feeding (days)	54	28 (17-42)	8	201 (98-386)	0.001
Length of hospital stay (days) [D]	55	34 (25-63)	8	122 (71-180)	0.001

Data presented as median (interquartile range) or n (%). [A] Intestinal atresia (n=6), intestinal atresia + perforation (n=1), intestinal atresia +necrosis (n=1), intestinal atresia + necrosis + volvulus (n=1). [B] Simple gastroschisis: cocaine (n=4), marihuana (n=2); complex gastroschisis: cocaine (n=1), marihuana (n=1). [C] Percentages do not necessarily add up to 100, as one infant can have multiple problems. One infant with complex gastroschisis died of sepsis at 8 months of age. [D] One infant with simple gastroschisis and one with complex gastroschisis were transferred to another hospital with an unknown discharge date to home; in these infants, length of hospital stay was documented as time to transfer.

Developmental course of stomach volume and stomach-bladder distance

Linear mixed modelling showed no significant contribution of a GA-squared term; a linear model fitted the ln-transformed data best. Fetal stomach volume did not differ significantly between fetuses with simple and those with complex gastroschisis at 20 weeks' gestation (figure 4, table 2; p=0.397), nor did stomach-bladder distance (figure 5, table 2; p=0.345). With advancing GA, stomach volume significantly increased, and stomach-bladder distance decreased (both p<0.001). The course of these changes did not differ significantly between simple and complex gastroschisis (table 2).

The infant who died of sepsis at 8 months of age had shown normal stomach volume at 24 weeks' gestation, stomach-bladder distance was not assessable; no 3D ultrasound measurements were available between 24 and 33 weeks' gestation for this infant. The infant was born at 33 weeks' gestation with an appropriate birth weight for GA.

For the two pregnancies resulting in IUD (beyond 20 weeks' gestation), we found fetal stomach volume and stomach-bladder distance comparable to those shown in figures 4 and 5, respectively. Neither had any other structural malformations at autopsy. The autopsy report of one fetus mentioned intestinal malrotation, the report of the other fetus stated signs of placental inflammation without specifically addressing intestinal malrotation.

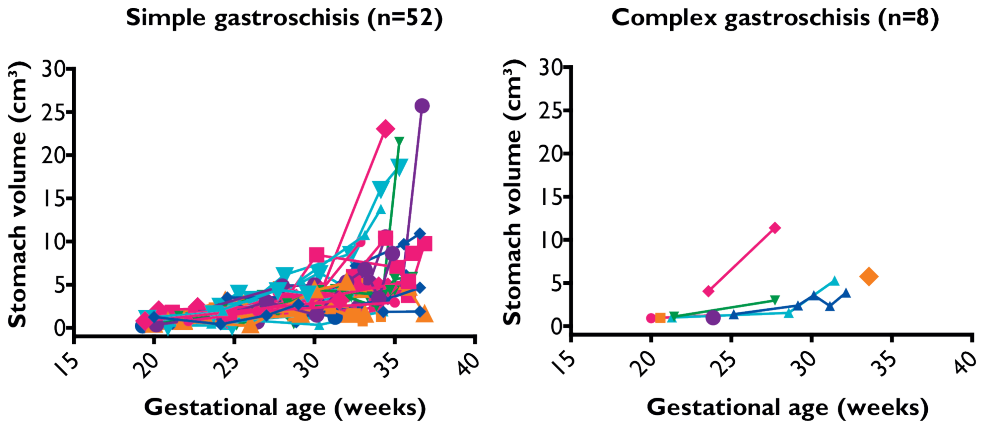

Figure 4 Stomach volumes in fetuses with simple or complex gastroschisis during gestational age

Different colors and symbols represent different fetuses. Location of intestinal atresia in complex gastroschisis (n=8): jejunal (pink rhombus, green triangle); jejunal + colonic (pink circle); ileal (light blue triangle, dark blue triangle, orange rhombus); unclear (orange square, purple circle).

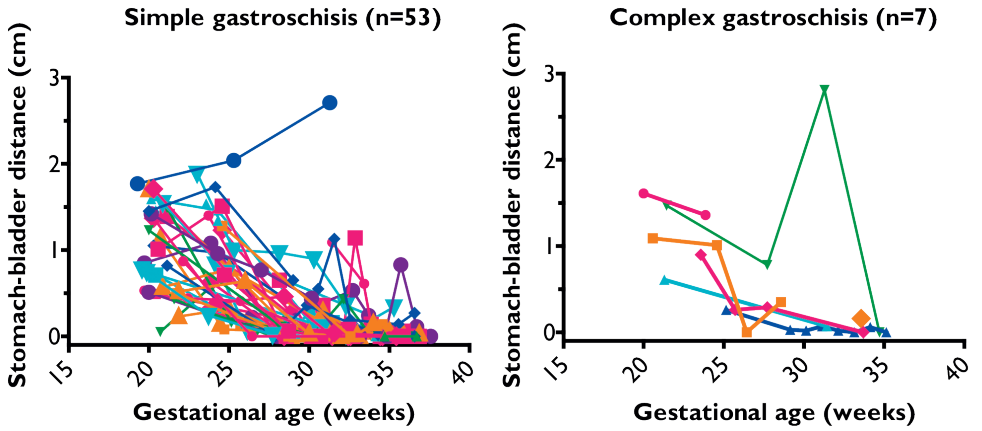

Figure 5 Stomach-bladder distances in fetuses with simple or complex gastroschisis during gestational age

Different colors and symbols represent different fetuses. Location of intestinal atresia in complex gastroschisis (n=7): jejunal (pink rhombus, green triangle); jejunal + colonic (pink circle); ileal (light blue triangle, dark blue triangle, orange rhombus); unclear (orange square).

Table 2 Estimates with 95% confidence intervals of linear mixed modelling for stomach volume and stomach-bladder distance (natural log transformed)

Variable	Estimate (mean)	95% Confidence Interval	*p* value
Stomach volume (ln)			
Intercept	-0.31	-0.49 to -0.13	0.001
Type of gastroschisis (complex versus simple)	0.25	-0.33 to 0.83	0.40
Gestational age (centered at 20 weeks)	0.13	0.11 to 0.15	<0.001
Gestational age by type of gastroschisis	0.01	-0.07 to 0.08	0.85
Stomach-bladder distance (ln)			
Intercept	0.06	-0.27 to 0.39	0.71
Type of gastroschisis (complex versus simple)	0.48	-0.53 to 1.48	0.35
Gestational age (centered at 20 weeks)	-0.26	-0.30 to -0.22	<0.001
Gestational age by type of gastroschisis	-0.02	-0.15 to 0.11	0.78

Discussion

This longitudinal prospective multicenter study is the first to evaluate the possible benefit of the use of 3D ultrasound in fetuses with gastroschisis. Stomach volume and stomach-bladder distance during pregnancy did not differ between simple and complex gastroschisis. Therefore, we were unable to predict complex gastroschisis using these prenatal variables.

Many attempts have been made to prenatally predict complex gastroschisis.[8] Fetal stomach dilatation has been found to be associated with the postnatal need for bowel resection,[14] but a recent meta-analysis showed no significant association between stomach dilatation and complex gastroschisis.[8] However, stomach dilatation in these fetuses was always evaluated retrospectively, using 2D ultrasound.[8] In addition, the cut-off values used in these studies were either not mentioned[14, 15] or were derived from healthy fetuses more than thirty years ago.[8, 16, 17] In our group of more than 100 fetuses that were evaluated with 2D ultrasound, we found that both intra- and extra-abdominal bowel diameters were of limited value in the prediction of complex gastroschisis.[10] Although both parameters were increased in those with complex gastroschisis, the large fluctuations over time and the overlap with simple cases made it difficult to identify complex gastroschisis prenatally. The best predictor appeared to be intra-abdominal bowel diameters ≥p97.7 measured at least three times during gestation, but the positive predictive value was low (i.e. 50%). Gastric size was not assessed in the 2D ultrasound part of the study.

As 3D ultrasound has been proposed to be superior to 2D ultrasound in evaluating fetal stomach volume,[18] we hypothesized that this method would be more accurate in

predicting complex gastroschisis. However, fetuses with complex gastroschisis showed stomach volumes comparable to those measured in simple gastroschisis fetuses.

Previous studies have reported an association between fetal stomach dilatation and death in the neonatal[8] or perinatal[14] period. In our study, the two cases ending in IUD had stomach volumes that were comparable to those who were live-born. No previous study has evaluated the association between fetal stomach-bladder distance and complex gastroschisis. *Brugger and Prayer*, however, did report extensive stomach-bladder contact on magnetic resonance imaging in fetuses who presented with simple gastroschisis at birth.[9] This was in contrast to the three fetuses with complex gastroschisis included in their study, who had shown absence of stomach-bladder contact in the third trimester due to IABD.[9] As IABD has previously been associated with complex gastroschisis,[8] we hypothesized that a greater stomach-bladder distance –as a reflection of IABD– could also be predictive of complex gastroschisis. Rather than measuring the largest bowel loop, stomach-bladder distance would reflect IABD in general. However, both in simple and in complex gastroschisis, we observed great variations in stomach-bladder distance, probably due to alternate filling and emptying of these organs. As no differences were observed between the two types of gastroschisis, we conclude that stomach-bladder distance is not helpful in predicting complex gastroschisis.

Strengths and limitations

The major strength of our study is its prospective, longitudinal study design, with a large number of measurements per fetus. Investigators were blinded to outcome during ultrasonography and during calculations of stomach volume and stomach-bladder distance. As we used 3D instead of 2D ultrasonography, we did not depend on certain geometric characteristics or regular contours of the stomach to calculate stomach volume, and we were able to reliably calculate the shortest stomach-bladder distance.

Several limitations need to be addressed. First, we excluded three centers because of low compliance of performing 3D ultrasound measurements. However, we found no significant differences in characteristics between cases of included centers and cases of excluded centers, apart from the number of cesarean sections. Therefore, we expect that selection bias can be considered minimal. Second, the small sample of fetuses with complex gastroschisis decreased the power of our tests. Since these fetuses showed comparable stomach volume and stomach-bladder distance to those with simple gastroschisis, we think this has not affected our conclusion. A third limitation is the substantial number of missing data for fetuses from included centers. Especially in the complex gastroschisis group, a relatively high number of volume datasets had to be excluded from stomach volume analyses, because no stomach was seen intra-

abdominally or because volume calculations were not assessable. We speculate that fetuses with complex gastroschisis may have an increased incidence of stomach evisceration, or increased presence of debris inside the stomach, which hampered SonoAVC to calculate stomach volumes. Nonetheless, all fetuses with complex gastroschisis included in our analysis showed comparable stomach volumes to those with simple gastroschisis. Even if the excluded volume datasets would have shown strongly deviating values, it would still be very difficult to predict complex gastroschisis using stomach volume. Last, we chose to focus on 3D ultrasound measures only. Future research may investigate whether combining 3D with 2D ultrasound measures leads to improved prediction of complex gastroschisis.

Conclusion

We conclude that fetal stomach volume and stomach-bladder distance, measured during pregnancy using 3D ultrasonography, cannot predict complex gastroschisis.

Acknowledgements

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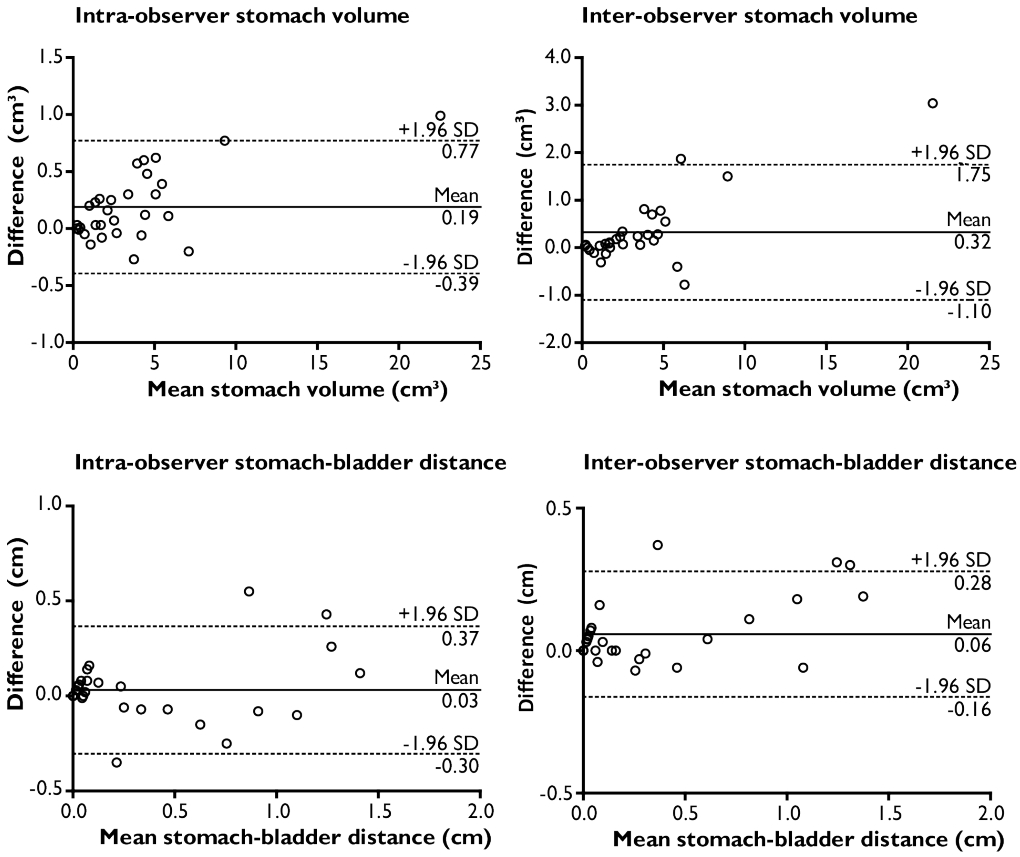
Supplemental material

Supplemental table 1 Maternal, perinatal and postnatal characteristics of fetuses with gastroschisis from included and excluded centers

	n	**Included centers (n=4)** 79 fetuses	n	**Excluded centers (n=3)** 25 fetuses	***p* value**
≥1 3D ultrasound assessment	79	66 (84%)	25	7 (28%)	<0.001
Maternal characteristics					
Age (years)	78	25 (22 – 31)	25	26 (23 – 31)	0.64
Primigravid	79	40 (51%)	25	14 (56%)	0.64
Smoking	68	24 (35%)	25	10 (40%)	0.68
Recreational drug use	69	13 (19%)	24	2 (8%)	0.34
Perinatal characteristics					
Live birth	79	75 (95%)	25	25 (100%)	0.57
Gestational age at birth (weeks)	75	36.7 (35.3 – 37.3)	25	36.7 (35.6 – 37.1)	0.93
Spontaneous onset of delivery	75	23 (31%)	25	9 (36%)	0.62
Cesarean section	75	23 (31%)	25	2 (8%)	0.02
Birth weight (grams)	75	2490 (2175 – 2775)	25	2395 (2165 – 2770)	0.82
Birth weight <p10	75	13 (17%)	25	3 (12%)	0.75
Male gender	75	38 (51%)	25	15 (60%)	0.42
Apgar at 5 min <7	74	4 (5%)	25	1 (4%)	1.00
Postnatal characteristics					
Complex gastroschisis	75	13 (17%)	25	6 (24%)	0.56
Primary closure	75	44 (59%)	24	19 (79%)	0.07
Complications [A]	75	45 (60%)	25	15 (60%)	1.00
- Necrotizing enterocolitis		1 (1%)		1 (4%)	0.44
- Cholestatic jaundice		26 (35%)		10 (40%)	0.63
- Line sepsis		27 (36%)		11 (44%)	0.48
- Wound infection		10 (13%)		3 (12%)	1.00
Mortality	75	3 (4%)	25	0 (0%)	0.57
Time to full enteral feeding (days)	71	29 (19 – 70)	23	36 (23 – 49)	0.79
Length of hospital stay (days) [B]	72	43 (26 – 81)	24	44 (27 – 80)	0.81

Data presented as median (interquartile range) or n (%). [A] Percentages do not necessarily add up to 100, as one infant can have multiple problems. [B] Three infants in the included group and one in the excluded group were transferred to another hospital with an unknown discharge date to home; in these infants, length of hospital stay was documented as time to transfer.



Supplemental figure 1 Bland-Altman plots showing intra- and interobserver agreement of stomach volume and stomach-bladder distance measurements



3

Prenatal markers and longitudinal follow-up in simple and complex gastroschisis

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Abstract

Objective

We aimed to identify gestational-age corrected prenatal ultrasound markers of complex gastroschisis, and to compare physical growth and neurodevelopment between children with simple and complex gastroschisis.

Design

We included prenatally diagnosed gastroschisis patients from 2000 to 2012 who joined our longitudinal follow-up program. Associations between complex gastroschisis and prenatal ultrasound markers collected at 30 weeks' gestation and prior to delivery were tested using logistic regression. Physical growth (SD scores (SDS)), mental and psychomotor developmental index (MDI, PDI; Bayley Scales of Infant Development) were recorded at 12 and 24 months. Data were analyzed using general linear models and compared with population
norms.

Results

Data of 61 children were analyzed (82% of eligible cases). Extra-abdominal bowel dilatation at 30 weeks' gestation was significantly associated with complex gastroschisis (OR (95% CI): 5.00 (1.09 to 22.98)), with a high negative (88%) but low positive (40%) predictive value. The mean (95% CI) height SDS at 12 months (−0.46 (–0.82 to –0.11)), and weight SDS at 12 and 24 months (−0.45 (–0.85 to –0.05), and −0.44 (−0.87 to –0.01), respectively) fell significantly below 0 SDS. MDI and PDI were significantly below 100 at 24 months; 93 (88 to 99) and 83 (78 to 87), respectively). Children with complex gastroschisis had a significantly lower PDI (76 (68 to 84)) than those with simple gastroschisis (94 (90 to 97), $p<0.001$).

Conclusions

Prenatal ultrasound markers could not reliably distinguish between simple and complex gastroschisis. Children with complex gastroschisis may be at increased risk for delayed psychomotor development; they should be monitored more closely, and offered timely intervention.

Introduction

Gastroschisis is a congenital abdominal wall defect with an estimated prevalence of 2.16 per 10 000 pregnancies.[1] Surgery is required shortly after birth, by means of primary closure when possible or by placing a silastic silo to allow gradual reduction into the abdominal cavity prior to definite closure.[2]

Gastroschisis patients who have additional intestinal defects, that is, intestinal atresia, perforation, necrosis or volvulus ('complex' gastroschisis),[3] have a higher risk of morbidity than children with 'simple' gastroschisis (without intestinal defects). This includes prolonged time to full enteral feeding (TFEF) and prolonged length of hospital stay (LOS).[3–5]

Over 90% of gastroschisis cases are diagnosed prenatally.[6] A recent meta-analysis evaluated several prenatal ultrasound markers and showed significant positive associations between intra-abdominal bowel dilatation (IABD) and intestinal atresia, between polyhydramnios and intestinal atresia, and between gastric dilatation and neonatal death.[7] These findings should be interpreted with caution, however, given that definitions of bowel and gastric dilatation differed between studies and data were not always corrected for gestational age (GA).

Additionally, adequate parental counselling should include expectations of the child's physical growth and neurodevelopment. Physical growth in children older than 1 year has only been studied in small groups (<40 patients).[8–11] No previous study has evaluated possible differences in neurodevelopment between children with simple and complex gastroschisis.

The aim of our study was to (1) identify GA-corrected prenatal ultrasound markers of complex gastroschisis and (2) to assess physical growth and neurodevelopment up to 2 years of age of children with either simple or complex gastroschisis.

Methods

Study population

A retrospective analysis was performed of prospectively collected data of all prenatally diagnosed gastroschisis cases delivered and treated at the Erasmus Medical Center-Sophia Children's Hospital Rotterdam between 2000 and 2012. Following the diagnosis, several prenatal characteristics were assessed every 4 weeks. From 2007 onwards, additional assessments were scheduled weekly, starting at 30 weeks' gestation.[12] Vaginal delivery was planned from 37 weeks onwards, unless obstetric reasons required otherwise. Survivors could join a longitudinal prospective follow-up program which since 1999 is standard of care for children with anatomical congenital malformations

treated in our hospital.[13] The Medical Ethical Review Board waived approval ('Medical Research in Human Subjects Act does not apply to this research proposal'; MEC-2015–308).

Prenatal and perinatal characteristics of simple and complex gastroschisis

We obtained the following ultrasound data at 30 weeks' gestation and at the last ultrasound examination prior to delivery: amniotic fluid index, considered abnormal if <5 cm (oligohydramnios) or >24 cm (polyhydramnios); intrauterine growth restriction, defined as estimated fetal weight ≤10th percentile for GA according to the Hadlock formula III[14]; IABD and extra-abdominal bowel dilatation (EABD) determined using a GA-specific nomogram, considering the bowel dilated if ≥13 mm at a GA of 25–30 weeks, ≥16 mm at 30–35 weeks, and if ≥26 mm at 35–40 weeks[15]; and intra-abdominal gastric dilatation, defined as measurements exceeding two SDs above the mean reference value, adjusted for GA.[16] Preterm birth was defined as delivery prior to 37 weeks' gestation. Small for GA was diagnosed if birth weight was below the 10th centile according to Dutch reference curves.[17] Socioeconomic status scores (with population mean 0 and SD 1) were based on postal codes.[18, 19]

Postnatal outcome in simple and complex gastroschisis

Complex gastroschisis was defined as presence of intestinal atresia, necrosis, perforation and/or volvulus at primary postnatal evaluation. We recorded duration of initial mechanical ventilation, LOS of the initial hospitalization, and additionally during follow-up: TFEF; number of procedures under general anesthesia; complications; and presence of intestinal failure, defined as TFEF ≥6 weeks.[20] If TFEF or LOS was ≥2 years, the duration was set at 730 days.

Physical growth and neurodevelopment

Height and weight were measured at 12 and 24 months (corrected for preterm birth). SD scores (SDS) were determined according to Dutch reference norms, with −2 to +2 SD considered as normal range.[21] Neurodevelopment was assessed using the Dutch version of the Bayley Developmental Scales (BOS 2–30)[22] and from December 2003, Bayley Scales of Infant Development-Second Edition (BSID-II-NL).[23] These tests are interchangeable,[23] and provide a mental developmental index (MDI) and psychomotor developmental index (PDI) with a mean score of 100 and an SD of 15.[22, 23] Scores 70–84 indicate mildly impaired development, scores 55–69 moderately impaired development, and scores <55 (recorded as 55) are indicative of severe developmental delay.

Statistical analysis

Categorical variables are presented as number (%) and continuous variables as median (IQR). Prenatal characteristics and postnatal outcome parameters of children with simple or complex gastroschisis were compared using chi-square tests or Fisher's exact tests (in case of expected counts <5) for categorical data, and the Mann-Whitney test for continuous data. We used logistic regression to find relevant ultrasound predictors of complex gastroschisis. Spearman's rank correlation coefficient was used to assess the association between GA at birth and TFEF. General linear models were used to analyze the repeated growth and neurodevelopment measurements over time. These models included both the time point (12 or 24 months) and the type of gastroschisis (simple or complex) as independent variables. To account for the within-subject correlations, an unstructured error covariance matrix for the repeated measurements of each patient was used in the general linear models. The results are presented using estimated marginal means (i.e. the predicted values of the dependent variable adjusted for covariates in the model). Estimated marginal means and their 95% CIs were compared with reference norms. A two-sided *p* value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS V.21.0.

Results

Of 82 prenatally diagnosed cases of gastroschisis, three (4%) pregnancies were terminated. Four (5%) other fetuses died in utero between 20 and 36 weeks' gestation. All four showed intrauterine growth restriction but not bowel or gastric dilatation. Of 75 live-born children, 12 (16%) were diagnosed with complex gastroschisis. One infant with simple gastroschisis died of sepsis at 5 months of age. Of 61 (82 %) children who joined the follow-up program, 46 (75%) were seen at both 12 and 24 months (figure 1). Prenatal, perinatal and postnatal data did not significantly differ between children who joined the follow-up program and children who did not (data not shown).

Prenatal and perinatal characteristics

Ultrasound examination at 30 weeks' gestation revealed EABD in 6/51 (12%) fetuses postnatally diagnosed with simple gastroschisis, versus 4/10 (40%) fetuses postnatally diagnosed with complex gastroschisis (OR (95% CI) 5.00 (1.09 to 22.98)). Thus the positive and negative predictive values of EABD for complex gastroschisis were 40% and 88%, respectively. These four children with complex gastroschisis all had intestinal atresia. No significant associations were found regarding any other assessed prenatal parameter at 30 weeks' gestation or at the last ultrasound examination prior to delivery. Perinatal data did not significantly differ between children with simple and children with complex gastroschisis (table 1).

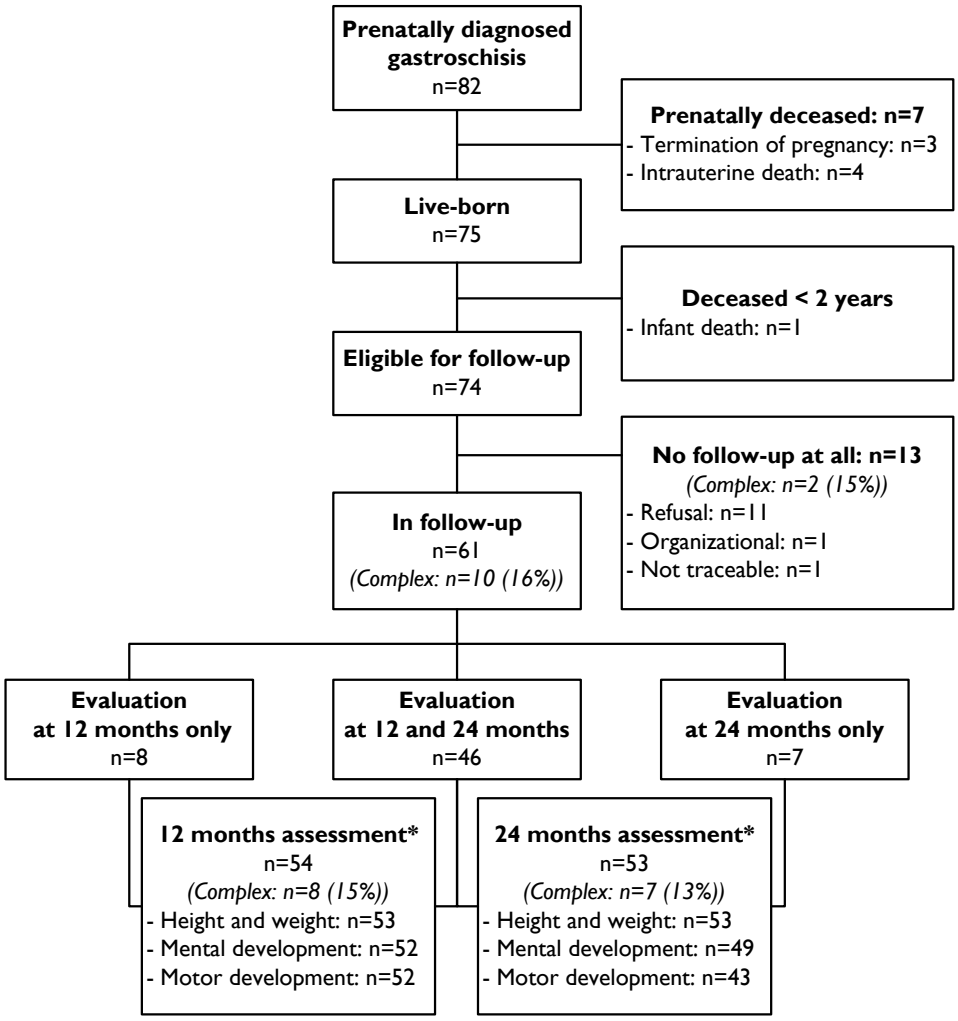

Figure 1 Inclusion flow chart

*Reasons for missing neurodevelopmental data at 12 months: non-cooperative n=2 (both motor/mental n=1; mental n=1); immobilization of foot n=1 (motor). At 24 months: non-cooperative n=6 (both motor/mental n=2, motor n=4); organizational n=3 (both motor/mental n=1; motor n=2), refusal n=1 (both motor/mental).

Table 1 Maternal, prenatal and perinatal characteristics of children in follow-up (n=61)

	Simple gastroschisis n=51	**Complex gastroschisis** [A] n=10	***p* value**
Maternal age (years)	23.2 (19.7 – 28.4)	26.7 (21.1 – 32.7)	0.45
Socioeconomic status score at birth	-0.52 (-1.45 – 0.34)	0.19 (-0.93 – 0.71)	0.18
- Low status score (< -1)	20 (39%)	2 (20%)	0.31
Prenatal characteristics			
30 weeks' gestation			
Gestational age (weeks)	30.3 (29.9 – 30.7)	30.1 (29.7 – 31.1)	0.85
Amniotic fluid volume, normal	51 (100%)	10 (100%)	-
Intrauterine growth restriction	20 (39%)	4 (40%)	1.00
Intra-abdominal bowel dilatation	3 (6%)	0 (0%)	1.00
Extra-abdominal bowel dilatation	6 (12%)	4 (40%)	0.049
Gastric dilatation	2 (4%)	1 (10%)	0.42
Last ultrasound examination prior to delivery			
Gestational age (weeks)	35.7 (34.0 – 36.6)	36.1 (35.8 – 36.5)	0.46
Amniotic fluid volume, normal [B]	46 (93%)	10 (100%)	1.00
Intrauterine growth restriction	26 (51%)	8 (80%)	0.16
Intra-abdominal bowel dilatation [C]	3 (6%)	2 (22%)	0.16
Extra-abdominal bowel dilatation	11 (22%)	4 (40%)	0.24
Gastric dilatation [D]	8 (17%)	2 (25%)	0.63
Perinatal characteristics			
Induced delivery	33 (65%)	8 (80%)	0.47
Cesarean section	14 (27%)	3 (30%)	1.00
Gestational age at birth (weeks)	36.9 (34.6 – 37.4)	36.8 (36.4 – 37.4)	0.76
Preterm birth [E]	26 (51%)	6 (60%)	0.74
Birthweight (grams)	2300 (2100 – 2700)	2385 (2228 – 2525)	0.75
Small for gestational age	8 (16%)	3 (30%)	0.37
Apgar score < 7 at 5 min	4 (8%)	0 (0%)	1.00
Umbilical cord pH [F]	7.30 (7.24 – 7.35)	7.31 (7.24 – 7.40)	0.59
- pH < 7.00	1 (2%)	0 (0%)	1.00

Data presented as median (interquartile range) or n (%). [A] Bowel atresia (n=3), intestinal atresia + necrosis (n=2), intestinal atresia + perforation (n=1), necrosis (n=1), necrosis + volvulus (n=1), perforation (n=2). [B] Data unknown in n=2, oligohydramnios in n=3 (all simple gastroschisis). [C] Data unknown in n=1. [D] Data unknown in n=6. [E] All preterm born babies were born after 32 weeks' gestation. [F] Data unknown in n=1.

Postnatal outcome

Children with complex gastroschisis needed over three times as many procedures under general anesthesia as those with simple gastroschisis (table 2). Moreover, median duration of initial mechanical ventilation was 24 days in infants with complex gastroschisis versus 2 days in infants with simple gastroschisis. Median durations of parenteral nutrition and hospitalization were less than 2 months in children with simple gastroschisis, and close to 6 months in those with complex gastroschisis. There was no significant correlation between GA at birth and TFEF (Spearman's r=−0.086, p=0.47). Intestinal failure developed in all children with complex gastroschisis, and in 25% of those with simple gastroschisis. Complications were common in both groups, especially sepsis and parenteral nutrition-related cholestasis.

Table 2 Postnatal characteristics of children in follow-up (n=61)

	Simple gastroschisis n=51	**Complex gastroschisis** [A] n=10	***p* value**
Postnatal characteristics			
Eviscerated organs [B]			
- Intestines only	21 (41%)	3 (30%)	0.73
- + stomach	25 (49%)	5 (50%)	1.00
- + bladder	6 (12%)	2 (20%)	0.61
Multiple congenital anomalies [C]	7 (13.7%)	2 (20%)	0.63
Primary closure, directly after birth	35 (69%)	4 (40%)	0.15
Procedures under general anesthesia	2 (1 – 3)	7 (4 – 14)	<0.001
Duration of initial mechanical ventilation (days) [D]	2 (1 – 6)	24 (7 – 30)	0.001
Time to full enteral feeding (days)	27 (20 – 47)	165 (66 – 624)	<0.001
- Intestinal failure	13 (25%)	10 (100%)	<0.001
Length of initial hospital stay (days)	42 (28 – 62)	173 (81 – 426)	<0.001
Complications [B]	30 (59%)	10 (100%)	0.01
- Sepsis	25 (49%)	9 (90%)	0.03
- Parenteral nutrition-related cholestasis	14 (27%)	9 (90%)	<0.001
- Cardiopulmonary resuscitation	5 (10%)	1 (10%)	1.00
- Central venous line-thrombosis	2 (4%)	2 (20%)	0.12
- Miscellaneous [E]	13 (25%)	5 (50%)	0.14

Data presented as median (interquartile range) or n (%). [A] Bowel atresia (n=3), intestinal atresia + necrosis (n=2), intestinal atresia + perforation (n=1), necrosis (n=1), necrosis +

volvulus (n=1), perforation (n=2). [B] Percentages do not necessarily add up to 100, as one patient can have multiple problems. [C] Polydactyly (n=2); dysmorphic features (n=2: retrognathia and short philtrum, frontal bossing and hypertelorism); hydronephrosis and atrial septal defect, spontaneous closure (n=1); small ventricular septal defect (n=1); benign peripheral hydrocephalus (n=1); hypospadias (n=1); and retrognathia and urethral valves (n=1). [D] Data unknown in n=1. [E] Surgery-related (n=8); preterm birth-related (n=4); infectious, not catheter-related (n=6); neurologic (n=4); catheter-related (n=2); drug-related (n=1).

Physical growth and neurodevelopment

Physical growth data of all gastroschisis patients in follow-up is shown in figure 2. The general linear model analysis showed significant improvement in height SDS from 12 to 24 months of +0.16 (95% CI: 0.01 to 0.31). The estimated marginal means (95% CI) of height SDS at 12 months (−0.46 (–0.82 to –0.11)), and weight SDS at 12 and 24 months (−0.45 (-0.85 to –0.05), and −0.44 (−0.87 to –0.01), respectively) fell significantly below 0 SD, but within the normal range of −2 to +2 SD. Growth parameters did not differ significantly between children with simple and complex gastroschisis. At 24 months, 4/53 (8%) children scored below −2 SD for weight; all four had simple gastroschisis. None of the children had abnormally low height SDS.

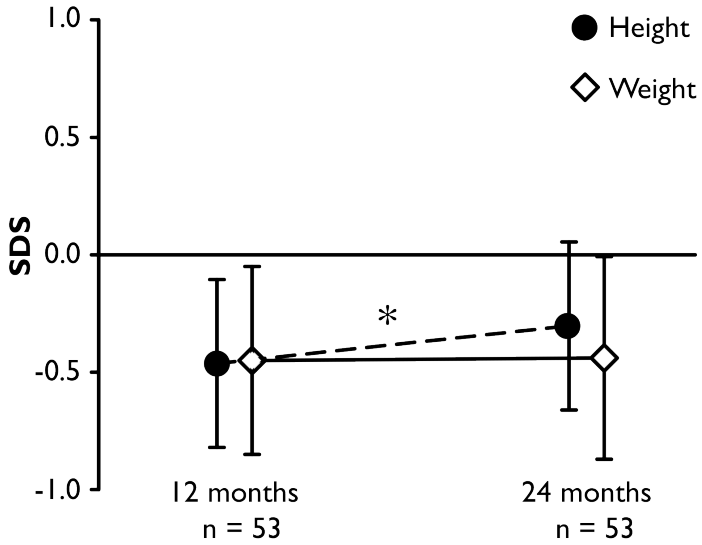

Figure 2 Physical growth at 12 and 24 months of all gastroschisis patients in follow-up

Symbols represent estimated marginal means with 95% confidence intervals. SDS: standard deviation score. * indicates a significant improvement in SDS ($p<0.05$).

Both MDI and PDI significantly declined over time (mean differences (95% CI): −8 (−3 to –13) and −4 (−1 to –8), respectively). The estimated marginal mean (95% CI) MDI at 24 months (93 (88 to 99)) was significantly below 100, but within the normal range of 85–115. The estimated marginal mean PDI was significantly below 100 at both 12 and 24 months, 87 (82 to 92) and 83 (78 to 87), respectively. Children with complex gastroschisis scored a significantly lower PDI than those with simple gastroschisis (76 (68 to 84) vs 94 (90 to 97), respectively, p<0.001), whereas MDI did not significantly differ between groups. At 24 months a higher percentage of children with simple gastroschisis versus children with complex gastroschisis showed normal mental development (86% vs 57%, figure 3), but this difference was not statistically significant (*p*=0.11). The same holds for psychomotor development (81% vs 50%, figure 3; *p*=0.13). One child with complex gastroschisis and dysmorphic features had severe neurodevelopmental delay. Re-analysis of our data after exclusion of this child did not change the results on development in terms of significance.

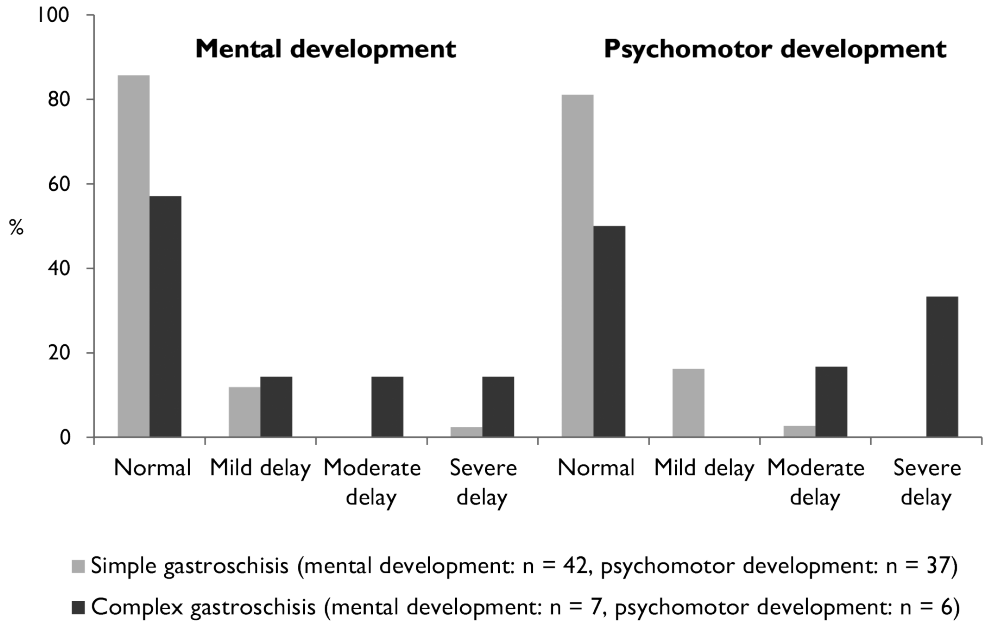

Figure 3 Proportions of children with simple or complex gastroschisis with normal or delayed mental (left panel) and motor (right panel) development at 24 months of follow-up.
Mild delay: developmental index 70–84; moderate delay: 55–69; severe delay:<55.

Discussion

In this longitudinal follow-up study, we assessed prenatal characteristics, growth and development of children born with simple or complex gastroschisis up to 2 years of age. We found a significant association between EABD at 30 weeks' gestation and complex gastroschisis. Despite the high morbidity in gastroschisis patients, their height and weight SDS at the age of 2 years fell within normal range. Although the differences between groups were not statistically significant, both mental and motor development were normal in over 80% of children with simple gastroschisis, and in half of those with complex gastroschisis.

We hypothesized that a GA-corrected definition of bowel and gastric dilatation would improve prediction of complex gastroschisis. The low prevalence of prenatal gastric dilatation may explain why this failed. Moreover, gastric dilatation might be physiological in gastroschisis, rather than a sign of complexity. Surprisingly, IABD at 30 weeks' gestation only occurred in simple gastroschisis, which suggests that IABD is not a clear sign of complex gastroschisis. A recent meta-analysis in contrast showed a significant association between IABD and bowel atresia, although the positive predictive value was low (22%, derived from table 4 of that paper) and thresholds of bowel dilatation differed between studies.[7] Furthermore, EABD –with thresholds ranging from 6 to 30 mm—did not predict bowel atresia.[7] One recent study showed an association between GA-corrected EABD and complex gastroschisis.[24] We showed that EABD at 30 weeks' gestation, but not at the last ultrasound prior to delivery, was significantly associated with complex gastroschisis. As evisceration of intra-abdominal organs continues during gestation, the colon—with a wider diameter than jejunum or ileum— may have eviscerated more frequently at later gestation also in simple gastroschisis. This may explain why uncorrected EABD is an unreliable predictor of complex gastroschisis, and why the association we found between EABD at 30 weeks' gestation and complex gastroschisis was no longer valid at the last ultrasound prior to delivery. In future studies, using up-to-date reference norms for bowel dilatation in healthy fetuses and gastroschisis fetuses, corrected for position (intra- or extra-abdominal), small and large intestine, and for GA will allow for valid comparison of study results and enable meta-analyses.

With the ultimate aim to optimize prenatal counselling, we evaluated physical growth and neurodevelopment up to 2 years of age, distinguishing between simple and complex gastroschisis. Previous studies on physical growth in gastroschisis patients reported suboptimal[10, 25] or normal growth[9] in infancy, and normal growth in childhood.[8, 11, 26, 27] The two studies that took into account the type of gastroschisis (simple or complex) found lower weight SDS in complex gastroschisis in infants aged 12 months,[25] and in children aged 5–17 years.[8] In contrast, we found no significant difference between

simple and complex gastroschisis; both groups had a height and weight SDS slightly below 0 SD, but within Dutch reference norms.

Neurodevelopment in gastroschisis patients has previously been studied in small cohorts,[9, 10, 28] sometimes combining different types of abdominal wall defects,[13, 29–31] or limited to simple gastroschisis.[32] Studies using formal neurodevelopmental assessment instruments reported favorable outcomes in gastroschisis patients aged 6–36 months, and a low incidence of adverse developmental outcome.[9, 10, 25, 28, 32] While Harris and coworkers reported normal intelligence in 39 gastroschisis patients aged 5–17 years,[33] Henrich and coworkers described parent-reported physical or intellectual delay in one-third of cases aged 1–10 years.[11] Giúdici and coworkers reported normal development in only half of 34 gastroschisis patients at the age of 3 years, and this proportion was even less at the age of 6 years.[27] The authors used a specific Argentine screening instrument, however, and did not differentiate between mental and motor development, which complicates comparison of results. To our knowledge, no previous study compared neurodevelopmental outcome between children with simple and complex gastroschisis.

We speculate that children with complex gastroschisis were more at risk for neurodevelopmental problems because of increased morbidity. We think social reasons have contributed less, as the prevalence of low status score was almost twice as low as in simple gastroschisis (although not significant). Because medical variables strongly correlate it is difficult to pinpoint the exact cause of delayed neurodevelopment. In addition, the sample of complex gastroschisis patients was too small to permit multivariable regression analysis.

We recommend close monitoring of psychomotor development of these children and referral to physical therapy at the earliest signs of disturbed development.
Strengths of our study are the relatively large sample size for such a rare disease; the high proportion of patients that joined the follow-up program with no significant differences in characteristics between children who did join and children who did not, so that selection bias can be considered to be minimal; and the use of standardized assessments both prenatally and postnatally.

Several limitations need to be addressed. First, the cut-off values for bowel dilatation were derived from a small cohort of healthy fetuses more than 25 years ago. Ultrasound techniques have been improved since then, and new cut-off values should be established for small bowel and colon dilatation. Second, the small sample of complex gastroschisis patients decreased the power of our tests. We think this has not affected the physical growth findings, as only 8% had weight below −2 SD and all of them had simple

gastroschisis. Still, failure to detect a significant difference between the proportions of children with normal and abnormal neurodevelopment may have derived from limited power.

In conclusion, prenatal ultrasound markers could not reliably distinguish between simple and complex gastroschisis. Two-year-old children with gastroschisis included in our study showed encouraging physical growth and neurodevelopment. Complex gastroschisis was associated with motor function delay within the first 2 years of life. Early start of pediatric physical therapy is recommended when motor function delay is suspected.

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4

Gastroschisis at school age: what do parents report?

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Abstract

Children with gastroschisis are at high risk of morbidity in early life, which could affect long-term outcomes. We determined parent-reported outcomes in school-aged children born in 2000-2012, using paper questionnaires. Parent-perceived child vulnerability and motor function were compared with the Dutch reference data; parent-rated data on cognition, health status, quality of life, and behavior were compared with those of controls matched for age, gender, and maternal education level. Of 77 eligible participants, 31 (40%) returned the questionnaires. Parent-reported motor function was normal in 23 (74%) children. Total scores on health status, quality of life, and behavior did not differ significantly from those of matched controls. Children with gastroschisis had lower scores on cognition (median (interquartile range); 109 (87-127)) than their matched controls (124 (113-140); $p = 0.04$). Neonatal intestinal failure and increased parent-perceived vulnerability were associated with lower scores on cognition (β - 25.66 (95% confidence interval - 49.41 to - 1.91); - 2.76 (- 5.27 to - 0.25), respectively).

Conclusion

Parent-reported outcomes of school-aged children with gastroschisis were mainly reassuring. Clinicians and parents should be aware of the higher risk of cognitive problems, especially in those with neonatal intestinal failure or increased parent-perceived vulnerability. We recommend multidisciplinary follow-up at school age of children with gastroschisis and neonatal intestinal failure.

Introduction

Gastroschisis is a life-threatening congenital abdominal wall defect requiring surgical treatment shortly after birth. Nowadays, over 90% of cases are diagnosed prenatally,[1] which allows for early parental counseling. Additional anomalies are relatively rare, and survival rates are over 90%.[2] However, these infants are at high risk of morbidity, especially those with associated intestinal defects (complex gastroschisis[3]). Morbidities include intestinal failure, prolonged length of hospital stay (LOS), and complications such as adhesive small bowel obstruction, parenteral nutrition-related cholestasis, and sepsis.[4, 5, 6, 7] In addition to having undergone surgery in early life, many of these infants are born small for gestational age (SGA)[8, 9] or preterm,[2] which may affect neurodevelopmental outcomes.[10, 11, 12, 13] Parent-reported outcome measures are becoming increasingly relevant, but data on outcomes at school age are scarce and conflicting.[14, 15, 16, 17, 18]

To optimize follow-up and to improve parental counseling, we evaluated parent-reported motor function, cognition, health status, quality of life, and behavior in school-aged children (i.e. 4–17 years) with gastroschisis. In addition, we sought to identify predictors of cognition and behavior at school age, including parent-perceived child vulnerability, infant clinical data, sociodemographic characteristics, and neurodevelopmental outcomes that had been evaluated in these children at 2 years of age.[7]

Materials and methods

Participants

We sent paper questionnaires with a self-addressed envelope to the caregivers of all surviving children born with gastroschisis between 2000 and 2012, and treated at our hospital. Questionnaires were sent once. In non-responders, a follow-up phone call was made after 2 to 4 weeks to check whether the questionnaires had been received. These caregivers had been offered to enter their child in the longitudinal prospective follow-up program that since 1999 is standard of care for children with anatomical congenital anomalies treated at our hospital.[19] Based on the favorable outcomes reported previously,[15, 19] the follow-up duration of children born with gastroschisis was limited to 2 years. Those with intestinal failure were invited to join an intestinal rehabilitation program.

At 2 years of age, the children's mental and motor development had been assessed using the Bayley Developmental Scales[20] or, from December 2003, the Bayley Scales of Infant Development-Second edition.[21] Both tests provide a psychomotor and mental developmental index (mean score 100, SD 15). Neurodevelopmental outcomes at 2

years of age in those with prenatally diagnosed gastroschisis have been published previously.[7] For the purpose of the current study, we excluded four children (figure 1). The Medical Ethical Review Board waived approval ('Medical Research in Human Subjects Act does not apply to this research proposal').

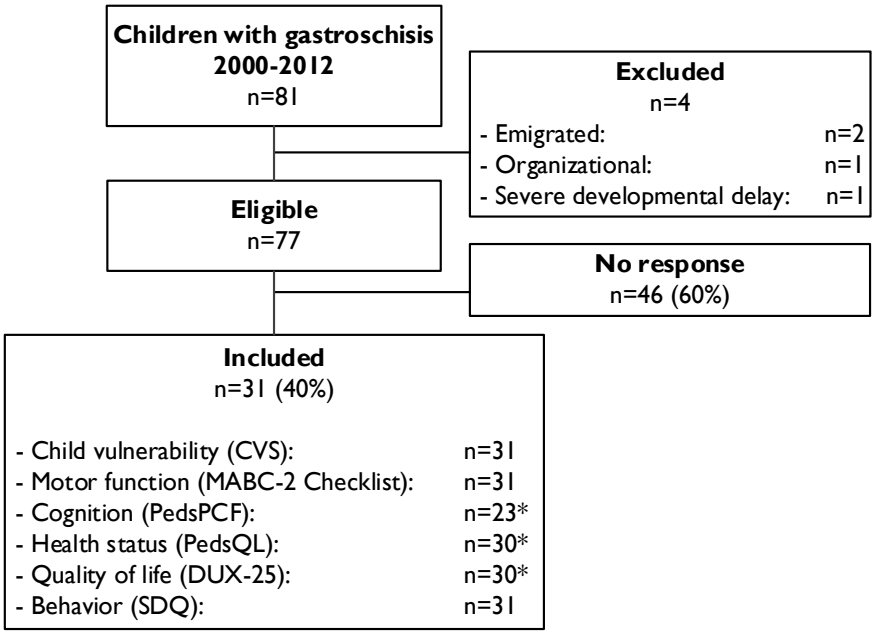

Figure 1 Inclusion flow chart
*Reasons for missing data: cognition (n = 8): child aged < 7 years (n = 8); health status (n = 1): questionnaire missing (n = 1); quality of life (n = 1): excluded because of > 3 missing values (n = 1).

Data collection

We retrieved infant clinical data from medical records. Preterm birth was defined as delivery <37 weeks of gestation. Infants with a birth weight <10th centile for Dutch reference curves were classified as SGA.[22] Those with additional intestinal defects (i.e. atresia, volvulus, necrosis, or perforation) were diagnosed with complex gastroschisis. We documented multiple congenital anomalies (MCA) that required surgery or multiple follow-up visits. If the time to full enteral feeding (TFEF) exceeded 2 years, the duration was set at 730 days. Intestinal failure was defined as TFEF >6 weeks. Socioeconomic status (SES) scores (population mean 0, SD 1) were based on postal codes at birth.[23, 24] The child's living situation, medical data, and educational information were retrieved from a background questionnaire (supplemental file 1). Maternal and paternal education level were classified according to the International Standard Classification of Education (ISCED) 2011, with ISCED 0–2 considered as low, ISCED 3–4 as middle, and ISCED 5–8 as high.[25]

Measures

We assessed the following outcome measures from parent-reported questionnaires (Dutch versions). A detailed description of each questionnaire is provided in supplemental file 1. For the analyses of cognition, health status, quality of life, and behavior, for each child with gastroschisis, we included two controls matched for age (maximum difference of 1 year), gender, and maternal education level (low, middle, or high[25]). Matched controls were randomly selected from three recently collected datasets for different outcome measures (supplemental file 2).

Child vulnerability: Child Vulnerability Scale (CVS).

Motor function: Movement Assessment Battery for Children-Second Edition (MABC-2) Checklist.

Cognition: Parents of children aged ≥ 7 years rated cognitive functioning via the Pediatric Perceived Cognitive Function (PedsPCF) questionnaire.

Health status and quality of life: Pediatric Quality of Life Inventory (PedsQL; health status) and DUX-25 (quality of life). As no matched controls were available for DUX-25 scores in 4–7 year-olds, these data were analyzed separately.

Behavior: Strengths and Difficulties Questionnaire (SDQ).

Statistical analysis

Continuous variables are presented as median (IQR), and categorical variables as number (%). Baseline characteristics of responders and non-responders were compared using Mann-Whitney tests (continuous variables), and chi-square or Fisher's exact tests (categorical variables). One-sample Wilcoxon signed-rank tests served to compare median scores of participants with those reported in the reference population; Mann-Whitney U tests and chi-square or Fisher's exact tests served to compare PedsPCF, PedsQL, DUX-25, and SDQ scores between participants and their matched controls.

To find possible predictors of cognition and behavior at school age, we used univariable linear regression analyses. These included parent-perceived child vulnerability, infant clinical data, sociodemographic characteristics, and neurodevelopmental outcomes at 2 years of age. Results were considered significant at $p<0.05$.

Results

Of 77 eligible participants, 31 (40%) caregivers returned the questionnaires (figure 1). Children of responders had a significantly higher SES score, were less often born SGA, and had shorter LOS than children of non-responders (table 1).

Table 1 Infant clinical data and sociodemographic data of responders (n=31) and non-responders (n=46)

	n	**Responders** n=31; 40%	n	**Non-responders** n=46; 60%	***p* value**
Age at current study (years)	31	9 (6-13)	46	9 (6-11)	0.38
Infant clinical data					
Prenatal diagnosis	31	27 (87%)	46	44 (96%)	0.21
Intoxications during pregnancy	24		43		
- Alcohol		-		-	n/a
- Smoking		11 (46%)		17 (40%)	0.62
- Recreational drugs		3 (13%)		2 (5%)	0.34
Male sex	31	17 (55%)	46	17 (37%)	0.12
Gestational age at birth (weeks)	31	37.0 (36.0-37.4)	46	36.4 (34.5-37.5)	0.39
Preterm birth	31	14 (45%)	46	27 (59%)	0.24
Birth weight (grams)	31	2500 (2200-2910)	46	2310 (2026-2663)	0.09
Small for gestational age	31	2 (6%)	45	12 (27%)	0.03
Complex gastroschisis	31	3 (10%)	46	8 (17%)	0.51
Primary closure	31	23 (74%)	46	31 (67%)	0.52
Multiple congenital anomalies [A]	31	4 (13%)	46	1 (2%)	0.15
Number of procedures under general anesthesia	31	2 (1-3)	46	2 (1-3)	0.24
Duration of initial mechanical ventilation (days)	29	2 (1-6)	46	2 (1-9)	0.49
Sepsis	31	10 (32%)	46	28 (61%)	0.02
Length of hospital stay (days)	31	35 (22-45)	46	50 (30-88)	0.02
Time to full enteral feeding (days)	31	25 (17-40)	45	36 (21-75)	0.06
Intestinal failure	31	7 (23%)	45	19 (42%)	0.08
- Time to full enteral feeding (days)	7	61 (48-67)	19	92 (64-159)	0.14
Sociodemographic data					
Maternal age at conception (years)	26	26.6 (20.6-30.9)	44	22.2 (19.7-27.4)	0.10
Socioeconomic status score	31	0.00 (-0.60 to 0.43)	46	-0.41 (-1.86 to 0.33)	0.04
- Low status score (< -1)	31	5 (16%)	46	21 (46%)	0.01

Table 1 (*continued*)

	n	Responders n=31; 40%	n	Non-responders n=46; 60%	*p* value
Maternal education level	30			n/a	
- Low (ISCED 0-2)		7 (23%)			
- Middle (ISCED 3-4)		15 (50%)			
- High (ISCED 5-8)		8 (27%)			
Paternal education level	24			n/a	
- Low (ISCED 0-2)		8 (33%)			
- Middle (ISCED 3-4)		12 (50%)			
- High (ISCED 5-8)		4 (17%)			
Two caregivers at home	31	23 (74%)		n/a	
Primary language at home: Dutch	31	31 (100%)		n/a	
Neurodevelopmental data at 2 years					
Mental developmental index [B]	25	101 (94-108)	28	101 (90-112)	0.90
- Delayed (<85)	25	4 (16%)	28	4 (14%)	1.00
Psychomotor developmental index [C]	20	91 (87-97)	27	94 (89-102)	0.37
- Delayed (<85)	20	4 (20%)	27	6 (22%)	1.00

Data are presented as median (IQR) or n (%). ISCED International Standard Classification of Education. [A] Responders: polydactyly (n = 2), cryptorchidism (n = 1), hypospadias (n = 1); non-responders: urethral valves (n = 1). [B] Missing data responders: organizational (n = 4), non-cooperative child (n = 1), parental refusal (n = 1); missing data non-responders: organizational (n = 4), non-cooperative child (n = 1), parental refusal (n = 12), migration (n = 1). [C] Missing data responders: organizational (n = 6), non-cooperative child (n = 4), parental refusal (n = 1); missing data non-responders: organizational (n = 5), non-cooperative child (n = 1), parental refusal (n = 12), migration (n = 1).

Background

Participating children had a median age of 9 years (IQR 6–13; range 4–16). Twenty-eight (90%) were raised by at least one biological parent, and three (10%) lived in a foster family. Twenty-three (74%) children had two caregivers at home. The questionnaires were answered by either the child's mother (n = 22), both parents (n = 6), or a foster parent (n = 3). Seven (23%) of 30 children required medication; one parent did not answer this question. Medication was prescribed for gastro-intestinal problems (n = 5), attention deficit hyperactivity disorder (ADHD; n = 1), or ADHD with an anxiety disorder (n = 1). Eleven (35%) parents reported that their child had behavioral or emotional problems, such as ADHD, autism, anxiety, or aggression. Five (16%) children attended special education; all five were reported to have behavioral or emotional problems.

Child vulnerability

The CVS score of children with gastroschisis (median 2 (IQR 0–5)) was significantly higher than that of the reference population (i.e. median CVS: 1,[26] p=0.004). Three (9%) children were perceived as being highly vulnerable; all had simple gastroschisis without MCA.

Motor function

MABC-2 Checklist scores were available for all 31 children (figure 1). Twenty-three (74%) scored within the normal range, four (13%) had borderline scores, and four (13%) were highly likely to have motor problems. One of these latter eight children had complex gastroschisis, none had MCA. Ball skills were particularly problematic.

Cognition

PedsPCF scores were analyzed in all 23 children aged 7 years or older. Their PedsPCF score (median 109 (IQR 87–127)) was significantly lower than that of matched controls (124 (113–140), p=0.04; table 2). The proportion of children scoring ≤ − 1 SD was significantly higher in the gastroschisis group (10/23, 43%) than in matched controls (5/46, 11%, p=0.002). Of the three children with complex gastroschisis, two scored ≤− 1 SD.

Table 2 Cognition, health status, quality of life and behavior of children with gastroschisis compared with control groups

	Gastroschisis [A]; n=23	**Matched control group;** n=46	***p* value**
Cognition (PedsPCF)			
Total score	109 (87-127)	124 (113-140)	0.04
	Gastroschisis [A]**;** n=30	**Matched control group;** n=60	***p* value**
Health status (PedsQL)			
Total score	86 (72-90)	84 (74-93)	0.82
- Physical functioning	92 (84-100)	91 (81-99)	0.42
- Emotional functioning	80 (64-86)	75 (61-89)	0.93
- Social functioning	85 (74-100)	90 (75-100)	0.50
- School functioning	78 (59-90)	80 (70-99)	0.04
Quality of life (DUX-25)			
Total score (4-7 year old); n=12	85 (76-97)	n/a	n/a
- Physical functioning	88 (72-99)		
- Emotional functioning	88 (76-100)		
- Social functioning	80 (71-96)		
- Home functioning	90 (76-100)		

Table 2 (*continued*)

	Gastroschisis [A]; n=30	**Matched control group; n=60**	***p* value**
Total score (8-17 year old); n=18	74 (64-95)	85 (75-93)	0.12
- Physical functioning	67 (58-94)	88 (75-96)	0.03
- Emotional functioning	73 (56-88)	82 (71-93)	0.19
- Social functioning	79 (67-90)	84 (69-93)	0.36
- Home functioning	78 (64-100)	93 (80-100)	0.04
	Gastroschisis [A]; n=31	**Matched control group; n=62**	***p* value**
Behavior (SDQ)			
Total difficulties score	10 (4-14)	6 (3-10)	0.15
- Emotional problems	2 (0-3)	1 (0-3)	0.39
- Conduct problems	2 (0-3)	1 (0-2)	0.31
- Hyperactivity-inattention	4 (1-6)	3 (1-6)	0.42
- Peer problems	1 (0-2)	1 (0-1)	0.07
- Prosocial behavior	9 (7-10)	9 (8-10)	0.71

Data presented as median (IQR). P-values were derived from Mann-Whitney U tests. [A] For one child, maternal education level was unknown. This child was matched to a control with middle maternal education level. PedsPCF: Pediatric Perceived Cognitive Function questionnaire; PedsQL: Pediatric Quality of Life Inventory; SDQ: Strengths and Difficulties Questionnaire.

Health status

PedsQL scores were available for 30 children. Their total score (median 86 (IQR 72–90)) was similar to that of matched controls (84 (74–93), p=0.82), as well as subscale scores for physical, emotional, and social functioning (table 2). The subscale score for school functioning was significantly lower in children with gastroschisis (median 78 (59–90) versus 80 (70–99), p=0.04; table 2).

Quality of life

DUX-25 total scores were available for 30 children, of whom 18 were 8–17 years old. In this latter group, the difference in median DUX-25 total score between children with gastroschisis (74 (IQR 64–95)) and matched controls (85 (75–93)) did not reach statistical significance (p=0.12; table 2). Children with gastroschisis had significantly lower subscale scores for physical functioning (67 (58–94)) and home functioning (78 (64–100)) than their matched controls (88 (75–96), p=0.03, and 93 (80–100), p=0.04, respectively). In the 4- to 7-year-olds, the median DUX-25 total score was 85 (76–97).

Behavior

SDQ scores were analyzed in all 31 children. Their total difficulties score (median 10 (IQR 4–14)) did not significantly differ from that of matched controls (6 (3–10), p=0.15;

table 2), and neither did the subscale scores. The total difficulty score was abnormally high in four (13%) children with gastroschisis, compared with seven (11%) matched controls (p=1.00).

Predictors of cognition and behavior

For cognition, univariable regression analysis revealed that both neonatal intestinal failure and increased parent-perceived child vulnerability were significantly associated with a lower PedsPCF total score (neonatal intestinal failure β −25.66 (−49.41 to −1.91); CVS score β −2.76 (95% CI −5.27 to −0.25); supplemental table 1).

For behavior, both older age and SGA were significantly associated with a lower SDS of the SDQ total difficulties score (older age, in years −0.13 (−0.24 to −0.02); SGA −2.18 (−3.79 to −0.57); supplemental table 2).

Discussion

We analyzed parent-reported daily functioning and developmental outcome of children with gastroschisis at school age. Scores on motor function, health status, overall quality of life, and behavior were comparable with those of healthy children. Cognitive problems were reported more frequently in children with gastroschisis, especially in those with neonatal intestinal failure or higher parent-perceived vulnerability.

Previous similar studies have shown contradicting results. Some have reported normal intelligence, motor function, or behavior, whereas others reported intellectual delay, problems regarding motor skills, or behavioral problems (supplemental table 3).

The studies that reported normal motor function either included children with omphalocele in their analyses[15] or used a non-standardized questionnaire,[16] which complicates comparison of results. A previous study in 16 children with gastroschisis showed normal motor function in only 7 on evaluation with the MABC-2 Test.[17] The difference with our finding of normal scores in 74% may be ascribed to the lower proportion of children born SGA in our study (6% vs. 44%), or to parents overestimating their child's motor function, or it might imply that the MABC-2 Checklist is less sensitive in diagnosing motor function delay than the MABC-2 Test itself. Our conclusion of normal motor function in children with gastroschisis should, therefore, be regarded with caution.

Children with gastroschisis appeared to be at risk for cognitive problems; PedsPCF scores were lower than those of matched controls, and 16% attended special education, which proportion is higher than in the Dutch reference population (i.e. approximately 5%).[27] A previous Dutch study in 16 children with gastroschisis found a lower total IQ

at school age, and three (19%) attended special education.[17] Two other studies, however, reported normal total IQ in 20 children with gastroschisis at 5 years of age[18] and in 39 children at school age.[14] Remarkably, both studies reported significant problems in working memory.[14, 18] Neonatal critical illness may well have contributed to cognitive problems; exposure to anesthetics, possible hypoxia, inflammation, and stress in early life increase the risk of hippocampal alterations, which may eventually lead to learning problems.[11]

Lower PedsPCF scores were associated with increased parent-perceived child vulnerability, which could have several causes. First, parents who perceive their child as highly vulnerable may report more problems, despite normal outcomes at medical evaluation. Early parental counseling and support may positively affect the child's outcomes as perceived by parents. Second, medical or sociodemographic factors such as intestinal failure or SES could act as confounders, by influencing both child vulnerability and cognitive functioning. Children with intestinal failure scored approximately 26 points (≈1 SD) less on the PedsPCF total score than those without intestinal failure. As the prevalence of intestinal failure in the non-responder group was almost twice that in the responder group, we may have underestimated the prevalence of cognitive problems.

In comparison with our study, previous literature showed overall health status in line with normative expectations.[5, 28, 29, 30] Our study showed that children with gastroschisis had slightly lower scores on the school functioning subscale of the PedsQL than their matched controls. As median scores differed with only 2 points on a scale of 0–100, we expect this difference not to be clinically relevant.

Although overall quality of life was reported as normal, the DUX-25 subscale scores of physical functioning and home functioning were significantly lower in the gastroschisis group. Negative feelings about physical appearance might be caused by poor physical growth, or by the scar. Home functioning might be impaired by factors associated with the risk of gastroschisis itself, such as teenage pregnancy or maternal mental disorders.[31] However, we acknowledge that these hypotheses are speculative.

Of all children eligible for our study, 18% had been born SGA versus only 6% in the group of parents who returned the questionnaires. Although we should note the very small sample size, being born SGA was significantly associated with behavioral problems. Consequently, the prevalence of behavioral problems in the total gastroschisis population may well be higher. In a previous study including 20 children with gastroschisis, of whom 40% were born SGA, one-third of parents reported behavioral executive problems at 5 years of age.[18] This might still be an underestimation, as we

found that older age was significantly associated with behavioral problems, despite the fact that SDS had already been corrected for age.

Strengths of our study include the assessment of outcomes in children beyond the age of 5 years rather than at pre-school age, the comparison of outcomes with those of matched controls, and the availability of neurodevelopmental data at 2 years of age. We used parent-reported outcome measures; since parents are largely responsible for seeking help for their children, we expect our results to be a relevant representation of the need for care in this group. Several limitations need to be addressed. First, while 45% of children with gastroschisis in our cohort were born preterm, we were unable to match controls on GA at birth. A second limitation is the low response rate of 40% and the positive selection bias. Low response rates are a common problem (supplemental table 3). As children in the responder group had higher SES, and had experienced less morbidity than non-responders, we may have underestimated the frequency and severity of problems regarding daily functioning. To improve response rates, future studies may limit the number and the length of questionnaires. Based on our outcomes, we would suggest to focus on cognitive functioning and on parent-perceived vulnerability. Additionally, home visits and computerized adaptive testing may help to encourage participation in follow-up studies.

In conclusion, parent-reported outcomes of children with gastroschisis at school age were mainly reassuring. Clinicians and parents should be aware of the higher risk of cognitive problems, especially in those with neonatal intestinal failure or increased parent-perceived vulnerability. We recommend multidisciplinary follow-up at school age of children with neonatal intestinal failure. Early parental counseling and support may positively affect the child's outcomes as perceived by parents.

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Supplemental material

Supplemental file 1 Description of questionnaires

We used Dutch versions of all questionnaires. All questionnaires were parent-reported. If two answers were selected for one question, we documented the most unfavorable score.

Background

Description: We asked caregivers to report the following background information: child's living situation (e.g. with biological parents or in a foster family, presence of two caregivers, number of children), maternal and paternal education levels (based on the International Standard Classification of Education 2011),[1] medical (use of medication, hospital admissions, use of medical aids such as a wheelchair or parenteral nutrition), educational (e.g. regular or special, grade repetition, learning difficulties, need of extra help at school), social-emotional functioning (presence of behavioral or emotional problems), and main language spoken at home.

Child vulnerability

Child Vulnerability Scale (CVS) [2, 3]

Description: The CVS is an 8-item questionnaire on parental perceptions of their child's vulnerability. Each item states a problem, for example 'my child gets more colds than other children I know'. Answers vary from strongly disagree (=0) to strongly agree (=3) on a 4-point Likert scale. Total scores range from 0-24; higher scores reflect higher perceived vulnerability. We used a cut-off of ≥10 for high perception of vulnerability.
Validated: This questionnaire has been validated for Dutch children aged 5-18 years.[2]

Motor function

Movement Assessment Battery for Children - Second Edition (MABC-2) Checklist [4-6]

Description: The M-ABC 2 Checklist is aimed at evaluating motor problems in daily life. Section A measures movement in a static (or predictable) environment; section B measures movement in a dynamic (or unpredictable) environment. Both sections consist of 15 items. Each of the 30 items states a skill, for example 'rides a bicycle without stabilizers'. The parent indicates to what extent the child is able to do this, varying from very well (=0) to not close (=3). Scores are reported using a Traffic Light color system, corrected for age, with high scores representing poor performance. 'Green zone' indicates a score within the normal range (< 85th centile); 'amber zone' means that the child is at risk for motor problems (85th-94th centile), and a score in the 'red zone' indicates a high possibility of serious motor problems (≥ 95th centile).

Validated: This questionnaire has been validated for Dutch children aged 3-16 years.[6] As no Dutch reference norms exist for 17-year old children, these children were scored according to reference norms for 16-year olds.

Cognition

Pediatric Perceived Cognitive Function (PedsPCF) questionnaire [7]

Description: The PedsPCF assesses the child's cognitive functioning as perceived by the parent, referring to the past four weeks. Each item reflects a problem, for example 'forgets things easily'. Answers vary from very much/all of the time (=1) to not at all/none of the time (=5) on a 5-point Likert scale. Based on preliminary results of the collection of Dutch reference data, we used only the first 30 items of the PedsPCF rather than the full-length PedsPCF (which counts 43 items), and we used the following cut-offs of ≤-1 standard deviation (SD): 102 (7-12 years), 104 (13-18 years). Total scores range from 30-150; higher scores reflect better cognitive functioning.

Validated: This questionnaire has been validated for Dutch children aged 7-18 years.[8]

Health status

Pediatric Quality of Life Inventory (PedsQL) [9]

Description: The PedsQL is an instrument for measuring health status in children and adolescents. It consists of four subscales: physical (8 items), emotional (5 items), social (5 items) and school functioning (5 items). Each item reflects a problem, for example 'problems with running'. Answers vary from never (=0) to almost always (=4) on a 5-point Likert scale. Each answer is reversed scored and rescaled to a 0-100 scale (0=100, 4=0). Total scores range from 0-100; higher scores reflect better quality of life. We used the version that referred to the past month.

Validated: This questionnaire has been validated for Dutch children aged 5-18 years.[10]

Quality of life

DUX-25

Description: The DUX-25 is a visual health-related quality of life questionnaire. Each question evaluates the child's feelings in daily life, for example 'your child often feels …'. It consists of four subscales: physical (6 items), emotional (7 items), social (7 items) and home functioning (5 items). Answers are scored on a happy-to-sad faces scale by use of smileys. These smileys visualize a 5-point Likert scale, ranging from sad (=0) to happy (=100). Total scores range from 0-100; higher scores reflect better quality of life.

Validated: Dutch reference data are currently being analyzed (age 8-17 years).

Behavior

Strengths and Difficulties Questionnaire (SDQ) [11]

Description: The SDQ covers the most important domains of child psychopathology and personal strengths. It consists of five subscales: emotional symptoms, conduct problems, hyperactivity-inattention, peer problems, and prosocial behavior. Each item is scored on a 3-point Likert scale; answer vary from not true (=0) to certainly true (=2). Higher scores reflect more difficulties, except for the prosocial scale where higher scores reflect strengths. All but the prosocial behavior subscale scores are summed to generate a total difficulties score. Total scores range from 0-40. The total difficulties score was categorized into 'normal' or 'abnormal' using age-dependent cut-off values.[11]

Validated: This questionnaire has been validated for Dutch children aged 2-18 years.[11] In children aged <6 years, no SD scores or cut-off values were available for 'conduct problems' and 'peer problems' due to insufficient internal consistency of these subscales in this age group.

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Supplemental file 2 Description of matched controls

We obtained matched controls from three different datasets, as described below. Controls were matched for age (maximum difference of one year), gender, and maternal education level (low, middle, or high; based on the International Standard Classification of Education 2011[1]). Controls were selected randomly using an online randomizer. If the maternal education level of a case was unknown, this case was matched with two controls with middle maternal education level.

Cognition

Pediatric Perceived Cognitive Function (PedsPCF) questionnaire

Matched controls were obtained from a study that collected Dutch normative data for the PedsPCF.[2] A general population sample of parents and their children had been approached through research agency Kantar TNS in January 2016. This study included children with a chronic health condition, such as asthma or diabetes mellitus. This study used online questionnaires. We used the parent-reported data.

Health status and quality of life

Pediatric Quality of Life Inventory (PedsQL) and DUX-25

Matched controls were obtained from a study that collected Dutch normative data for the PedsQL (4-17 years) and the DUX-25 (8-17 years) (publications in preparation). Children with a chronic health condition had been excluded from this study; those with attention deficit hyperactivity disorder had been included. Online questionnaires had been sent to caregivers and their children, who were recruited via primary and secondary schools in the Netherlands from April 2015 till March 2016. We used the parent-reported data.

Behavior

Strengths and Difficulties Questionnaire (SDQ)

Matched controls were obtained from the database of Maurice-Stam and coworkers.[3] A general population sample of parents had been approached through research agency Kantar TNS in November and December 2014.

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Supplemental table 1 Univariable linear regression analysis showing possible predictors of the PedsPCF total score (n=23)

	Unstandardized beta	95% confidence interval	*p* value
Age at current study (years)	0.19	-3.56 to 3.94	0.92
Child Vulnerability Scale score	-2.76	-5.27 to -0.25	0.03
Infant clinical data			
Intoxications during pregnancy			
- Smoking	-17.71	-45.66 to 10.24	0.20
- Recreational drugs	n/a		
Male sex	-9.32	-32.18 to 13.55	0.41
Preterm	-13.82	-36.21 to 8.57	0.21
Small for gestational age	-14.61	-55.29 to 26.08	0.46
Complex gastroschisis	-19.66	-52.97 to 13.65	0.23
Secondary closure	4.55	-21.82 to 30.92	0.72
Multiple congenital anomalies	6.52	-27.84 to 40.88	0.70
Number of procedures under general anesthesia	-5.41	-11.12 to 0.29	0.06
Duration of initial mechanical ventilation (days)	-0.30	-2.10 to 1.51	0.73
Sepsis	-1.63	-26.00 to 22.75	0.89
Length of hospital stay (days)	-0.06	-0.14 to 0.01	0.10
Intestinal failure	-25.66	-49.41 to -1.91	0.04
Sociodemographic data			
Maternal age at conception (years)	-0.56	-2.47 to 1.35	0.55
Low status score (<-1)	23.95	-8.78 to 56.68	0.14
Highest parental education level (ISCED level low to high) [A]	-7.89	-22.01 to 6.24	0.26
One caregiver at home	4.86	-20.29 to 30.00	0.69

Supplemental table 1 (continued)

	Unstandardized beta	95% confidence interval	*p* value
Neurodevelopmental data at 2 years			
Delayed mental developmental index (<85)	-39.16	-91.36 to 13.04	0.13
Delayed psychomotor developmental index (<85)	20.50	-32.95 to 73.94	0.42

PedsPCF: Pediatric Perceived Cognitive Function; ISCED: International Standard Classification of Education. [A] If paternal education level was unknown, we documented maternal education level as highest parental education level.

Supplemental table 2 Univariable linear regression analysis showing possible predictors of the SDS of the SDQ total difficulties score (n=31)

	Unstandardized beta	95% confidence interval	*p* value
Age at current study (years)	-0.13	-0.24 to -0.02	0.02
Child Vulnerability Scale score	-0.10	-0.21 to 0.00	0.06
Infant clinical data			
Intoxications during pregnancy			
- Smoking	-0.46	-1.49 to 0.57	0.37
- Recreational drugs	0.26	-1.32 to 1.85	0.73
Male sex	-0.12	-1.02 to 0.77	0.78
Preterm	0.02	-0.88 to 0.91	0.97
Small for gestational age	-2.18	-3.79 to -0.57	0.01
Complex gastroschisis	0.16	-1.34 to 1.67	0.83
Secondary closure	-0.03	-1.05 to 0.99	0.95
Multiple congenital anomalies	0.03	-1.30 to 1.36	0.96
Number of procedures under general anesthesia	-0.11	-0.38 to 0.15	0.38
Duration of initial mechanical ventilation (days)	-0.04	-0.12 to 0.04	0.29
Sepsis	-0.34	-1.28 to 0.61	0.47
Length of hospital stay (days)	0.00	0.00 to 0.00	0.63
Intestinal failure	-0.25	-1.31 to 0.81	0.63
Sociodemographic data			
Maternal age at conception (years)	0.00	-0.07 to 0.08	0.94
Low status score (<-1)	0.44	-0.76 to 1.63	0.46
Highest parental education level (ISCED level low to high) [A]	0.07	-0.57 to 0.71	0.82
One caregiver at home	-0.48	-1.53 to 0.57	0.36

Supplemental table 2 (continued)

	Unstandardized beta	95% confidence interval	*p* value
Neurodevelopmental data at 2 years			
Delayed mental developmental index (<85)	-0.01	-1.46 to 1.44	0.99
Delayed psychomotor developmental index (<85)	-0.30	-1.81 to 1.21	0.68

SDS: standard deviation score; SDQ: Strengths and Difficulties Questionnaire; ISCED: International Standard Classification of Education. [A] If paternal education level was unknown, we documented maternal education level as highest parental education level.

Supplemental table 3 Overview of follow-up studies assessing motor function, cognition, health status, quality of life and/or behavior in children with gastroschisis at school age

Reference	Outcome	Assessment or questionnaire	Tests	Group	Number of children	Year of birth	Age at follow-up	Normative data	Most important results
Amin et al. 2018 [1]	Health status	Questionnaire (parent)	PedsQL	GS	32	not stated	1-17 (median: 4) years	PedsQL parent-report: 88±12	*Health status:* in line with normative expectations (mean 80 (95% CI: 73-86)).
Arnold et al. 2018 [2]	Health status	Questionnaire (parent, telephone)	PedsQL	GS	45/143 (31%)	2009-2012	>3 (median: 5) years	PedsQL parent-report: 88±12	*Health status:* in line with normative expectations (median 100 (IQR: 96-100)).
Burnett et al. 2018 [3]	Cognition	Assessment	WPPSI-III	GS	20/35 (57%)	2006-2014	5 years	TIQ: 100±15	*Cognition*: in line with normative expectations (mean±SD TIQ: 100±10).
	Behavior	Questionnaires (parent)	BRIEF-P and BASC-2					Elevated scores: BRIEF-P: 7%, BASC-2: 16%	*Behavior*: a substantial number of children fell in the elevated range across BRIEF-P scales (e.g. over 40% scored abnormal for the working memory scale).

Supplemental table 3 (*continued*)

Reference	Outcome	Assessment or questionnaire	Tests	Group	Number of children	Year of birth	Age at follow-up	Normative data	Most important results
Lap et al. 2017 [4]	Motor function	Assessment	M-ABC	GS	16	1999-2006	5-13 (median: 9) years	Normal: 85%; at risk: 10%; problem: 5%	*Motor function*: significantly poorer than matched controls on all M-ABC scores, especially on fine motor skills.
	Cognition	Assessment	WISC-III					TIQ: 100±15	*Cognition:* significantly lower TIQ and verbal IQ than matched controls (mean±SD TIQ: 92±13; median verbal IQ: 95 (IQR: 88-100)). 19% received special education, 58% had repeated a grade.
	Behavior	Questionnaires (parent)	CBCL BRIEF					Normal: 85%; at risk: 10%; problem: 5%	*Behavior*: not significantly different from matched controls (normal: 75%, borderline: 6%, abnormal: 19%).

Supplemental table 3 (*continued*)

Reference	Outcome	Assessment or questionnaire	Tests	Group	Number of children	Year of birth	Age at follow-up	Normative data	Most important results
Rankin et al. 2016 [5]	Health status	Questionnaire (child and parent)	KID-SCREEN	GS	10/53 (19%)	not stated	8-11 (median 10) years	KID-SCREEN self-report: 10 domains (between 45±12 and 53±10)	*Health status*: all domains in line with normative expectations (e.g. mean±SD physical well-being: 54±12). All children described health as good/very good or excellent.
Carpenter et al. 2016 [6]	Health status	Questionnaire (parent)	PedsQL	GS	28/119 (24%)	2005-2011	>2 (mean: 6) years	PedsQL parent-report: 88±12	*Health status:* in line with normative data (mean±SD simple GS: 82±20, complex GS: 79±20)
Harris et al. 2016 [7]	Cognition	Assessment	WPPSI-III (if <6 years) or WISC-IV	GS	39/99 (39%)		5-17 (median: 10) years	TIQ: 100±15	*Cognition:* in line with normative data (mean±SD: 98±11)
	Behavior	Questionnaire (parent)	SDQ	GS	39/99 (39%)		5-17 (median: 10) years	SDQ total difficulties score: 7±6	*Behavior*: more problems than healthy children (mean±SD: 11±7).

Supplemental table 3 (*continued*)

Reference	Outcome	Assessment or questionnaire	Tests	Group	Number of children	Year of birth	Age at follow-up	Normative data	Most important results
Giúdici et al. 2016 [8]	Motor function / cognition	Assessment	PRUNAPE	GS	17/62 (27%)	2002-2013	6 years	n/a	*Motor function / cognition:* normal in 35%. 35% attended a special school.
Hamrick et al. 2010 [9]	Cognition	Linkage with education files public schools	n/a	GS	134 (128 isolated, 6 non-isolated)	1982-2001	Ever received special education between 3-10 years	Use of special education services: 8%	*Cognition*: use of special education services in line with normative data for isolated gastroschisis (6%), and higher for non-isolated gastroschisis (50%).
Van der Cammen-van Zijp et al. 2010 [10]	Motor function	Assessment	M-ABC	GS+OC	24/33 (73%)	1999-2003	5 years	Normal: 85%; at risk: 10%; problem: 5%	*Motor function*: in line with normative data (normal: 79%, at risk: 13%, problem: 8%).

Supplemental table 3 (*continued*)

Reference	Outcome	Assessment or questionnaire	Tests	Group	Number of children	Year of birth	Age at follow-up	Normative data	Most important results
Henrich et al. 2008 [11]	Motor function	Questionnaire (not stated)	not standard-ized	GS	22/40 (55%)	1994-2004	1-10 (median 6) years	n/a	*Motor function*: 9% problems with physical exercise, one child felt restricted in sporting activities.
	Cognition	Questionnaire (not stated)	not standard-ized					n/a	*Cognition*: 77% had attended kindergarten or school at usual age.
Ginn-Pease et al. 1991 [12]	Cognition	Assessments	WISC-R WJ-R	GS+OC	22/93 (24%)	1972-1981	6-16 (mean: 11) years	TIQ: 100±15	*Cognition*: in line with normative data (mean±SD: 100±16).
	Behavior	Questionnaires (parent)	VABS CBCL					VABS ≥ 85. ACBC < 63	*Behavior*: mean scores within normal range (VABS: 95±16; CBCL: 57±10); however, 18% exceeded the 90th percentile on the CBCL.

GS: gastroschisis; OC: omphalocele; CI: confidence interval; IQR: interquartile range; TIQ: total intelligence quotient; SD: standard deviation; PedsQL: Pediatric Quality of Life Inventory; WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence-3rd edition; BRIEF: Behavior Rating Inventory of Executive Functioning (-P: preschool version); BASC-2: Behavior Assessment System for Children – 2nd edition (preschool); M-ABC: Movement Assessment Battery for Children; WISC: Wechsler Intelligence Scale for Children (-R: revised; -III: 3rd edition; IV: 4th edition); CBCL: Child Behavior Checklist; SDQ: Strengths and Difficulties Questionnaire; PRUNAPE: Prueba Nacional de Pesquisa [Argentine screening instrument]; WJ-R: Woodcock-Johnson Psycho-Educational Battery-revised; VABS: Vineland Adaptive Behavior Scale.

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OMPHALOCELE



5

The validity of the viscero-abdominal disproportion ratio for type of surgical closure in all fetuses 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 center (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.

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 1-2 per 10 000 live births.[2] Multiple congenital anomalies (MCA) are observed in 30-70% of fetuses with an omphalocele, and chromosomal abnormalities are present in 10-30%.[1, 3, 4] Infants with MCA or chromosomal abnormalities carry a significantly higher risk of co-morbidity 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, i.e. 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 weeks' 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 analyzed prospectively stored data of live-born infants who were prenatally diagnosed with an omphalocele in our tertiary referral center 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 intra-uterine 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 analyzed (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 (11-16 weeks' gestation; US1), mid second trimester (17-26 weeks' gestation; US2) and in the third trimester (30-38 weeks' 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 supplemental figure 1. All measurements were performed in retrospect by two experienced physicians (TECO and NCJP), who were unaware of postnatal 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 MCA 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 weeks' 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 >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 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 0.75 and for excellent agreement the ICC has to be higher than 0.90. 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 2 or 3 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 one 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 odds 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 <0.05 was considered statistically significant.

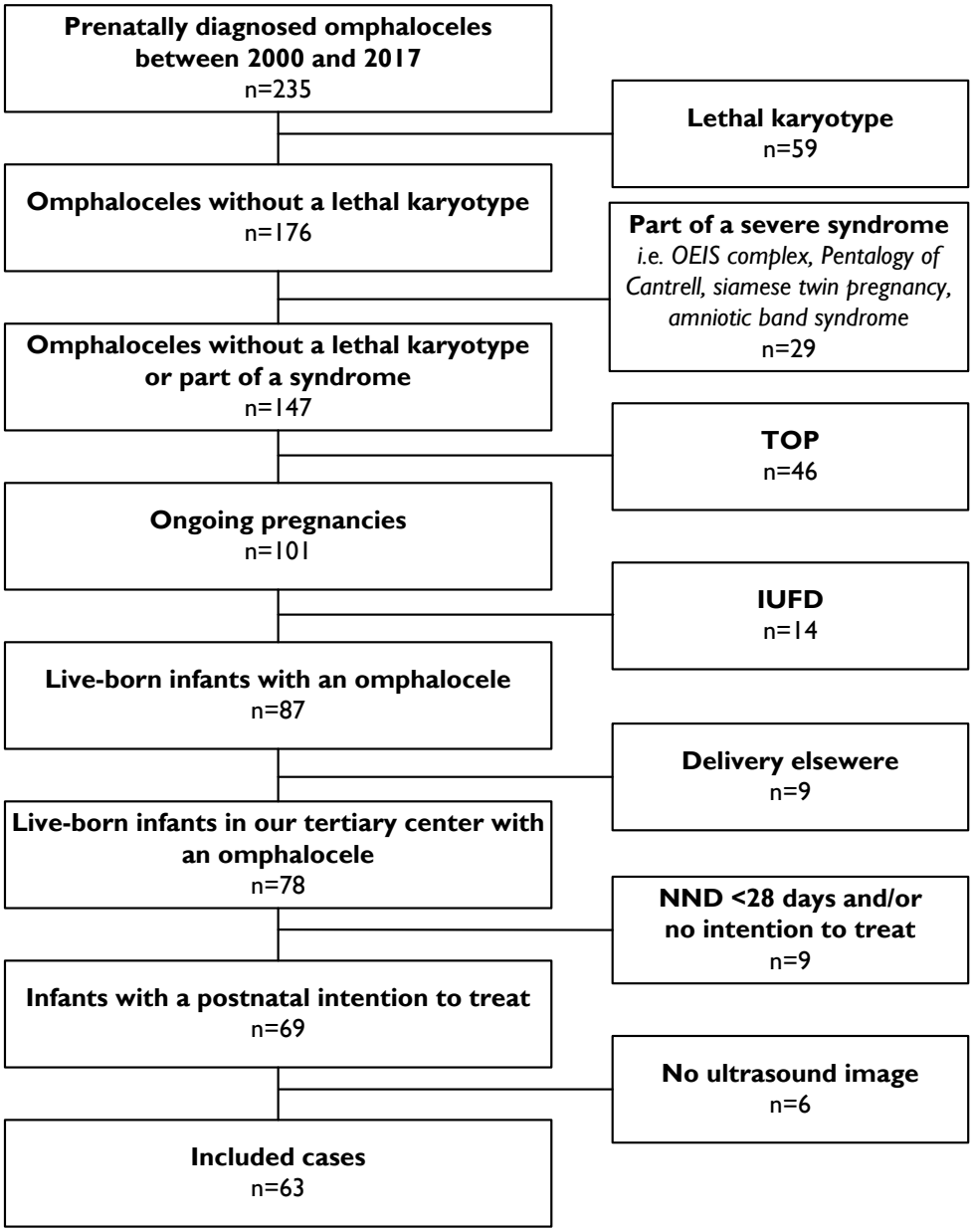

Figure 1 Inclusion flow chart of fetuses diagnosed prenatally with an omphalocele
OEIS: omphalocele-exstrophy-imperforate anus-spinal defects; TOP: termination of pregnancy; IUFD: intrauterine fetal death; NND: neonatal death

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 2 fetuses at US1 and 2 fetuses at US3. There were no differences between the assessments of liver location (extra-abdominal versus intra-abdominal) at the different time periods per fetus. Interobserver agreement calculations resulted in an ICC of 0.97 (95% CI: 0.92–0.99), representing excellent agreement. Patient characteristics are summarized in table 1.

Table 1 Patient characteristics

	Primary closure n=37	**Delayed closure** n=26	***p* value**
Prenatal parameters			
11-16 weeks' gestation			
Gestational age (w^{+d})	13^{+1} (12^{+4}-15^{+4})	16^{+1} (13^{+5}-16^{+6})	0.02
OC/AC-ratio (n=22;P=9/D=13)	0.51 (0.44-0.68)	0.94 (0.79-1.00)	<0.001
Liver herniation (n=21;P=8/D=13)	2 (25%)	13 (100%)	0.001
18-26 weeks' gestation			
Gestational age (w^{+d})	20^{+4} (20^{+0}-21^{+5})	20^{+5} (19^{+5}-21^{+2})	0.63
OC/AC-ratio (n=50; P=28/D=22)	0.46 (0.30-0.56)	0.84 (0.76-0.92)	<0.001
Liver herniation (n=51;P=28/D=23)	5 (18%)	23 (100%)	<0.001
30-38 weeks' gestation			
Gestational age (w^{+d})	31^{+4} (30^{+4}-32^{+1})	31^{+1} (30^{+1}-32^{+0})	0.58
OC/AC-ratio (n=58; P=36/D=22)	0.40 (0.32-0.46)	0.77 (0.72-0.88)	<0.001
Liver herniation (n=58;P=35/D=23)	5 (14%)	23 (100%)	<0.001
Liver herniation	5 (14%)	26 (100%)	<0.001
Isolated	23 (62%)	23 (89%)	0.02
Postnatal parameters			
GA at delivery (w^{+d})	38^{+1} (36^{+3}-38^{+6})	38^{+3} (35^{+6}-38^{+6})	0.93
Delivery <32 weeks GA	3 (8%)	3 (12%)	0.65
Spontaneous vaginal delivery	25 (68%)	15 (58%)	0.42
Apgar score at 5 minutes	9 (8-10)	8 (6-9)	0.002
Birth weight (grams)	2960 (2433-3330)	2815 (1994-3378)	0.40
Gender female	21 (57%)	12 (46%)	0.41
Isolated	19 (51%)	17 (66%)	0.19
Giant omphalocele	2 (5%)	24 (92%)	<0.001
Survival (until 1 year of age)	36 (97%)	18 (69%)	0.002

Table 1 (*continued*)

	Primary closure n=37	**Delayed closure** n=26	***p*** **value**
Chronic lung disease	7 (19%)	15 (58%)	0.002
Length of initial hospital stay (days)	10 (7-35)	52 (19-107)	<0.001

Data are presented as median (IQR) or number (%). Per ultrasound time period the number of cases (n) are described per analysis for the total group and per type of closure, where P represents primary closure, and D represents delayed closure. w^{+d}: weeks+days; OC/AC: omphalocele circumference / abdominal circumference.

Additional anomalies were diagnosed in 19/63 (30%) of fetuses in the prenatal period. In 9/44 (20%) cases where the omphalocele was assumed isolated, additional anomalies were detected after birth. In 6 of these cases the anomalies were major (table 2). Eleven fetuses were diagnosed with a clinically significant syndrome and/or chromosomal abnormality, 9 of them had Beckwith 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 compared with 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=0.002, compared to 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, supplemental table 1 for logistic regression). Based on ROC curve analysis, 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<0.001), 0.66 at US2 (sensitivity 0.88 and specificity 0.93, AUC 0.98 (0.95-1.00), p<0.001), and 0.63 at US3 (sensitivity 0.95 and specificity 0.94, AUC 0.98 (0.95-1.00), p<0.001) (figure 3).

The mean OC/AC-ratio differed significantly between the three time periods (p=0.002), showing a decreasing trend throughout gestation. On the basis of the different optimal cut-offs per time period, 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 4/5 a primary closure was performed.

Table 2 Omphalocele cases with additional anomalies detected prenatally and postnatally

OC/AC-ratio			Survival	Prenatal liver	Closure	Prenatal anomalies	Postnatal anomalies
US1	US2	US3					
	0.31	0.40	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, nevus 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 mutation [A]	Bicuspid aortic valve, X-linked ALAS2 mutation [A]
		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 [B]
	0.52	0.65	No	No	Primary	AVSD, ToF, suspicion of small intestinal atresia	AVSD, ToF, TAPVR, hiatus hernia, asplenia, UPJ stenosis
	0.56		Yes	No	Primary	SUA, paternal microdeletion	Paternal microdeletion (16p13.11)
	0.72	0.42	Yes	No	Primary	Turner syndrome [C]	Turner syndrome [C]
		0.78	No	Yes	Delayed	Dilated right atrium (cardiomegaly)	Dilated right atrium and ventricle
0.80	0.66	0.85	No	Yes	Delayed	Postaxial polydactyly [D]	Postaxial polydactyly [D]
	0.37	0.35	Yes	Yes	Primary	Femur length <p5	BWS, soft palate schisis
		0.39	Yes	No	Primary	Suspicion of small intestine atresia	Small intestine atresia, bilateral polydactyly
		0.50	Yes	No	Primary	Suspicion of BWS	BWS, intestinal volvulus
	0.74	0.65	Yes	Yes	Delayed	Thoracic situs inversus, ascites	Dextrocardia, ASD, VSD, ODB, desmoid torticollis

Table 2 (*continued*)

OC/AC-ratio			Survival	Prenatal liver	Closure	Prenatal anomalies	Postnatal anomalies
US1	US2	US3					
0.96	0.81		Yes	Yes	Delayed	SUA with umbilical cord cyst	Hydroureter and hydronephrosis, ASD
	0.90	0.75	Yes	Yes	Delayed	Narrow thorax, dilated stomach	Bicuspid aortic valve with stenosis/insufficiency
0.46	0.30	0.32	Yes	No	Primary	-	Pierre Robin, sliding hernia
	0.37	0.31	Yes	No	Primary	-	BWS [E]
		0.40	Yes	No	Primary	-	Clasped thumb
0.52	0.56	0.42	Yes	No	Primary	-	BWS, two mVSDs [E]
	0.66	0.74	Yes	Yes	Primary	-	Mild pelvic dysplasia, sIUGR [F]
0.89	0.81	0.78	Yes	Yes	Delayed	-	Aplasia cutis congenita, Morgagni hernia, ASD type 2 [E]
0.76	0.91	0.73	No	Yes	Delayed	-	Large pVSD with overriding aorta, ODB [E]
1.00	1.05		No	Yes	Delayed	-	Small ASD and VSD (clinically irrelevant), CCA [E]
		1.11	No	Yes	Delayed	-	ToF, esophageal atresia with fistula [E]

Cases are ranked by concordance between prenatal and postnatal anomalies, severity of anomalies and OC/AC-ratio. [A] Mutation causing congenital sideroblastic anemia; [B] CHARGE-syndrome; [C] prenatal anomalies: enlarged nuchal translucency 4,1 mm, suspicion of CoAo with left ventricle < right ventricle, dilated bowel, IUGR and postnatal anomalies: CoAo, bicuspid aortic valve, bilateral dilated renal pelvis, dysplastic ears; [D] dichorionic triamniotic triplet; [E] fetus prenatally assumed isolated with postnatally major associated congenital anomalies; [F] monochorionic twin; OC/AC: omphalocele circumference/abdominal circumference; US: ultrasound; US1: 11-16 weeks' gestation; US2: 17-26 weeks' gestation; US3: 30-38 weeks' gestation; BWS: Beckwith-Wiedemann syndrome; mVSD: muscular ventricular septal defect; CoAo: coarctation aortae; mPVS: mild pulmonary valve stenosis; ToF: tetralogy of Fallot; SUA: single umbilical artery; AVSD: atrial ventricular septal defect; TAPVR: total anomalous pulmonary venous return; UPJ: uteropelvic junction; ASD: atrial septal defect; ODB: open ductus Botalli; pVSD: perimembranous ventricular septal defect; CCA: corpus callosum agenesis.

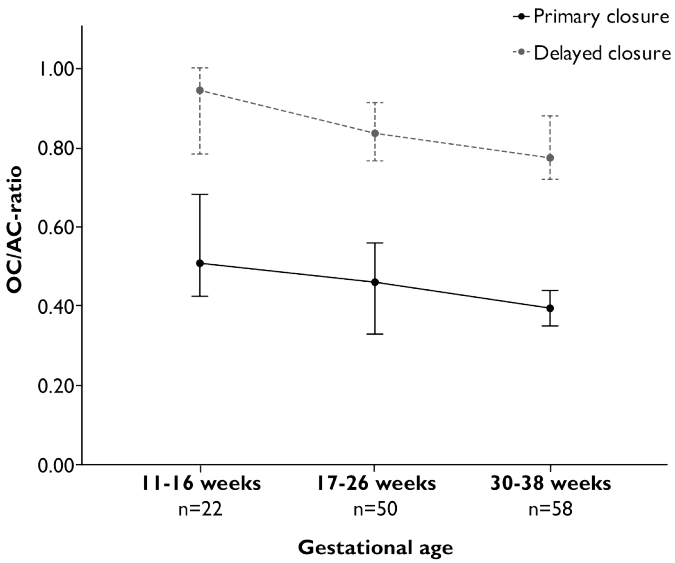

Figure 2 The OC/AC-ratio throughout gestation per type of postnatal closure
Data are presented as median OC/AC-ratio with 95% confidence interval, per ultrasound time period and stratified for type of closure. The dashed line represents cases with delayed closure. The solid line represents cases with primary closure. OC/AC: omphalocele circumference/abdominal circumference.

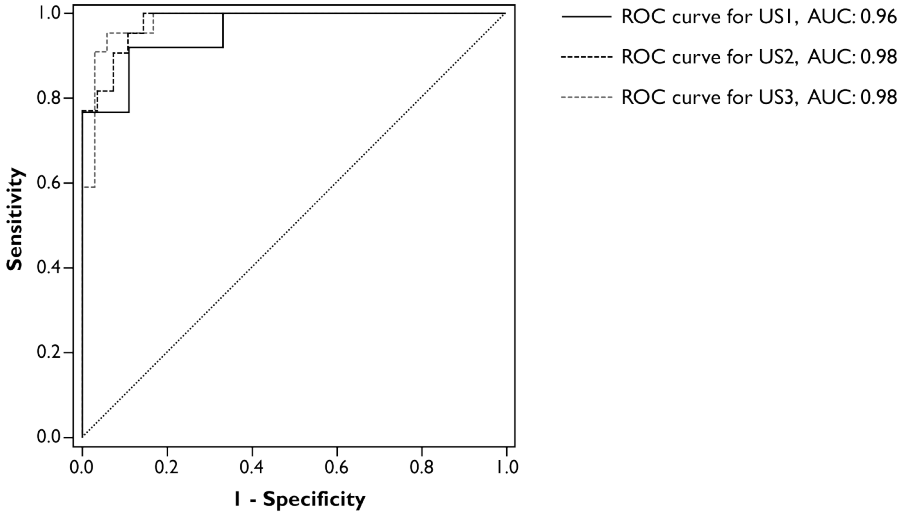

Figure 3 ROC analysis of the OC/AC-ratio at different time periods for type of closure
ROC for delayed closure according to cut-off values of the OC/AC-ratio. ROC: receiver operating characteristic; OC/AC: omphalocele circumference/abdominal circumference; AUC: area under the curve; US1: first ultrasound time period (11-16 weeks' gestation); US2: second ultrasound time period (17-26 weeks' gestation); US3: third ultrasound time period (30-38 weeks' gestation).

Using 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=0.01), but not for the slope (OR: 0.82; p=0.79), i.e. no association was found between the trend in OC/AC-ratio throughout gestation and type of postnatal closure (supplemental figure 2).

The presence of MCA prenatally was found predictive of type of surgical closure (p=0.02), the presence of MCA postnatally was not significantly predictive of type of surgical closure (p=0.18). In the group of infants with delayed closure, we found a significantly lower median Apgar score at 5 minutes, longer length of initial hospital stay (LOS), more frequently CLD, more often a giant omphalocele and worse survival rates compared with infants who underwent primary closure (table 1). Using logistic regression analysis, we found a significant association between the OC/AC-ratio at US2 and US3 and presence of CLD (p=0.01 and p=0.003, respectively). Using Spearman's rank correlation, we also found a significant correlation between the OC/AC-ratio at US2 and US3 and LOS (p<0.001 and p<0.001, 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=0.001) and US3 (p=0.04). 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 flow chart 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).

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=0.15), at US2 an AUC of 0.81 (with a 95% CI of (0.61-1.00), p=0.01), and at US3 an AUC of 0.89 (with a 95% CI of (0.79-0.98), p=0.001).

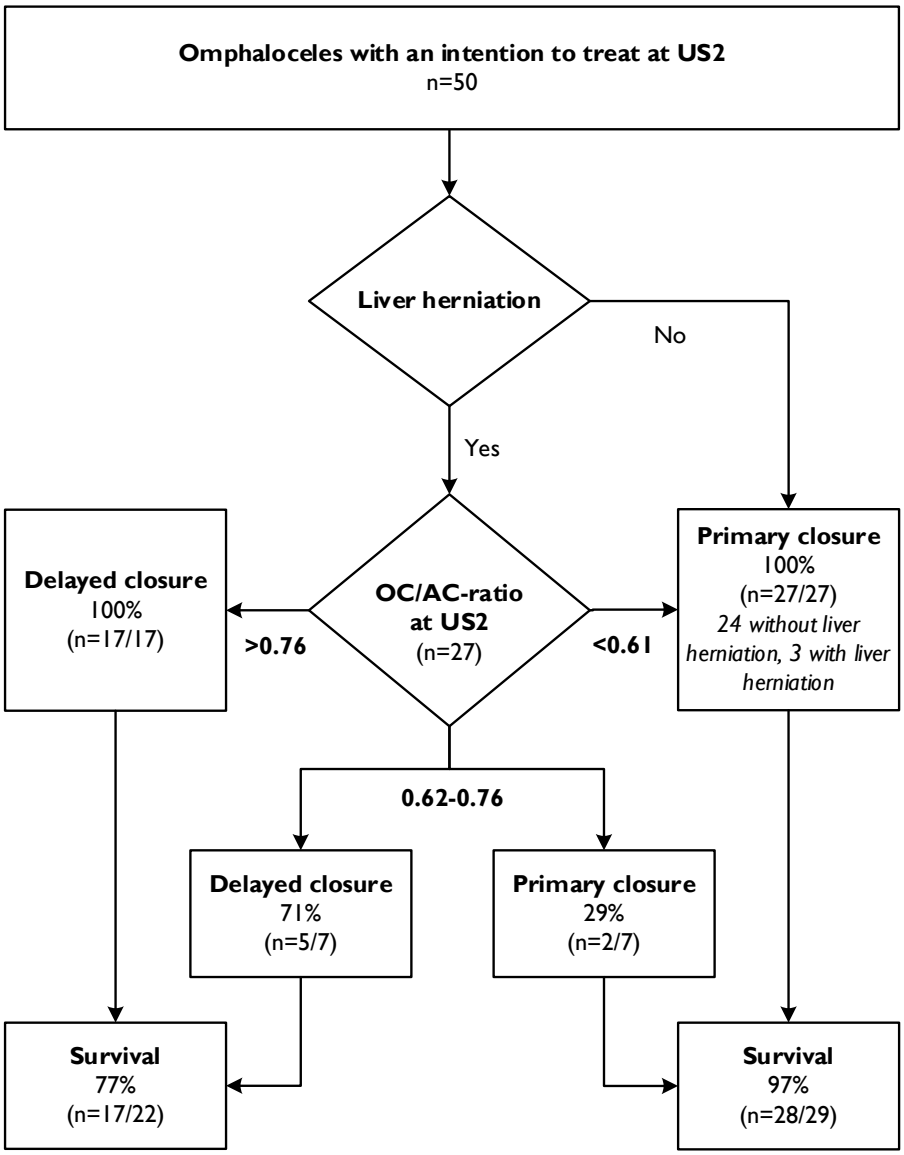

Figure 4 Counseling flow chart for type of surgical closure and survival rate according to prenatal liver position and the OC/AC-ratio in fetuses with an omphalocele and an intention to treat

OC/AC: omphalocele circumference/abdominal circumference; US2: second ultrasound time period (17-26 weeks' gestation).

Thirty-six (97%) of the 37 infants who underwent primary closure of the defect survived. One infant who did not survive had multiple congenital anomalies, 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 8 (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=0.01) of the OC/AC-ratio for survival, as well as for the intercept (OR 1.07 with a 95% CI of (1.01-1.13); p=0.02). 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 (supplemental figure 3).

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 (supplemental figure 4). For 4/9 IUFD cases no cause for the intrauterine demise was found other than the presence of an omphalocele. For the remaining 5 cases, other factors next to the omphalocele contributed to the cause of death (supplemental table 2). 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 2 NND cases were born at 27 and 28 weeks' gestation. 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=0.76 and p=0.75, 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 criteria 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 to 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 (abdominal circumference, 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 gestational age could result in a constant cut-off throughout gestation, without negatively affecting the predictive value.

An omphalocele is usually diagnosed prior to 24 weeks' gestational age 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 weeks' 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 smaller 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 4/11 cases in our study there was no apparent cause found for the occurrence of an IUFD and/or NND. Further multicenter 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 weeks' 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 weeks' 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 type of postnatal surgical closure and survival. The predictive value increases with increasing 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.

Acknowledgements

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Supplemental material

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	0.01
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. OR: odds ratio; OC/AC-ratio: omphalocele circumference / abdominal circumference-ratio; US: ultrasound; GA: gestational age

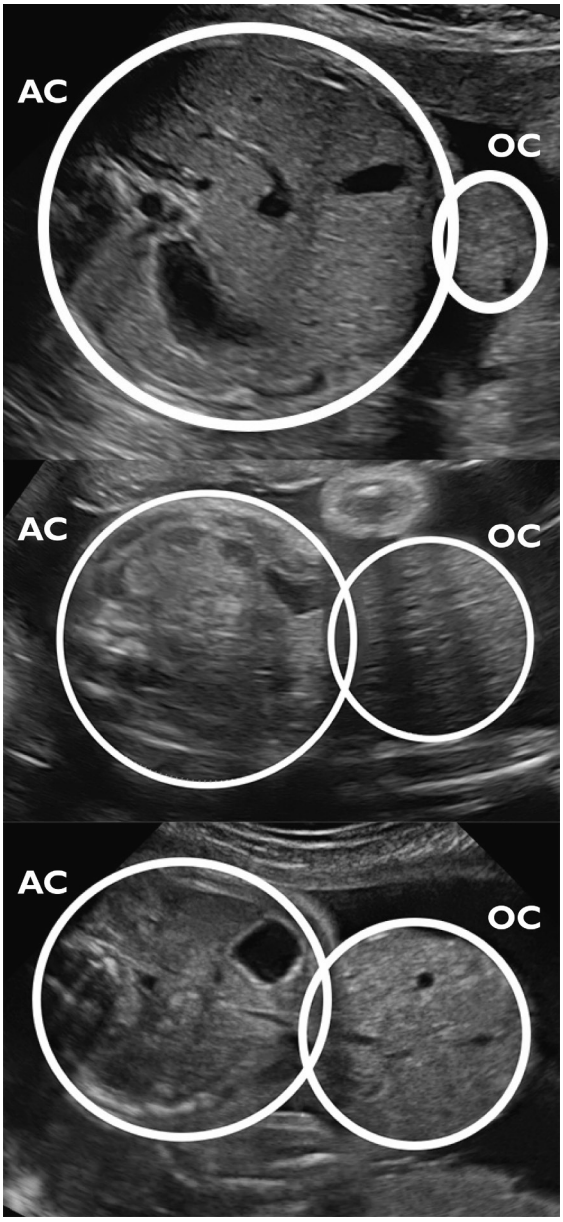
Supplemental table 2 Omphalocele cases and their cause of death

	OC/AC-ratio			Liver herni-ation	GA at birth	AS 5 min	Giant	Sex	Closure	CLD	LOS	Time of death	MCA	Cause of death
	US1	US2	US3											
IUFD		0.66		No	n/a	n/a	n/a	M	n/a	n/a	n/a	30^{+0}	-	Unknown[A]
IUFD	0.50	0.55		No	n/a	n/a	n/a	-	n/a	n/a	n/a	29^{+0}	Anencephaly	MCA
IUFD	0.83			Yes	n/a	n/a	n/a	M	n/a	n/a	n/a	27^{+0}	*SUA*	Unknown
IUFD	1.26			Yes	n/a	n/a	n/a	F	n/a	n/a	n/a	26^{+4}	*Deviated heart axis*	Unknown
IUFD		0.54		No	n/a	n/a	n/a	M	n/a	n/a	n/a	24^{+5}	-	Early IUGR with placental redistribution
IUFD		0.93		Yes	n/a	n/a	n/a	-	n/a	n/a	n/a	21^{+2}	-	Unknown
IUFD	0.91			Yes	n/a	n/a	n/a	M	n/a	n/a	n/a	18^{+4}	Unilateral MCKD	PROM with CHIV
IUFD	0.30			No	n/a	n/a	n/a	M	n/a	n/a	n/a	15^{+1}	Trisomy 21	MCA
IUFD	0.68			No	n/a	n/a	n/a	F	n/a	n/a	n/a	13^{+0}	Umbilical cord cysts	MCA
NND		0.48		No	27^{+6}	7	No	F	n/a	n/a	0	0	BWS	Circulatory failure
NND	0.74	0.48		Yes	28^{+5}	7	Yes	M	n/a	Severe	9	9	Twin-to-twin transfusion syndrome	Pulmonary hypoplasia and pulmonary hypertension
Infant death			0.78	Yes	37^{+4}	6	Yes	M	Delayed	Severe	36	91	Dilated right atrium + ventricle	Pulmonary hypertension
Infant death			1.11	Yes	32^{+3}	7	Yes	M	Delayed	Severe	54	54	ToF, esophageal atresia with fistula	MCA, septic shock, respiratory failure
Infant death			0.90	Yes	37^{+0}	4	Yes	M	Delayed	Severe	84	84	-	Respiratory failure

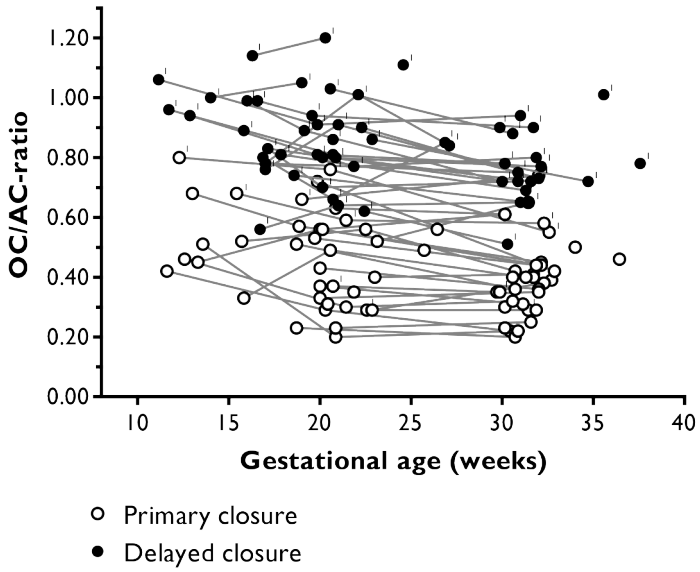
Supplemental table 2 *(continued)*

	OC/AC-ratio			Liver herni-ation	GA at birth	AS 5 min	Giant	Sex	Closure	CLD	LOS	Time of death	MCA	Cause of death
	US1	US2	US3											
Infant death	1.00	1.05		Yes	38^{+6}	6	No	M	Delayed	Severe	101	101	Small ASD and VSD (clinically irrelevant), CCA	Pulmonary hypertension
Infant death	1.14	1.20		Yes	30^{+6}	7	Yes	M	Delayed	Severe	106	106	-	Pulmonary hypoplasia and " hypertension
Infant death	0.80	0.66	0.85	Yes	27^{+0}	5	Yes	M	Delayed	Severe	111	111	Postaxial polydactyly	Pulmonary hypertension[C]
Infant death		0.52	0.65	No	39^{+1}	9	No	M	Primary	Severe	126	126	AVSD, ToF, TAPVR, hiatus hernia, asplenia, UPJ stenosis	MCA, insufficient cardiac circulation with hypoxia, no treatment options
Infant death	0.76	0.91	0.73	Yes	35^{+5}	6	No	F	Delayed	Mild	156	156	Large pVSD with overriding aorta, ODB	MCA, cardiac failure, pulmonary hypertension
Infant death	0.78	1.01	0.84	Yes	30^{+0}	6	Yes	M	Delayed	Severe	192	192	-	Cardiac and respiratory failure

Cases are ranked by time of death (IUFD: weeks^{+days}; NND/infant death: days) and LOS. [A] dichorionic twin; [B] monochorionic twin; [C] dichorionic triamniotic triplet. OC/AC: omphalocele circumference/abdominal circumference; US: ultrasound; GA: gestational age; AS: Apgar score; CLD: chronic lung disease; LOS: length of hospital stay; MCA: multiple congenital anomalies; n/a: not applicable; IUFD: intrauterine fetal death; NND: neonatal death; M: male; F: female; SUA: single umbilical artery; IUGR: intrauterine growth restriction; MCKD: multicystic kidney disease; PROM: premature rupture of membranes; CHIV: chronic histiocytic intervillositis; BWS: Beckwith-Wiedemann syndrome; ToF: tetralogy of Fallot; ASD: atrial septal defect; (p)VSD: (perimembranous) ventricular septal defect; CCA: corpus callosum agenesis; AVSD: atrial ventricular septal defect; TAPVR: total anomalous pulmonary venous return; UPJ: uteropelvic junction; ODB: open Ductus Botalli.

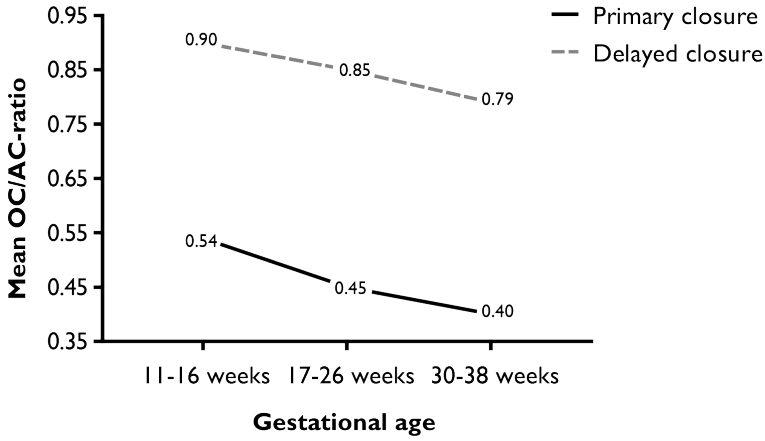


Supplemental figure 1 Examples of measurement of the OC/AC-ratio at US3
Figure showing three examples of measurement of the OC/AC-ratio at ultrasound examination between 30-38 weeks' gestation. The circle on the left is the measurement of the abdominal circumference (AC), the circle on the right is the measurement of the omphalocele circumference (OC).



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

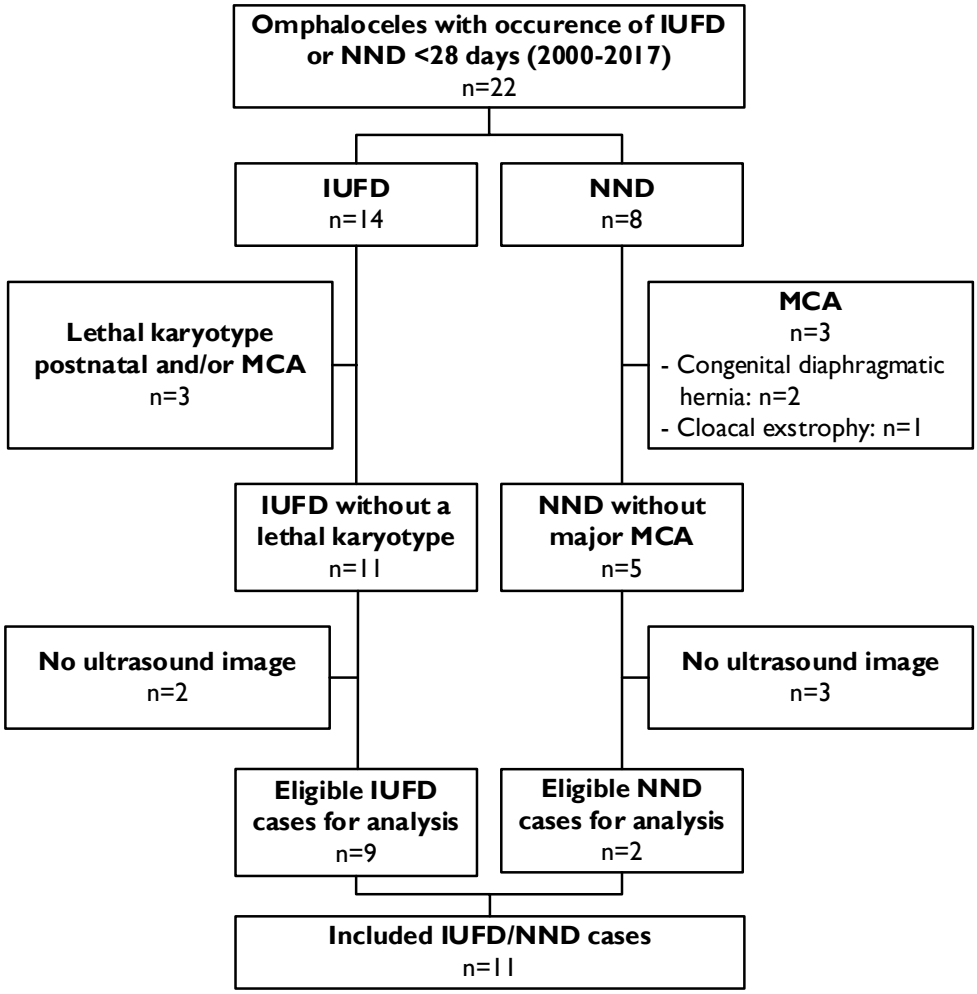
Figure showing the trend of the OC/AC-ratio per case throughout gestation per type of postnatal surgical closure. The open dots are cases with postnatal primary closure, the solid black dots represent cases with delayed closure. The grey lines represent the trend of the OC/AC-ratio throughout gestation for cases with ≥2 measurements. Cases with liver herniation are marked with the number 1. OC/AC: omphalocele circumference / abdominal circumference.





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

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



Supplemental figure 4 Inclusion flow chart of fetuses diagnosed with an omphalocele and occurrence of IUFD or NND
IUFD: intrauterine fetal death; NND: neonatal death; MCA: multiple congenital anomalies



6

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

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Abstract

Objective

To compare the prenatal frame of reference of omphalocele (i.e. survival of fetuses) with that after birth (i.e. survival of live-born 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 2000-2012. Physical growth (SD scores, SDS) and mental and motor development at 12 and 24 months were analyzed using general linear models, and outcomes were compared with reference norms. Giant omphalocele was defined as defect ≥5cm, with liver protruding.

Results

We included 145 fetuses and neonates. Of 126 (87%) who were diagnosed prenatally, 50 (40%) were live-born, and 35 (28%) survived at least 2 years. Nineteen (13%) neonates were diagnosed after birth. Of the 69 live-born 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 intra-uterine death (IUD). Therefore, we hypothesize a striking difference between the frame of reference of prenatal specialists and that of pediatric surgeons and pediatricians.

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 analyzed data of all fetuses and neonates diagnosed with omphalocele between 1 January 2000 and 31 December 2012 at the Erasmus Medical Center-Sophia Children's Hospital, Rotterdam. All parents of survivors were offered to enter their child in the longitudinal prospective follow-up program 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 (e.g. trisomy 18; anencephaly), very poor (e.g. congenital diaphragmatic hernia; large encephalocele) or uncertain (e.g. suspected intestinal atresia; congenital heart defect). Fetuses with isolated omphalocele were categorized 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 ≥5cm, 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 (i.e. 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 analyze 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 (i.e. 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.

Results

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

Prenatal frame of reference

Overall, 50/126 (40%) fetuses diagnosed with omphalocele were live-born, 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 live born 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 live-born 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 live-born, compared to 12/25 (48%) fetuses with OC/AC ≥0.82 (p=0.003). With TOPs excluded, 93% versus 71% of continuing pregnancies resulted in live birth, respectively (p=0.09). Of 38 live-born neonates with an isolated omphalocele, 29 (76%) survived.

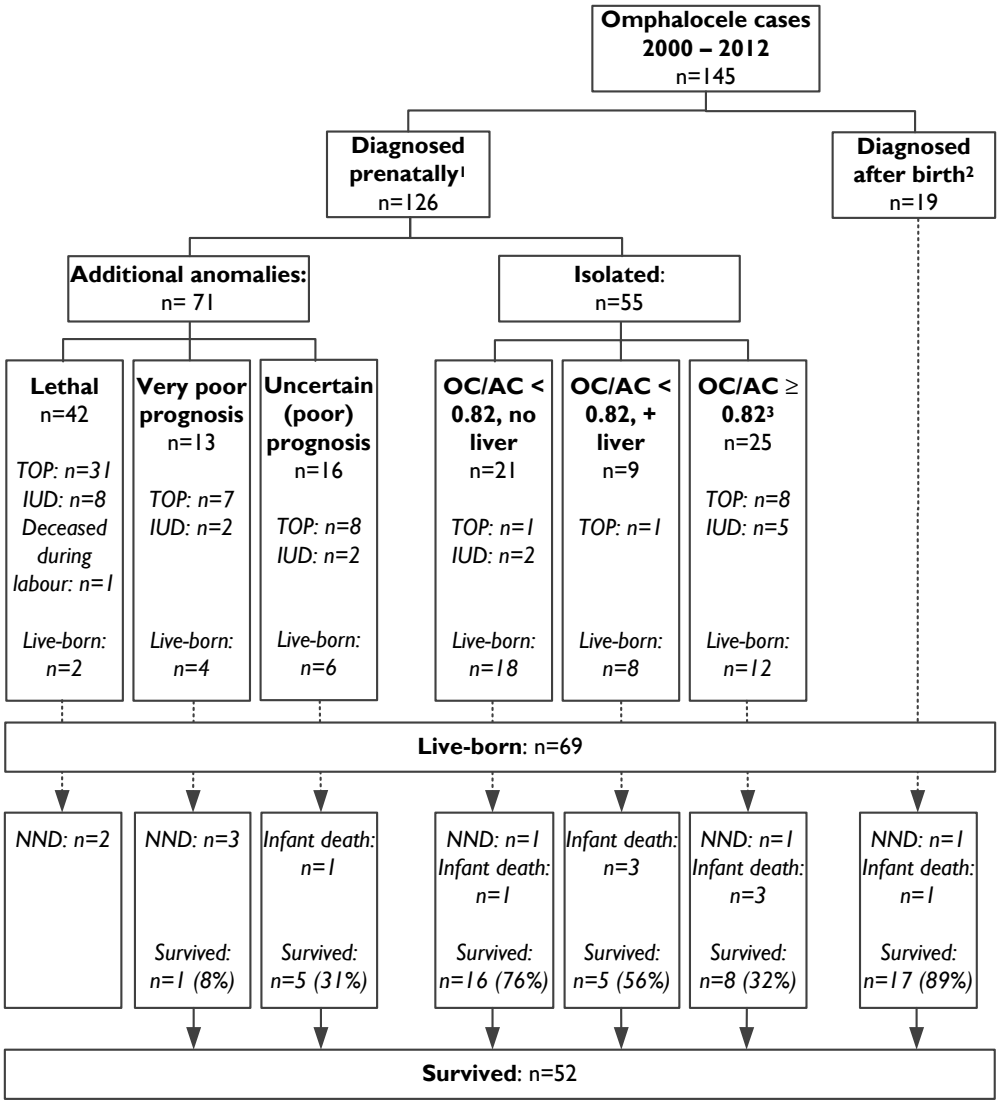

Figure 1 Flow chart of survival in all fetuses and neonates with omphalocele

IUD: intrauterine death; MCA: multiple congenital anomalies; NND: neonatal death; OC/AC: omphalocele circumference/abdominal circumference; TOP: termination of pregnancy. [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).

Postnatal frame of reference

Including the nineteen (13%) neonates diagnosed after birth, 69 neonates were live-born. 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).

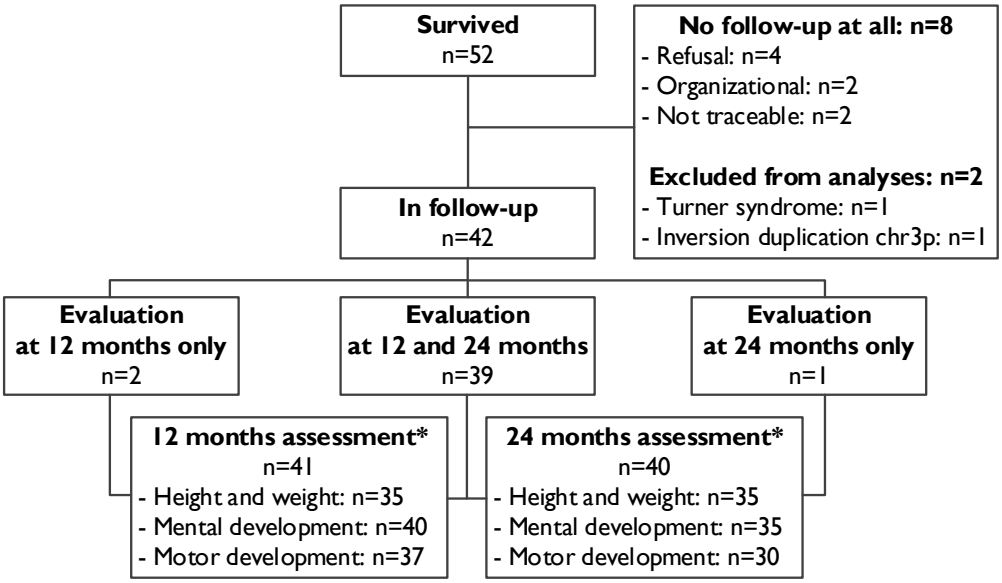

Figure 2 Flow chart of children with omphalocele included in follow-up analyses of physical growth and neurodevelopment

*Reasons for missing data on growth at 12 months: excluded because of Beckwith-Wiedemann syndrome (n=5) and organizational (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); immobilization of legs n=1 (motor); organizational 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).

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 anesthesia 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. 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).

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

	Minor omphalocele n=31	**Giant omphalocele** n=11	***p* value**
Maternal age (years) [A]	31 (28-35)	31 (29-33)	0.89
Male sex	15 (48%)	4 (36%)	0.73
Multiple pregnancy	3 (10%)	0 (0%)	0.55
Socio-economic status score at birth	0.08 (-0.53-0.88)	0.06 (-0.95-0.53)	0.46
- Low status score (<-1)	8 (26%)	2 (18%)	1.00
Prenatal characteristics			
Prenatal diagnosis	18 (58%)	10 (91%)	0.07
- Gestational age (weeks) at diagnosis	22.9 (19.5-30.4)	21.2 (15.6-33.4)	0.65
- 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			
Cesarean section	8 (26%)	6 (55%)	0.14
Gestational age at birth (weeks)	38.9 (38.0-39.9)	38.4 (37.0-38.9)	0.16
Preterm birth	3 (10%)	2 (18%)	0.59
Birth weight (grams)	3180 (2500-3640)	2750 (2140-3430)	0.12
Small for gestational age	6 (19%)	3 (27%)	0.68
Apgar score at 5 min [A]	10 (9-10)	9 (8-9)	0.04
- Apgar score <7 at 5 min [A]	0 (0%)	1 (9%)	0.28
Postnatal characteristics			
Ruptured omphalocele	5 (16%)	3 (27%)	0.41
Content of omphalocele [C]			
- Liver	5 (16%)	11 (100%)	<0.001
- Stomach	0 (0%)	3 (27%)	0.01
- Bladder	0 (0%)	1 (9%)	0.26
Multiple congenital anomalies [D]	11 (35%)	3 (27%)	0.72
Primary closure	31 (100%)	1 (9%) [E]	<0.001
Number of procedures under general anesthesia [F]	1 (1-2)	3 (2-5)	0.003
Duration of initial mechanical ventilation	0 (0-1)	3 (0-119)	0.06
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 [G]	2 (6%)	3 (27%)	0.10
Length of initial hospital stay (days)	7 (5-13)	50 (23-108)	<0.001

Table 1 (*continued*)

	Minor omphalocele n=31	**Giant omphalocele** n=11	***p* value**
Pediatric physiotherapy			
- At 12 months of age	4 (13%) [H]	6 (55%)	0.01
- At 24 months of age	2 (7%) [I]	2 (18%)	0.30

Data presented as n (%) or median (interquartile range). OC/AC: omphalocele circumference/abdominal circumference. [A] Unknown in n=3 minor omphalocele; [B] unknown in n=4 prenatally diagnosed minor omphalocele; [C] Percentages do not necessarily add up to 100, as multiple organs can be herniated; [D] Minor omphalocele: cryptorchidism (n=1); cryptorchidism + ren arcuatus (n=1); Beckwith-Wiedemann Syndrome (n=4); enlarged monokidney (n=1); intestinal atresia (n=2); intestinal atresia + microcolon (n=1); ileal cyst (n=1); Giant omphalocele: Beckwith-Wiedemann Syndrome (n=1); aortic stenosis (n=1); cryptorchidism + epiglottic dysfunction (n=1); [E] ruptured omphalocele; [F] unknown in n=1 minor omphalocele. [G] Time to full enteral feeding: 49->730 days. Minor omphalocele: intestinal atresia (n=1); intestinal atresia + microcolon (n=1); Giant omphalocele: respiratory insufficiency due to sepsis, therefore nil per os (n=1); intestinal passage problems (n=2). [H] unknown in n=1 (no follow-up at 12 months); [I] unknown in n=2 (no follow-up at 24 months).

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 six with giant omphalocele (-0.22 (-1.18 to -0.05)), with no statistically significant difference between those groups (p=0.85).

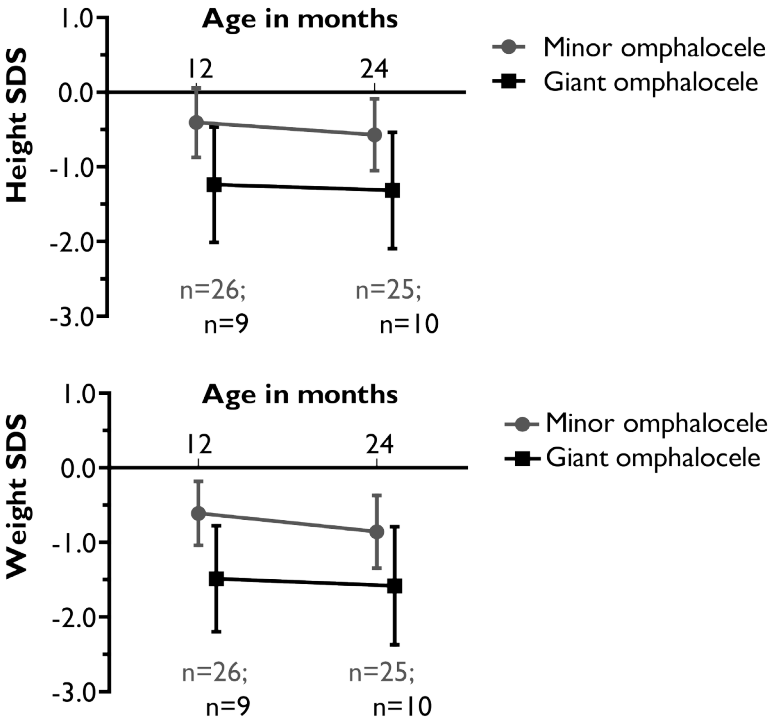

Figure 3 Height and weight standard deviation scores (SDS) of children with minor or giant omphalocele

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.

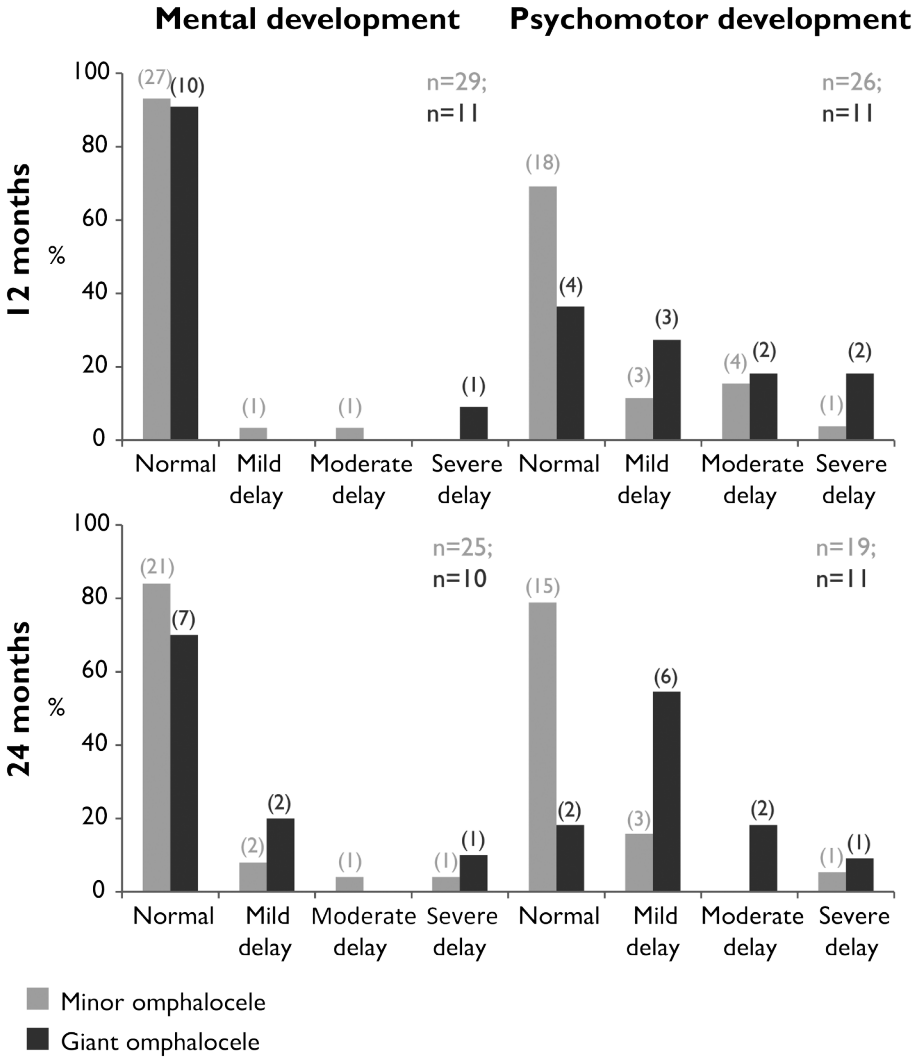

Figure 4 Proportions of children with minor or giant omphalocele with normal or delayed mental (left panel) and motor (right panel) at 12 and 24 months of follow-up. Mild delay: developmental index: 70–84; moderate delay: 55–69; severe delay: <55. Numbers of children are shown in brackets.

Discussion

We evaluated the course of omphalocele from diagnosis to growth and development at 2 years of age. As we hypothesized, the prenatal frame of reference was considerably worse than that after birth; additional structural or chromosomal anomalies–mainly 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 live-born 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 individualized 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 live-born 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 emphasizes the importance of a multidisciplinary approach in parental counselling; pediatric surgeons and pediatricians 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 reported weight <p3 in 3/15 (20%) children with omphalocele aged 1-10 years, and height <p3 in two (13%) children.[29] These proportions are similar to our results in 2-year-olds, and higher than those in the reference population (i.e. 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 hospitalization 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 reported motor function delay in 2-year-old children with omphalocele.[32] 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 program of mostly prenatally diagnosed children; the high proportion (81%) of children that entered this program; the relatively large sample size for such a rare disease; and the use of standardized 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 pediatric physical therapist and prolonged follow-up, at least until these children have reached school age.

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7

Omphalocele at school age: what do parents report? A call for long-term follow-up of complex omphalocele patients

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Abstract

Objective

Many children with omphalocele experience morbidity in early life, which could affect long-term outcomes. We determined parent-reported outcomes in school-aged children treated for minor or giant omphalocele.

Methods

We sent paper questionnaires to the parents of all children treated for omphalocele in 2000 – 2012. Giant omphalocele was defined as defect diameter ≥ 5 cm with liver protruding. Motor function (MABC-2 Checklist) was compared with Dutch reference data; cognition (PedsPCF), health status (PedsQL), quality of life (DUX-25) and behavior (Strengths and Difficulties Questionnaire; SDQ) were compared with those of controls (two per child) matched for age, gender and maternal education level. Possible predictors of cognition and behavior were evaluated using linear regression analyses.

Results

Of 54 eligible participants, 31 (57%) returned the questionnaires. MABC-2 Checklist scores were normal for 21/26 (81%) children. Cognition, health status, quality of life and behavior were similar to scores of matched controls. One quarter (26%) of children with omphalocele scored ≤ -1 standard deviation on the PedsPCF, compared with 9% of matched controls (p=0.07). Giant omphalocele and presence of multiple congenital anomalies (MCA) were most prominently associated with lower PedsPCF scores (giant omphalocele: β -22.11 (95% CI: -43.65 to -0.57); MCA -23.58 (-40.02 to -7.13)), although not significantly after correction for multiple testing.

Conclusion

Parent-reported outcomes of children with omphalocele at school age are reassuring. Children with an isolated, minor omphalocele do not need extensive long-term follow-up of daily functioning. Those with a giant omphalocele or MCA might be at risk for delayed cognitive functioning at school age; we recommend long-term follow-up to offer timely intervention.

Introduction

Omphalocele is a congenital abdominal wall defect with an estimated prevalence of 3.5 per 10 000 births.[1] Almost 90% of omphalocele cases are diagnosed prenatally,[2] which allows for early parental counseling. Approximately 50-80% of fetuses have multiple congenital anomalies (MCA), leading to high rates of termination of pregnancy and intrauterine death.[3, 4] Of live-born neonates with omphalocele, approximately 35% present with MCA (i.e. non-isolated omphalocele).[5] For infants with an isolated omphalocele, survival rates up to 90% have been reported.[3]

As medical options and survival rates have improved during the last decades,[6] the focus of outcome research is shifting towards the long term, and parent-reported outcome measures are becoming increasingly relevant.[7, 8] Many infants with omphalocele, especially those with giant omphalocele or MCA, have experienced morbidity in early life.[4, 9] This morbidity includes respiratory failure, feeding difficulties, and having undergone surgery and other procedures under general anesthesia. Although these factors could negatively affect long-term outcomes,[9, 10] information on outcomes beyond the age of five years is limited.[11-13]

To optimize follow-up and to improve parental counseling, we evaluated parent-reported motor function, cognition, health status, quality of life and behavior in school-aged children (i.e. 4-17 years) treated for omphalocele. We hypothesized that these children would have more problems in daily life than healthy children; especially those with either giant omphalocele or MCA, considering the increased morbidity in early life. Secondarily, we sought to identify predictors of cognition and behavior at school age, including parent-perceived child vulnerability, infant clinical data, sociodemographic characteristics, and neurodevelopmental outcomes that had been evaluated at 2 years of age.[4]

Methods

Participants

We sent paper questionnaires with a self-addressed envelope to the parents of all surviving children born with omphalocele between 2000 and 2012 and treated at our hospital. After birth, the parents had been offered to enter their child in the longitudinal prospective follow-up program that since 1999 is the standard of care for children with anatomical congenital anomalies treated at our hospital.[14] Based on the favorable outcomes reported in 2009 and 2010,[14, 15] the follow-up duration of children born with a minor omphalocele was limited to 2 years.

At 2 years of age, the children's mental and motor development had been assessed using the Dutch version of the Bayley Developmental Scales[16] or, from December 2003, the Bayley Scales of Infant Development-Second edition.[17] Both tests provide a psychomotor and mental developmental index (mean score 100, SD 15). Neurodevelopmental outcomes at 2 years of age have been published previously.[4] For the purpose of the current study, four children were excluded (figure 1). The Medical Ethical Review Board waived approval ('Medical Research in Human Subjects Act does not apply to this research proposal').

Data collection

Infant clinical data were retrieved from medical records. Infants born <37 weeks' gestation were considered preterm. Those with a birth weight <10th centile for Dutch reference curves were classified as small for gestational age.[18] The omphalocele was labeled 'giant' if the defect diameter was ≥5 cm with liver protruding.[19] We documented MCA that required surgery or multiple follow-up visits. Infants with time to full enteral feeding (TFEF) >6 weeks were diagnosed with intestinal failure. In one infant, TFEF exceeded 2 years, and data were documented as 730 days. Chronic lung disease was diagnosed in neonates who required supplemental oxygen for at least 28 days.[20]

Socioeconomic status scores (population mean 0, SD 1) were based on postal codes at birth.[21, 22] In addition, data on the child's living situation, medical information, and education were retrieved from a background questionnaire (supplemental file 1). Maternal and paternal education levels were based on the International Standard Classification of Education (ISCED) 2011, with ISCED 0-2 considered as low, ISCED 3-4 as middle, and ISCED 5-8 as high level of education.[23]

Measures

We assessed the following outcome measures from parent-reported questionnaires (Dutch versions). A detailed description of each questionnaire is provided in supplemental file 1. Motor function was compared with Dutch reference data.[24] For the analyses of cognition, health status, quality of life and behavior, for each child with omphalocele we included two healthy controls matched for age (maximum difference of one year), gender, and maternal education level (low, middle, or high; based on ISCED 2011).[23] Matched controls were randomly selected from three recently collected datasets for different outcome measures (supplemental file 2).

Child vulnerability: Child Vulnerability Scale (CVS).[25, 26]

Motor function: Movement Assessment Battery for Children- Second Edition (MABC-2) Checklist.[24, 27, 28]

Cognition: Parents of children aged ≥7 years rated cognitive functioning via the Pediatric Perceived Cognitive Function (PedsPCF) questionnaire.[29]

Health status and quality of life: Pediatric Quality of Life Inventory (PedsQL; health status)[30] and DUX-25 (quality of life). As no matched controls were available for DUX-25 scores in 4 – 7 year-olds, these data were excluded.
Behavior: Strengths and Difficulties Questionnaire (SDQ).[31]

Statistical analysis
Continuous variables are presented as median (IQR), and categorical variables as number (%). Baseline characteristics of responders and non-responders were compared using Mann-Whitney tests (continuous variables), and chi-square tests or Fisher's exact tests (categorical variables). One-sample Wilcoxon signed rank tests served to compare median scores of participants with those reported in the reference population; Mann-Whitney U tests and Fisher's exact tests served to compare PedsPCF, PedsQL, DUX-25 and SDQ scores between children with omphalocele and their matched controls.

In this exploratory study, we used univariable linear regression analysis to find possible predictors of cognition and behavior at school age. These included parent-perceived child vulnerability, infant clinical data, sociodemographic characteristics, and neurodevelopmental outcomes at 2 years. A Bonferroni-adjusted significance level of 0.05/18=0.003 was used in the linear regression analyses to correct for multiple testing of 18 possible predictors. Other results were considered significant at $p<0.05$. Statistical analyses were performed using SPSS V.24.0.

Results

Of 76 children treated for omphalocele, 58 (76%) survived. Four of them were excluded because of morbidities or diagnoses that influenced their development (figure 1). Of 54 eligible participants, 31 (57%) returned the questionnaires (figure 1). The clinical or demographic characteristics did not differ significantly between responders and non-responders (table 1); the difference in median socioeconomic status score between responders (0.36 (IQR: -0.31 to 0.90)) and non-responders (-0.68 (-1.06 to 0.35)) did not reach statistical significance ($p=0.06$).

Background
Participating children had a median age of 9 (IQR: 6 – 13; range: 5 – 17) years. All were raised by at least one biological parent; 27 (87%) children had two caregivers at home. Either the child's mother (n=23, 74%) or father (n=1, 3%), or both parents (n=7, 23%) completed the questionnaires. Eleven (35%) children used medication, because of gastrointestinal problems such as reflux or obstipation (n=5), attention deficit hyperactivity disorder (ADHD; n=2), sleeping problems (n=2), asthma (n=1), or eczema (n=1). Eight (26%) parents reported that their child had behavioral or emotional problems (ADHD and autism spectrum disorder: n=2; ADHD: n=1; dysfunctional

emotion regulation: n=3; tics: n=1; 'possible attachment disorder': n=1); three of these attended special education. In total, six (19%) children attended special education.

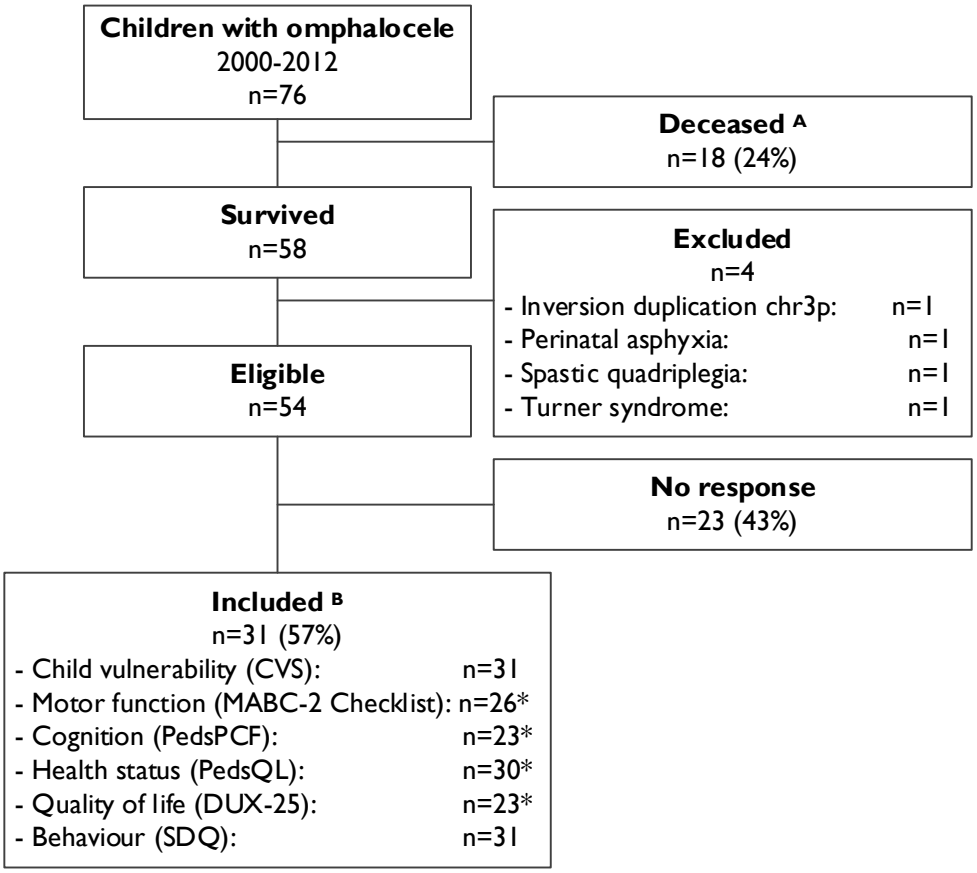

Figure 1 Inclusion flow chart

[A] Cause of death: pulmonary hypertension (n=5), chromosomal abnormality (n=4), multiple congenital anomalies (n=4), very large omphalocele with no treatment options (n=3), circulatory failure (n=1), midgut volvulus (n=1). [B] One parent with Dutch as a second language received also the English versions of the following questionnaires: CVS, MABC-2 Checklist, PedsPCF, PedsQL, and SDQ. * Reasons for missing data: motor function (n=5): excluded because of >3 missing answers (n=4), questionnaire missing (n=1); cognition (n=8): child aged <7 years (n=8); health status (n=1): questionnaire missing (n=1); quality of life (n=8): child aged <8 years (n=8). CVS: Child Vulnerability Scale; MABC-2 Checklist: Movement Assessment Battery for Children- Second Edition Checklist; PedsPCF: Pediatric Perceived Cognitive Function questionnaire; PedsQL: Pediatric Quality of Life Inventory; SDQ: Strengths and Difficulties Questionnaire.

Table 1 Infant clinical data and sociodemographic data of responders (n=31) and non-responders (n=23)

	n	**Responders** n=31 (57%)	n	**Non-responders** n=23 (43%)	***p* value**
Age at current study (years)	31	9 (6-13)	23	10 (7-13)	0.92
Infant clinical data					
Prenatal diagnosis	31	19 (61%)	23	16 (70%)	0.53
Male sex	31	13 (42%)	23	15 (65%)	0.09
Gestational age at birth (weeks)	31	38.7 (37.0-39.6)	23	38.3 (37.7-39.6)	0.97
Preterm birth	31	7 (23%)	23	2 (9%)	0.27
Birth weight (grams)	31	3180 (2435-3900)	23	3180 (2730-3550)	0.94
Small for gestational age	31	4 (13%)	23	5 (22%)	0.47
Giant omphalocele	31	10 (32%)	23	7 (30%)	0.89
Primary closure	31	22 (71%)	23	17 (74%)	0.81
Multiple congenital anomalies [A]	31	11 (37%)	23	6 (26%)	0.46
Number of procedures under general anesthesia	29	2 (1-3)	23	2 (1-3)	0.93
Duration of initial mechanical ventilation	29	0 (0-1)	23	1 (0-3)	0.35
Chronic lung disease	29	6 (21%)	23	2 (9%)	0.28
Length of hospital stay (days)	29	13 (6-42)	23	11 (6-50)	0.73
Time to full enteral feeding (days)	28	7 (3-15)	22	8 (4-14)	0.78
Intestinal failure	28	2 (7%)	22	3 (14%)	0.64
Sociodemographic data					
Socio-economic status score	31	0.36 (-0.31 to 0.90)	23	-0.68 (-1.06 to 0.35)	0.06
- Low status score (< -1)		6 (19%)		8 (35%)	0.20
Maternal education level	30			n/a	
- Low (ISCED 0-2)		5 (17%)			
- Middle (ISCED 3-4)		8 (27%)			
- High (ISCED 5-8)		17 (57%)			
Paternal education level	28			n/a	
- Low (ISCED 0-2)		4 (14%)			
- Middle (ISCED 3-4)		8 (29%)			
- High (ISCED 5-8)		16 (57%)			
Two caregivers at home	31	27 (87%)		n/a	

Table 1 (*continued*)

	n	Responders n=31 (57%)	n	Non-responders n=23 (43%)	*p* value
Children in the household	31			n/a	
- Single (=patient)		4 (13%)			
- Two children		16 (52%)			
- More than two children		11 (35%)			
Neurodevelopmental data at 2 years					
Mental developmental index [B]	22	105 (96-113)	13	96 (84-108)	0.34
- Delayed (<85)	22	3 (14%)	13	3 (23%)	0.65
Psychomotor developmental index [C]	17	89 (82-99)	11	83 (75-93)	0.24
- Delayed (<85)	17	6 (35%)	11	6 (55%)	0.44

Data are presented as median (IQR) or n (%). ISCED: International Standard Classification of Education. [A] Responders: Beckwith-Wiedemann Syndrome (n=3), intestinal atresia + microcolon (n=1), ileal cyst (n=1), cryptorchidism (n=1), cryptorchidism + ren arcuatus (n=1), aortic stenosis (n=1), patent ductus arteriosus (n=1), annular pancreas (n=1), urachal fistula + congenital neuroblastoma (n=1); non-responders: Beckwith-Wiedemann Syndrome (n=2), intestinal atresia (n=2), hemifacial microsomia (n=1), enlarged monokidney (n=1). [B] Missing data responders: organizational (n=4), non-cooperative child (n=3), parental refusal (n=2); missing data non-responders: organizational (n=2), non-cooperative child (n=1), parental refusal (n=6), emigrated (n=1). [C] Missing data responders: organizational (n=5), non-cooperative child (n=7), parental refusal (n=2); missing data non-responders: organizational (n=3), non-cooperative child (n=2), parental refusal (n=6), emigrated (n=1).

Child vulnerability

The CVS score of children with omphalocele (median 2 (IQR: 0-4)) was significantly higher than that reported in the reference population (i.e. median CVS: 1,[25] p=0.005). Four (13%) children were perceived as being highly vulnerable; three had a giant omphalocele, and none of them had MCA.

Motor function

MABC-2 Checklist scores were available for 26 children (figure 1; giant omphalocele n=8). Twenty-one (81%) scored within the normal range, two (8%) had borderline scores, and three (12%) were highly likely to have motor problems. Most difficulties in these five children were reported on ball skills. Two of them had a giant omphalocele; two others had MCA.

Cognition

We analyzed PedsPCF scores for all 23 children aged 7 years or older. The median PedsPCF total score of children with omphalocele (122 (IQR: 97-137) was comparable with that of matched controls (125 (115-134), p=0.45) (table 2). Six (26%) children with omphalocele scored ≤-1 SD, compared with 4/46 (9%) matched controls (p=0.07). All six children with omphalocele who scored ≤-1 SD had MCA (of whom three had Beckwith-Wiedemann Syndrome); three of them had a giant omphalocele (figure 2).

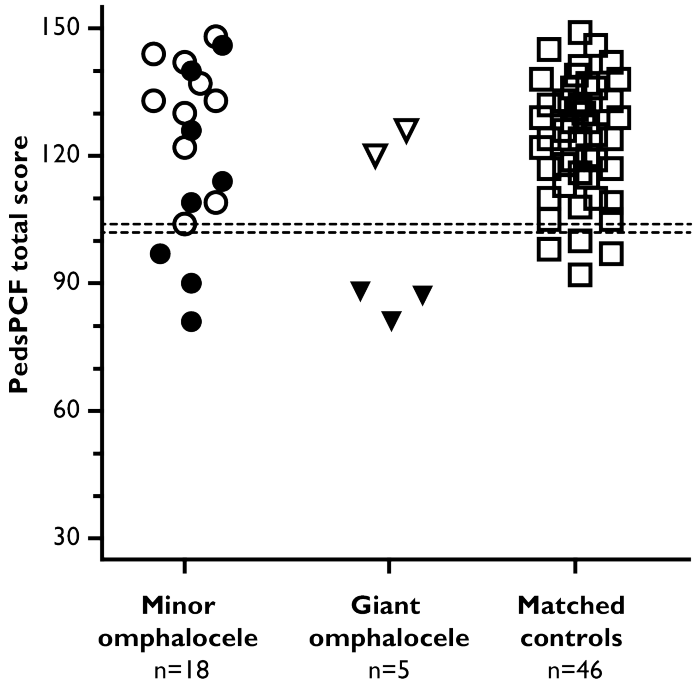

Figure 2 Scatter plot showing PedsPCF total scores
Open symbols represent children with an isolated omphalocele, closed symbols represent children with multiple congenital anomalies. Dashed lines represent -1 standard deviation (102 for age 7-12 years; 104 for age 13-18 years).

Health status

PedsQL scores were available for 30 children. Their total score (median 88 (IQR: 70-96)) was comparable to that of matched controls (83 (76-91), p=0.54), and so were the subscale scores (table 2).

Quality of life

The DUX-25 total score was analyzed in all 23 children aged 8 years or older. The DUX-25 total score of the latter (median 78 (IQR: 63-88) did not differ significantly from that of matched controls (82 (70-90), p=0.44), and neither did the subscale scores (table 2).

Behavior

SDQ scores were available for all 31 children. Their total difficulties score (median 8 (IQR: 3-14)) did not differ significantly from that of matched controls (6 (2-10), p=0.30), and neither did the subscale scores (table 2). Two (6%) children with a minor omphalocele and MCA had an abnormal total difficulties score, compared with five (8%) matched controls (p=1.00).

Predictors of cognition and behavior

In univariable regression analyses for cognition, the most prominent associations were between giant omphalocele and a lower PedsPCF total score (unstandardized β -22.11 (95% CI: -43.65 to -0.57), and between presence of MCA and a lower PedsPCF total score (-23.58 (-40.02 to -7.13); supplemental table 1).

In the analyses for behavior, the most prominent associations were between higher parental education level and higher standard deviation score of the SDQ total difficulties score (0.56 (0.07 to 1.05)), and between presence of one caregiver at home and a lower standard deviation score (-1.29 (-2.39 to -0.20); supplemental table 2). The aforementioned associations all had p values <0.05 (i.e. they would be significant without adjustment for multiple testing), but were not statistically significant after adjustment for multiple testing.

Table 2 Cognition, health status, quality of life and behavior of children with omphalocele compared with matched controls

	Omphalocele [A] n=23	**Matched control group** n=46	***p* value**
Cognition (PedsPCF)			
Total score (7-17 year old); n=23	122 (97-137)	125 (115-134)	0.45
	Omphalocele [A] n=31	**Matched control group** n=62	***p* value**
Health status (PedsQL) [B]			
Total score (4-17 year old); n=30	88 (70-96)	83 (76-91)	0.56
- Physical functioning	92 (84-98)	91 (79-94)	0.35
- Emotional functioning	78 (63-95)	75 (65-89)	0.84
- Social functioning	93 (64-100)	90 (75-99)	0.88
- School functioning	83 (60-95)	83 (71-95)	0.49
Quality of life (DUX-25)			
Total score (8-17 year old); n=23	78 (63-88)	82 (70-90)	0.48
- Physical functioning	79 (54-92)	83 (70-100)	0.14
- Emotional functioning	75 (54-96)	73 (63-89)	0.87
- Social functioning	79 (64-89)	79 (68-89)	0.90
- Home functioning	85 (65-95)	90 (80-100)	0.15
	Omphalocele [A] n=31	**Matched control group** n=62	***p* value**
Behavior (SDQ)			
Total difficulties score (4-17 year old); n=31	8 (3-14)	6 (2-10)	0.30
- Emotional problems	2 (0-4)	1 (0-3)	0.55
- Conduct problems	1 (0-2)	1 (0-2)	0.38
- Hyperactivity-inattention	3 (1-6)	3 (0-5)	0.22
- Peer problems	1 (0-2)	1 (0-2)	0.24
- Prosocial behavior	8 (7-9)	9 (8-10)	0.11

Data are presented as median (IQR). *p* values were derived from Mann-Whitney U tests.
[A] For one child, maternal education level was unknown. This child was matched to a control with middle maternal education level. [B] Complete questionnaire missing in n=1. PedsPCF: Pediatric Perceived Cognitive Function questionnaire; PedsQL: Pediatric Quality of Life Inventory; SDQ: Strengths and Difficulties Questionnaire.

Discussion

We analyzed parent-reported motor function, cognition, health status, quality of life, and behavior in school-aged children with omphalocele. Most children with a minor, isolated omphalocele performed in line with normative expectations. Cognitive problems were reported more frequently in those with either a giant omphalocele or MCA.

Few follow-up studies have addressed developmental outcomes and daily functioning of children with omphalocele at school age (supplemental table 3). Those studies usually had smaller sample sizes than our study (i.e. ≤20 children), and – in contrast to our study – used non-standardized questionnaires, combined different types of abdominal wall defects, or included only children with a giant omphalocele. In accordance with our results, these studies concluded that motor function,[11, 13, 15] cognition,[13, 32, 33] health status,[34-36] and behavior[32] fell within normal range.

Thirteen percent of parents included in this study perceived their child as highly vulnerable, which is much higher than reported in previous literature on Dutch children (i.e. 2%).[25] As developmental outcomes and daily functioning in children with omphalocele appeared to be normal, these parents may have heightened perceptions of their child's vulnerability. Parental concerns regarding the vulnerability of their child with an omphalocele are a natural reaction to an exceptional situation. Early parental counseling and support may help to lower the level of perceived vulnerability.

In a previous study, we showed that over 80% of two-year-old children with a giant omphalocele had delayed motor development.[4] In the current study, the parents of only two of eight children with a giant omphalocele reported delayed motor function at school age. This finding suggests that impaired motor function may be caught-up later in childhood. However, as questionnaires may not be sufficiently sensitive in diagnosing motor problems,[37] and as these patient numbers are small, further research is warranted to draw more definite conclusions.

Nineteen percent of children with omphalocele in our study attended special education. This is higher than reported in previous literature,[12, 38] and almost four times higher than in the Dutch reference population (i.e. approximately 5%).[39] Despite this, median PedsPCF scores were comparable with those of matched controls. Most likely, referral to special education is not mainly based on cognitive functioning, but could also be based on behavioral or emotional problems. Another explanation may be that parents perceive little discrepancy between the child's cognition and the level of education in special education. Linear regression analyses showed that especially children with a giant omphalocele and/or MCA may be a vulnerable group regarding cognitive functioning at

school age. These children might benefit from prolonged follow-up and early intervention.

Strengths of our study are the assessment of outcomes beyond the age of five years rather than at pre-school age, the use of matched controls, the fact that we considered omphalocele as a separate entity rather than combining data of all types of abdominal wall defects, and the availability of neurodevelopmental data at 2 years of age for most children. We used standardized parent-reported outcome measures, i.e. questionnaires were psychometrically validated and found to be sufficiently reliable and valid. One could say that parents may either over- or underestimate the child's abilities, which would make parent-reported outcome measures less reliable or robust than more objective measures, such as IQ. However, despite the fact that global IQ testing can give valuable insight into overall cognitive functioning, it does not always identify children at risk for academic problems.[40] In addition, as parents are largely responsible for seeking help for their children, using parent-reported outcomes may better reflect the care needs of these children. This also fits well within the family-centered approach to care, in which the vision of parents is essential.[41] For more detailed evaluation of different influences on children's problems, we assume that future studies could include multiple informants.[42]

A limitation of our study is the low response rate of 57% and the higher median socioeconomic status score of responders compared with that of non-responders. Although this difference did not reach statistical significance, we cannot exclude the possibility of positive selection bias. Another potential limitation is the use of different control populations rather than using a personal control population; future studies may include siblings as matched controls to increase homogeneity.

In conclusion, parent-reported outcomes of children with omphalocele at school age are reassuring. Children with an isolated, minor omphalocele do not need extensive long-term follow-up of daily functioning. Those with a giant omphalocele or multiple congenital anomalies might be at risk for delayed cognitive functioning at school age; we recommend long-term follow-up to offer timely intervention.

Acknowledgements

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Supplemental material

Supplemental file 1 Description of questionnaires

We used Dutch versions of all questionnaires. All questionnaires were parent-reported. If two answers were selected for one question, we documented the most unfavorable score.

Background

Description: We asked caregivers to report the following background information: child's living situation (e.g. with biological parents or in a foster family, presence of two caregivers, number of children), maternal and paternal education levels (based on the International Standard Classification of Education 2011),[1] medical (use of medication, hospital admissions, use of medical aids such as a wheelchair or parenteral nutrition), educational (e.g. regular or special, grade repetition, learning difficulties, need of extra help at school), social-emotional functioning (presence of behavioral or emotional problems), and main language spoken at home.

Child vulnerability

Child Vulnerability Scale (CVS) [2, 3]

Description: The CVS is an 8-item questionnaire on parental perceptions of their child's vulnerability. Each item states a problem, for example 'my child gets more colds than other children I know'. Answers vary from strongly disagree (=0) to strongly agree (=3) on a 4-point Likert scale. Total scores range from 0-24; higher scores reflect higher perceived vulnerability. We used a cut-off of ≥10 for high perception of vulnerability.
Validated: This questionnaire has been validated for Dutch children aged 5-18 years.[2]

Motor function

Movement Assessment Battery for Children - Second Edition (MABC-2) Checklist [4-6]

Description: The M-ABC 2 Checklist is aimed at evaluating motor problems in daily life. Section A measures movement in a static (or predictable) environment; section B measures movement in a dynamic (or unpredictable) environment. Both sections consist of 15 items. Each of the 30 items states a skill, for example 'rides a bicycle without stabilizers'. The parent indicates to what extent the child is able to do this, varying from very well (=0) to not close (=3). Scores are reported using a Traffic Light color system, corrected for age, with high scores representing poor performance. 'Green zone' indicates a score within the normal range (< 85th centile); 'amber zone' means that the child is at risk for motor problems (85th-94th centile), and a score in the 'red zone' indicates a high possibility of serious motor problems (≥ 95th centile).

Validated: This questionnaire has been validated for Dutch children aged 3-16 years.[6] As no Dutch reference norms exist for 17-year old children, these children were scored according to reference norms for 16-year olds.

Cognition

Pediatric Perceived Cognitive Function (PedsPCF) questionnaire [7]

Description: The PedsPCF assesses the child's cognitive functioning as perceived by the parent, referring to the past four weeks. Each item reflects a problem, for example 'forgets things easily'. Answers vary from very much/all of the time (=1) to not at all/none of the time (=5) on a 5-point Likert scale. Based on preliminary results of the collection of Dutch reference data, we used only the first 30 items of the PedsPCF rather than the full-length PedsPCF (which counts 43 items), and we used the following cut-offs of ≤-1 standard deviation (SD): 102 (7-12 years), 104 (13-18 years). Total scores range from 30-150; higher scores reflect better cognitive functioning.

Validated: This questionnaire has been validated for Dutch children aged 7-18 years.[8]

Health status

Pediatric Quality of Life Inventory (PedsQL) [9]

Description: The PedsQL is an instrument for measuring health status in children and adolescents. It consists of four subscales: physical (8 items), emotional (5 items), social (5 items) and school functioning (5 items). Each item reflects a problem, for example 'problems with running'. Answers vary from never (=0) to almost always (=4) on a 5-point Likert scale. Each answer is reversed scored and rescaled to a 0-100 scale (0=100, 4=0). Total scores range from 0-100; higher scores reflect better quality of life. We used the version that referred to the past month.

Validated: This questionnaire has been validated for Dutch children aged 5-18 years.[10]

Quality of life

DUX-25

Description: The DUX-25 is a visual health-related quality of life questionnaire. Each question evaluates the child's feelings in daily life, for example 'your child often feels …'. It consists of four subscales: physical (6 items), emotional (7 items), social (7 items) and home functioning (5 items). Answers are scored on a happy-to-sad faces scale by use of smileys. These smileys visualize a 5-point Likert scale, ranging from sad (=0) to happy (=100). Total scores range from 0-100; higher scores reflect better quality of life.

Validated: Dutch reference data are currently being analyzed (age 8-17 years).

Behavior

Strengths and Difficulties Questionnaire (SDQ) [11]

Description: The SDQ covers the most important domains of child psychopathology and personal strengths. It consists of five subscales: emotional symptoms, conduct problems, hyperactivity-inattention, peer problems, and prosocial behavior. Each item is scored on a 3-point Likert scale; answer vary from not true (=0) to certainly true (=2). Higher scores reflect more difficulties, except for the prosocial scale where higher scores reflect strengths. All but the prosocial behavior subscale scores are summed to generate a total difficulties score. Total scores range from 0-40. The total difficulties score was categorized into 'normal' or 'abnormal' using age-dependent cut-off values.[11]

Validated: This questionnaire has been validated for Dutch children aged 2-18 years.[11] In children aged <6 years, no SD scores or cut-off values were available for 'conduct problems' and 'peer problems' due to insufficient internal consistency of these subscales in this age group.

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Supplemental file 2 Description of matched controls

We obtained matched controls from three different datasets, as described below. Controls were matched for age (maximum difference of one year), gender, and maternal education level (low, middle, or high; based on the International Standard Classification of Education 2011[1]). Controls were selected randomly using an online randomizer. If the maternal education level of a case was unknown, this case was matched with two controls with middle maternal education level.

Cognition

Pediatric Perceived Cognitive Function (PedsPCF) questionnaire

Matched controls were obtained from a study that collected Dutch normative data for the PedsPCF.[2] A general population sample of parents and their children had been approached through research agency Kantar TNS in January 2016. This study included children with a chronic health condition, such as asthma or diabetes mellitus. This study used online questionnaires. We used the parent-reported data.

Health status and quality of life

Pediatric Quality of Life Inventory (PedsQL) and DUX-25

Matched controls were obtained from a study that collected Dutch normative data for the PedsQL (4-17 years) and the DUX-25 (8-17 years) (publications in preparation). Children with a chronic health condition had been excluded from this study; those with attention deficit hyperactivity disorder had been included. Online questionnaires had been sent to caregivers and their children, who were recruited via primary and secondary schools in the Netherlands from April 2015 till March 2016. We used the parent-reported data.

Behavior

Strengths and Difficulties Questionnaire (SDQ)

Matched controls were obtained from the database of Maurice-Stam and coworkers.[3] A general population sample of parents had been approached through research agency Kantar TNS in November and December 2014.

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Supplemental table 1 Univariable linear regression analysis showing possible predictors of the PedsPCF total score (n=23)

	Unstandardized beta	95% confidence interval	*p* value
Age at current study (years)	-0.96	-4.10 to 2.17	0.53
Child Vulnerability Scale score	-3.14	-6.48 to 0.19	0.06
Infant clinical data			
Male sex	4.83	-14.67 to 24.33	0.61
Preterm	6.26	-17.33 to 29.85	0.59
Small for gestational age	3.41	-25.65 to 32.47	0.81
Giant omphalocele	-22.11	-43.65 to -0.57	0.05
Delayed closure	-16.89	-41.58 to 7.81	0.17
Multiple congenital anomalies	-23.58	-40.02 to -7.13	0.01
Number of procedures under general anesthesia	-3.06	-7.21 to 1.09	0.14
Duration of initial mechanical ventilation (days)	-0.31	-1.51 to 0.90	0.60
Chronic lung disease	-18.40	-42.87 to 6.07	0.13
Length of hospital stay (days)	-0.15	-0.39 to 0.08	0.19
Intestinal failure	-17.90	-53.72 to 17.92	0.31
Sociodemographic data			
Low status score (<-1)	8.93	-19.89 to 37.75	0.53
Highest parental education level (ISCED level low to high) [A]	5.74	-9.00 to 20.49	0.43
One caregiver at home	-27.60	-60.05 to 4.85	0.09
Neurodevelopmental data at 2 years			
Delayed mental developmental index (<85)	-14.29	-43.37 to 14.79	0.31
Delayed psychomotor developmental index (<85)	-15.75	-44.23 to 12.73	0.25

PedsPCF: Pediatric Perceived Cognitive Function; ISCED: International Standard Classification of Education. [A] If paternal education level was unknown, we documented maternal education level as highest parental education level.

Supplemental table 2 Univariable linear regression analysis showing possible predictors of the SDS of the SDQ total difficulties score (n=31)

	Unstandardized beta	95% confidence interval	*p* value
Age at current study (years)	-0.08	-0.19 to 0.02	0.12
Child Vulnerability Scale score	-0.06	-0.15 to 0.02	0.13
Infant clinical data			
Male sex	0.34	-0.46 to 1.15	0.39
Preterm	0.54	-0.40 to 1.48	0.25
Small for gestational age	0.01	-1.19 to 1.20	0.99
Giant omphalocele	-0.28	-1.13 to 0.58	0.52
Delayed closure	-0.16	-1.04 to 0.73	0.72
Multiple congenital anomalies	-0.50	-1.31 to 0.32	0.23
Number of procedures under general anesthesia	-0.03	-0.23 to 0.18	0.81
Duration of initial mechanical ventilation (days)	-0.01	-0.06 to 0.05	0.84
Chronic lung disease	-0.12	-1.16 to 0.92	0.82
Length of hospital stay (days)	0.00	-0.01 to 0.01	0.67
Intestinal failure	-0.32	-2.05 to 1.41	0.71
Sociodemographic data			
Low status score (<-1)	-0.01	-1.03 to 1.01	0.98
Highest parental education level (ISCED level low to high) [A]	0.56	0.07 to 1.05	0.03
One caregiver at home	-1.29	-2.39 to -0.20	0.02
Neurodevelopmental data at 2 years			
Delayed mental developmental index (<85)	-0.60	-2.01 to 0.80	0.38
Delayed psychomotor developmental index (<85)	-0.55	-1.82 to 0.72	0.37

SDS: standard deviation score; SDQ: Strengths and Difficulties Questionnaire; ISCED: International Standard Classification of Education. [A] If paternal education level was unknown, we documented maternal education level as highest parental education level.

Supplemental table 3 Overview of follow-up studies assessing motor function, cognition, health status, quality of life and/or behavior in children with omphalocele at school age

Reference	Outcome	Assessment or questionnaire	Tests	Group	Number of children	Year of birth	Age at follow-up	Normative data	Most important results
Amin et al. 2018 [1]	Health status	Questionnaire (parent)	PedsQL	OC	26	not stated	0-13 (median: 4) years	PedsQL parent-report: 88±12	*Health status:* in line with normative expectations (mean 79 (95% CI: 72-86)).
Burnett et al. 2018 [2]	Cognition	Assessment	WPPSI-III	OC	10/16 (63%)	2006-2014	5 years	TIQ: 100±15	*Cognition*: in line with normative data (mean±SD: 104±15).
	Behavior	Questionnaires (parent)	BRIEF-P and BASC-2					Elevated scores: BRIEF-P: 7%, BASC-2: 16%	*Behavior*: in line with normative data (abnormal BRIEF-P: 0%, abnormal BASC-2: 20%).
Fawley et al. 2016 [3]	Health status	Questionnaire (not stated)	PedsQL	OC	20/30 (67%)	2002-2013	not stated	PedsQL self-report: 83 ±15, parent-report: 88 ±12	*Health status*: in line with normative data (mean±SD PedsQL: 86±11).
Van Eijck et al. 2013 [4]	Motor function	Assessment and questionnaire (parent)	MABC-2, and not standard-ized	Giant OC	8/11 (73%)	2004-2007	4-12 (mean: 6) years	Normal: 85%; at risk: 10%; problem: 5%	*Motor function:* in line with normative data (normal: 88%, at risk: 13%). No difficulties in running, walking, cycling and trampoline jumping.

Supplemental table 3 (*continued*)

Reference	Outcome	Assessment or questionnaire	Tests	Group	Number of children	Year of birth	Age at follow-up	Normative data	Most important results
Van Eijck et al. 2013 [4]	Motor function	Assessment and questionnaire (parent)	MABC-2, questionnaire not standardized	Giant OC	8/11 (73%)	2004-2007	4-12 (mean: 6) years	Normal: 85%; at risk: 10%; problem: 5%	*Motor function*: in line with normative data (normal: 88%, at risk: 13%). None of the children showed any difficulty in running, walking, cycling and trampoline jumping.
Hamrick et al. 2010 [5]	Cognition	Linkage with education files public schools	n/a	OC	91 (63 isolated, 28 non-isolated)	1982-2001	Ever received special education between 3-10 years	Use of special education services: 8%	*Cognition*: in line with normative data (use of special education services 13% in isolated omphalocele, 11% in non-isolated omphalocele).
Van der Cammen-van Zijp et al. 2010 [6]	Motor function	Assessment	M-ABC	OC+GS	24/33 (73%)	1999-2003	5 years	Normal: 85%; at risk: 10%; problem: 5%	*Motor function*: in line with normative data (normal: 79%, at risk: 13%, problem: 8%).
Van Eijck et al. 2009 [7]	Cognition	Questionnaire	not standard-ized	OC	64/89 (72%)	1971-2004	1-32 (median: giant 11; minor 17) years	n/a	*Cognition*: 9% attended a special school.

Supplemental table 3 (*continued*)

Reference	Outcome	Assessment or questionnaire	Tests	Group	Number of children	Year of birth	Age at follow-up	Normative data	Most important results
Henrich et al. 2008 [8]	Motor function	Questionnaire (not stated)	not standard-ized	OC	15/26 (58%)	1994-2004	1-10 (median: 6.3) years	n/a	*Motor function*: 7% problems with everyday activities, 13% felt their sporting activities were limited.
	Cognition	Questionnaire (not stated)	not standard-ized					n/a	*Cognition*: 93% had attended kindergarten or school at usual age.
Biard et al. 2004 [9]	Health status	Questionnaire (parent)	PedsQL	Giant OC	2/6 (33%)	1996-2001	not stated.	PedsQL parent-report: 88±12	*Health status:* scores of 2 children were calculated: 81 and 95; comparable to normative data.
Ginn-Pease et al. 1991 [10]	Cognition	Assessments	WISC-R WJ-R	OC+ GS	22/93 (24%)	1972-1981	6-16 (mean: 10.6)	TIQ: 100±15	*Cognition*: in line with normative data (mean±SD:100±16).
	Behavior	Questionnaires (parent)	VABS CBCL					VABS ≥85. CBCL <63	*Behavior*: mean scores within normal range (mean±SD VABS: 95±16; CBCL: 57± 10); however, 18% exceeded the p90 on the CBCL.

OC: omphalocele; GS: gastroschisis; CI: confidence interval; TIQ: total intelligence quotient; SD: standard deviation; PedsQL: Pediatric Quality of Life Inventory; WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence-3rd edition; BRIEF-P: Behavior Rating Inventory of Executive Functioning – Preschool version; BASC-2: Behavior Assessment System for Children – 2nd edition (preschool); M-ABC: Movement Assessment Battery for Children (2: 2nd edition); WISC-R: Wechsler Intelligence Scale for Children-Revised; WJ-R: Woodcock-Johnson Psycho-Educational Battery; VABS: Vineland Adaptive Behavior Scale; CBCL: Child Behavior Checklist.

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CONGENITAL LUNG MALFORMATIONS



8

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

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Abstract

Objective

To predict the need for respiratory support and surgery in fetuses with a congenital lung malformation (CLM) by the congenital pulmonary airway malformation (CPAM) volume ratio (CVR), and to evaluate the concordance between prenatal appearance and postnatal type of CLM.

Methods

In all included fetuses (2007-2016) the CVR was measured on ultrasound at 20-24 (US1), 24-30 (US2), and 30-36 (US3) weeks' gestation. Primary outcomes were need for respiratory support <24 hours, and surgery <2 years after birth. Postnatal diagnosis of CLM was based on computed tomography/histology.

Results

Of 80 fetuses, 14 (18%) required respiratory support, 17 (21%) required surgery. The CVR at US2 and US3 was predictive for the need for surgery (cut-off 0.80 and 0.46, respectively), but not for respiratory support. Four of 16 (25%) fetuses who showed prenatal regression of the CLM required respiratory support. Type of CLM could not be diagnosed based on prenatal ultrasound characteristics; 15/35 (43%) microcystic CPAM on prenatal ultrasound appeared to be congenital lobar emphysema after birth.

Conclusion

The CVR predicts the need for surgery, but not respiratory support. Prenatal 'disappearance' does not rule out respiratory problems. We propose a prenatal description of the CLM and postnatal diagnosis following CT-imaging.

Introduction

Congenital lung malformations (CLM) are a heterogeneous group that include congenital pulmonary airway malformations (CPAM), bronchogenic cysts (BC), bronchopulmonary sequestrations (BPS), and congenital lobar emphysema (CLE).[1] Since the introduction of the 20-week fetal anomaly scan, CLM are increasingly being detected prenatally.[2, 3] The current estimated incidence is 4.2 per 10,000 births.[2] Multiple prenatal ultrasound parameters have been suggested for the prediction of postnatal outcome.[4-8] Crombleholme et al.[4] found that fetuses with a CPAM volume ratio (CVR) >1.6 show an 80% chance of fetal hydrops. In addition, an increased CVR has been associated with higher prenatal intervention rates and adverse postnatal outcome.[5, 6, 8-11]

Postnatal outcome is dependent on prenatal course and type of CLM; a CPAM is asymptomatic in most cases, whereas the majority of infants with CLE are expected to show respiratory problems after birth.[12] This information is relevant for perinatal planning (e.g. location of the delivery), and for prenatal counselling of future parents. A prenatal diagnosis regarding the type of CLM is challenging, as fetal lungs are not aerated yet, and because different types of CLM can look similar on prenatal ultrasound. In addition, the prenatal ultrasound classification of CPAM (i.e. microcystic, macrocystic, mixed)[10] differs from the histopathological Stocker classification,[13] which is used after birth.

In this study, we assessed the correlation between prenatal ultrasound parameters, including the CVR as either a cross-sectional as well as a repeated measurement, and postnatal outcome. The primary aim was to predict the need for respiratory support because of the CLM within 24 hours after birth, and the need for surgical intervention within the follow-up period of 2 years after birth. Secondarily, we evaluated the concordance between prenatal appearance and postnatal type of CLM.

Methods

Study population

We analyzed data of all fetuses diagnosed with a CLM in the Erasmus Medical Centre-Sophia Children's Hospital Rotterdam between January 2007 and December 2016. We excluded pregnancies that were terminated, fetuses with a bilateral lesion and/or major multiple congenital anomalies (MCA), and infants who were either lost to follow-up or whose follow-up was incomplete (i.e. no available CT-scan or histology). The Medical Ethical Review Board waived approval because data obtained during routine care were retrospectively analyzed (MEC-2018-1086).

Prenatal parameters

The CVR was measured retrospectively by an experienced physician (NP), who was blinded for postnatal diagnosis and outcome. The CVR was measured as described by Crombleholme et al.[4] at three time periods during gestation (US1:18-24 weeks' gestation, US2: 24-30 weeks' gestation and US3: 30-37 weeks' gestation) dependent on availability of ultrasound images. At these times points we also registered type of CLM (CPAM/BPS), presence of mediastinal shift, presence of fetal hydrops, and presence of MCA. The CLM were classified according to findings on prenatal ultrasound. CPAMs were classified according to the Adzick criteria,[10] i.e. microcystic, macrocystic or mixed type. The CLM was classified as BPS when arterial blood supply directly from the aorta was visualized. A CLM was classified as hybrid when arterial blood supply was visualized from both the aorta as well as the pulmonary arteries. For cases with multiple measurements of the lesion throughout gestation, we noted whether regression in lesion size occurred. We regarded a full regression of the lesion when the lesion was not visible by ultrasound on the last prenatal ultrasound exam (>30 weeks' gestation). Partial regression was defined as an absolute decrease in lesion area (length x width x height) and/or a decrease of at least 0.1 in the CVR, indicating a relative decrease in lesion size.

Perinatal characteristics

Data on delivery mode, gestational age at delivery, birth weight (grams) and Apgar scores at 1 and 5 minutes 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 hours after birth (i.e. low flow, humidified high flow nasal cannula (HHFNC), continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation (NIPPV), or mechanical ventilation. A pediatric intensivist (SCO) blinded for prenatal parameters reviewed the charts and assessed whether the need for respiratory support <24 hours after birth was (most likely) caused by the CLM.

Postnatal outcomes

We recorded the length of initial hospital stay (LOS), duration of respiratory support during first hospital stay, the presence of chronic lung disease (CLD), and the need for surgery – including embolization of an aberrant artery in case of BPS – within 2 years after birth from patient records. We included outcome data of each infant until the age of 2 years. CLD was defined as requiring supplemental oxygen for at least 28 days.[14] According to the policy in our tertiary hospital, only infants who developed symptoms after birth, e.g. respiratory insufficiency or volume overload, underwent surgical resection. Resection was followed by histological evaluation, in most cases after CT imaging. In asymptomatic infants CT-imaging was scheduled approximately 6 months

after birth. CT-scans were made according to clinical imaging protocols at that time; the scan with the least slice thickness was reviewed. A trained observer (SH), experienced in systematic assessment of CT-imaging in CLM, independently assessed all scans, blinded for patient data. The type of CLM was diagnosed according to the following criteria:

- *CPAM*: cystic abnormalities in the absence of systemic arterial blood supply. CPAM type 1 was defined as an abnormality with a large dominant cyst, optionally surrounded by multiple smaller cysts, whereas type 2 was defined as a cluster of cysts.
- *BPS:* a solid lesion with systemic arterial blood supply.
- *Hybrid*: if the BPS was accompanied by adjacent cystic abnormalities (i.e. CPAM/BPS).
- *Bronchogenic cyst*: (partial) fluid-filled cysts with a close relation to the mediastinum.
- *CLE with or without atresia*: hyperinflated, hypoechoic lung lobes, occasionally occurring with mass-effect on adjacent structures. We classified atresia under CLE as this produces similar CT-imaging abnormalities; we regarded atresia as a possible component of the aforementioned lung abnormalities rather than an abnormality by itself.[15]
- *CLM in regression*: small remnant lesions visible, or no lesion visible.

In case of a discrepancy between the assessment of SH and the radiology report in the patient records, findings were evaluated by an independent pediatric radiologist blinded for patient data to reach consensus.

Statistical analysis

Data are described as number (%) or median (interquartile range, IQR), as appropriate. We compared prenatal, perinatal and postnatal characteristics between neonates who needed respiratory support within 24 hours after birth and those who did not, using chi-square or Fisher's exact tests (categorical variables) and Mann-Whitney tests (continuous variables).

The intraclass correlation coefficient (ICC) was used to quantify the interobserver agreement. TCO and NP both measured the CVR in 20 randomly selected cases, where they were blinded to each other's result. For good agreement, the ICC has to be 0.75 and for excellent agreement the ICC has to be higher than 0.90. The ICC was calculated in a two-way mixed model, with absolute agreement and reported as single measures.

To examine the trend in CVR throughout gestation, we used a linear mixed model analysis to assess the difference in mean CVR between the different time periods. We performed a linear regression of the CVR at the three time periods for each patient separately, with gestational age (coded as a continuous variable) as the only independent

variable. To summarize the longitudinal data of the CVR, 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 multiple CVR measurements were available. The resulting estimates of the intercept and slope in the linear regressions served as independent variables in logistic regression analyses for need for respiratory support within 24 hours after birth and surgical intervention within 2 years of age. The slope was calculated per one day difference in gestation.

To calculate the predictive value and optimal cut-off points of the CVR, we performed receiver operating characteristic (ROC) analyses for each time period. Data are presented as area under the curve (AUC) with 95% confidence intervals (CIs). The cut-off with the highest value of the Youden index (sensitivity plus specificity minus 1) was regarded as the most suitable.

Results

Of 103 fetuses who had been diagnosed with CLM, data of 80 (78%) were included (supplemental figure 1). Prenatal and postnatal characteristics of included fetuses are summarized in table 1 and figure 1. The CVR was calculated for 70 fetuses at US1, for 54 at US2, and for 76 at US3. Considering the low number of fetuses with an available CVR at US2 compared to US1 and US3 we checked for selection bias. Fetuses with a CVR measurement at US2 did not show a significantly increased need for respiratory support or surgical intervention compared to fetuses without a measurement at US2 (p=0.76 and p=0.39, respectively). Multiple CVR measurements were available in 74 (93%) fetuses. The GA of US3 was statistically significantly higher in fetuses who required respiratory support after birth compared to those who did not. The CVR differed significantly between US1 or US2 and US3 (p<0.001), showing an overall decrease in CVR after 30 weeks' gestation. Interobserver agreement calculations resulted in an ICC of 0.891 (95% CI: 0.751–0.955), representing good agreement.

Table 1 Patient characteristics

	n	No respiratory support <24 hours n=66	n	Respiratory support <24 hours[A] 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	24 (40%)	10	5 (50%)	0.73

Table 1 (*continued*)

	n	No respiratory support <24 hours n=66	n	Respiratory support <24 hours[A] n=14	*p* value
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 [B]	66	64 (97%)	14	13 (93%)	0.44
Prenatal diagnosis	66		14		n/a
- 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 5min	66	10 (9-10)	14	8 (7-9)	<0.001
Birth weight (grams)	66	3340 (3133-3643)	14	3422 (2989-3958)	0.80
Gender female	66	32 (49%)	14	6 (43%)	0.84
Isolated [B]	66	61 (92%)	14	12 (86)	0.60
Surgical intervention <2 years of age	66	10 (15%)	14	7 (50%)	0.008

Table 1 (*continued*)

	n	No respiratory support <24 hours n=66	n	Respiratory support <24 hours[A] n=14	*p* value
Age at surgical intervention (days)	10	102 (25-271)	7	19 (7-29)	0.03
Length of initial hospital stay (days)	66	2 (2-3)	12	7 (4-18)	<0.001
Chronic lung disease	66	0 (0%)	14	3 (21%)	0.004
Postnatal diagnosis	66		14		n/a
- 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%)	
- CLE		12 (18%)		3 (21%)	
- Bronchogenic cyst		1 (2%)		0 (0%)	
- In regression		3 (5%)		2 (14%)	

Data are presented as median (interquartile range) or number (%). US: ultrasound; w^{+d}: weeks+days; CVR: CPAM volume ratio; CPAM: congenital pulmonary airway malformation (type 1: large dominant cyst, optionally surrounded by multiple smaller cysts; type 2: a cluster of cysts); BPS: bronchopulmonary sequestration; CLE: congenital lobar emphysema. [A] 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%)). [B] 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).

Need for respiratory support within 24 hours after birth

Of 80 included fetuses, 14 (18%) required respiratory support within 24 hours after birth because of the CLM (table 1, figure 1). Five infants received low flow supplemental oxygen, one required HHFNC, four required CPAP, one infant required NIPPV, and two required mechanical ventilation. In one infant, the type of support was unclear. This infant required respiratory support for only a few minutes during transportation. Details of respiratory support are shown in the legends of table 1.

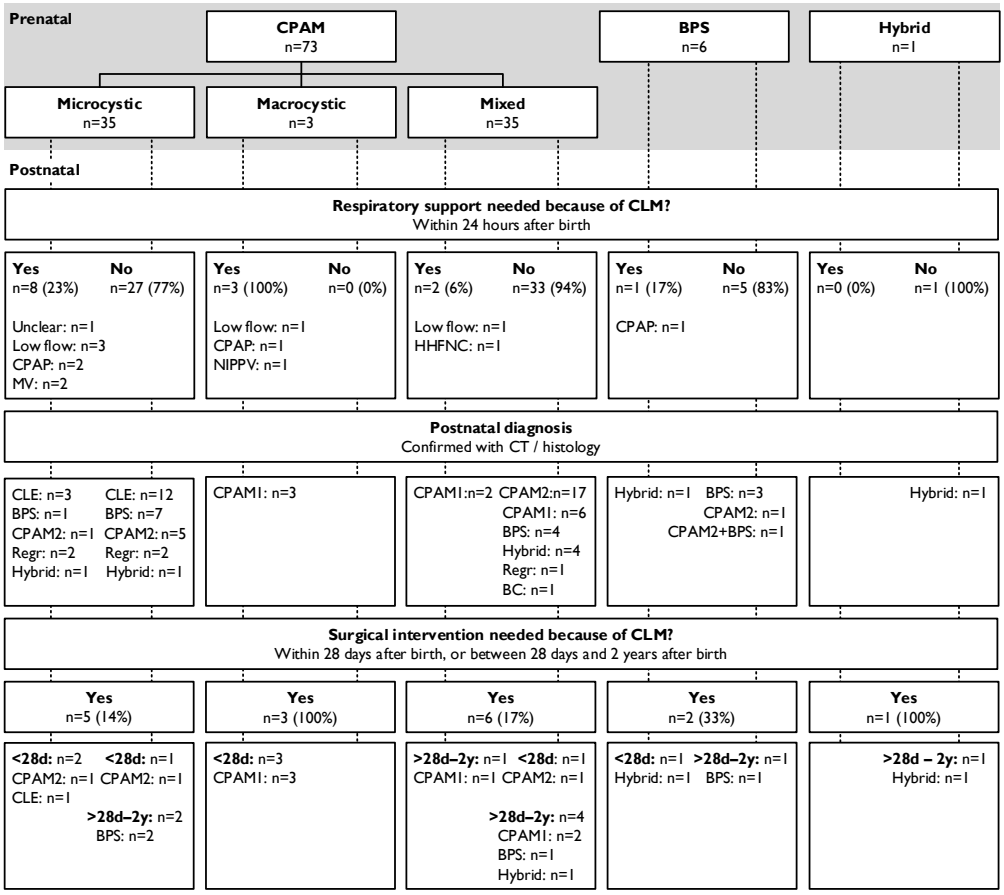

Figure 1 Flow chart showing the need for respiratory support, postnatal diagnosis, and the need for surgery – stratified for prenatal appearance
CPAM: congenital pulmonary airway malformation (prenatal classification according to Adzick, postnatal type 1: large dominant cyst, optionally surrounded by multiple smaller cysts; postnatal type 2: a cluster of cysts); BPS: bronchopulmonary sequestration; CLE: congenital lobar emphysema; BC: bronchogenic cyst; CPAP: continuous positive airway pressure; MV: mechanical ventilation; NIPPV: non-invasive positive pressure ventilation; HHFNC: humidified high flow nasal cannula; regr: regression.

The median duration of respiratory support was 3 days (IQR: 1-22 days; range: 1-387 days). None of the included infants required extra-corporal membrane oxygenation. Only 1/66 (2%) infants who did not need respiratory support within 24 hours, developed respiratory distress within the first 28 days after birth due to the CLM.

The group of infants who required respiratory support showed a significantly higher CVR at US2 than those who did not (p=0.04; table 1, figure 2). At US1 and US3, the

difference in CVR between these groups did not reach significance. ROC curve analyses showed low accuracy at every cut-off for prediction of the need for respiratory support by the CVR at any of the time periods (supplemental table 1, supplemental figure 2).

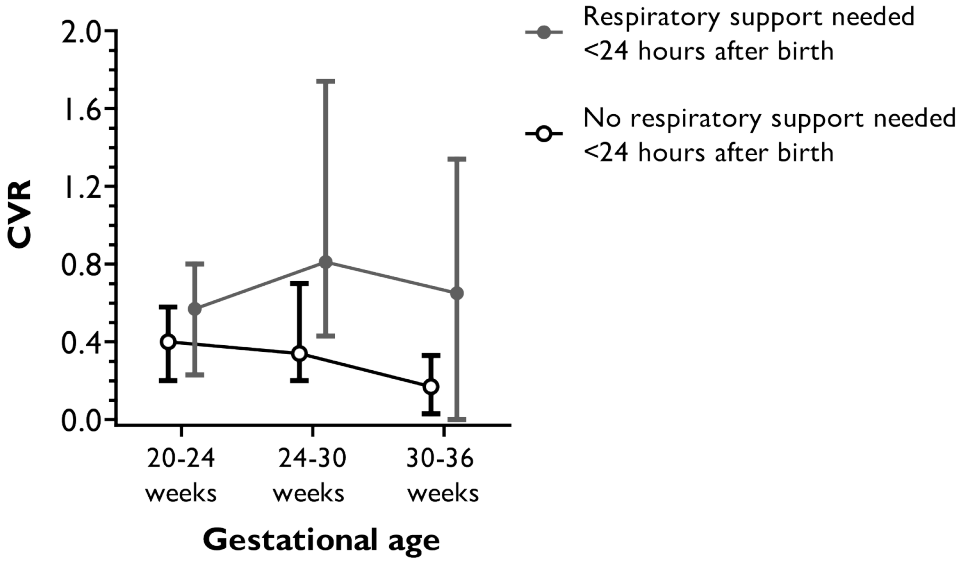

Figure 2 Line chart showing the CPAM volume ratio (CVR) throughout gestation, both for those who required respiratory support <24 hours after birth and for those who did not
CVR: CPAM volume ratio. Symbols represent medians with interquartile ranges.

Of 74 fetuses with multiple CVR measurements, 48 (65%) had shown regression of their CLM throughout pregnancy. Of the 16 lesions that were not visible on prenatal ultrasound from 30 weeks' gestation onwards (i.e. full regression), 15 (94%) were visible on CT-imaging after birth. The majority of these lesions concerned either BPS (n=6) or CLE (n=5) (supplemental figure 3). Regression of the CLM, either partial or full, was not significantly associated with the need for respiratory support (OR 0.60 (95% CI: 0.16-2.20), p=0.44): of the 7 fetuses with increasing lesion size, 2 (29% required respiratory support after birth; of the 16 fetuses who had shown full regression of their lesion, four (25%) needed respiratory support, of whom two because of a bilateral pneumothorax (postnatal diagnosis: BPS n=1; CLE: n=1).

Using multivariable logistic regression analyses we found a significant association between the intercept of the CVR and need for respiratory support (p=0.03), but not for the slope (p=0.62), i.e. no association was found between the trend in CVR throughout gestation and need for respiratory support.

Surgical intervention within 2 years after birth

Seventeen (21%) infants required surgery within 2 years after birth, of whom 8 within 28 days. One infant with an intralobar BPS had undergone embolization of the aberrant artery at the age of 6 months because of cardiac failure. Features of malignancy were found in one case of CPAM type 1 on histological evaluation; follow-up of this child is ongoing. This child showed no symptoms nor signs of malignant recurrence on magnetic resonance imaging at the last follow-up visit.

At US2 and US3, the need for surgical intervention could reliably be predicted by the CVR, with an optimal cut-off value of 0.80 at US2 (sensitivity 70%, specificity 82%) and 0.46 at US3 (sensitivity 71%, specificity 90%; supplemental table 1, supplemental figure 4). ROC curve analyses showed low accuracy for prediction of surgical intervention by the CVR at US1.

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). Of the seven fetuses with increasing lesion size, four (57%) needed to be operated on within 2 years after birth. Of the 16 fetuses whose CLM had disappeared prenatally, one (6%) required surgical intervention. Fifty percent (n=7/14) of the infants who needed respiratory support required surgery within 2 years compared to 15% (n=10/66) of the infants without need of respiratory support (p=0.008)

Eight infants required surgery within 28 days, all because of respiratory insufficiency. We designed a counseling flow chart for prediction of the need for surgery within 28 days after birth based on the type of CLM and the CVR at US3 (n=76). Cut-offs were based on ROC analysis (AUC 0.98 (95% CI: 0.93-1.00), p<0.001). All infants with a macrocystic CPAM or a CVR of ≥1.47 required surgery within 28 days (n=7). One of the 9 infants (11%) with a CVR between 0.57 and 1.46 required surgery. This case showed a hybrid lesion both on prenatal ultrasound as well as after birth. The remaining 60 fetuses did not require surgery within 28 days after birth, and all showed other types of CLM and a CVR <0.57 (figure 3). Of 68 infants who did not require surgery within 28 days after birth, 9 (13%) were still operated on within 2 years (range: 42-433 days). Three of them (33%) had respiratory insufficiency because of a CPAM type 1 (n=2) or a hybrid lesion (n=1), 3 (33%) other infants had cardiac failure because of a BPS, and 1 (11%) underwent surgery because of increasing size of a CPAM type 1. In the remaining 2 (22%) infants, the indication for surgery was unclear from patient records. Using multivariable logistic regression analyses, we found a significant association between the intercept of the CVR and need for surgery (p=0.001), but not for the slope (p=0.27), i.e. no association was found between the trend in CVR throughout gestation and need for surgery.

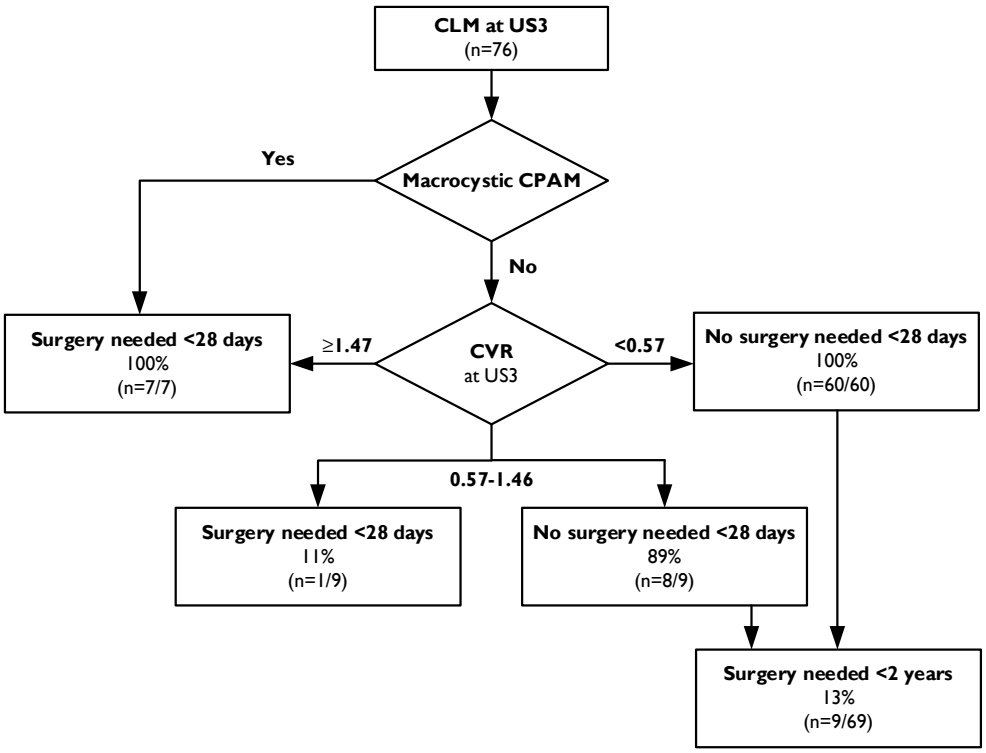

Figure 3 Counseling flow chart for the need for surgery, according to prenatal type of CLM and the CPAM volume ratio at 30-37 weeks' gestation
CLM: congenital lung malformation; CPAM: congenital pulmonary airway malformation; CVR: CPAM volume ratio; ROC: receiver operating characteristic. Cut-offs are based on ROC analyses.

Concordance between prenatal appearance and postnatal type of CLM

Concordance between prenatal appearance and postnatal type of CLM is shown in figure 1. Postnatal type of CLM was based on CT-imaging in 64 (80%) infants; and based on both CT-imaging and histological examination in 16 (20%) infants.

Microcystic CPAM (n=35; 48%)

Microcystic CPAM on prenatal ultrasound appeared to be CLE in 15 (43%) infants after birth. Eight (23%) infants showed arterial blood supply on CT imaging, those were subsequently diagnosed with BPS. The remaining infants with a microcystic CPAM on prenatal ultrasound were diagnosed after birth with CPAM type 2 (n=5, 14%), a hybrid lesion (n=2, 6%), or CLM in regression (n=4, 11%).

Macrocystic CPAM (n=3, 4%)

In all fetuses prenatally diagnosed with macrocystic CPAM, postnatal CT imaging and histological examination showed CPAM type 1.

Mixed CPAM (n=35, 48%)
Twenty-five (71%) fetuses with a mixed type CPAM on prenatal ultrasound, were diagnosed with a CPAM after birth (type 1: n=8, type 2: n=17). Four (11%) infants were diagnosed with BPS, 4 (11%) others had a hybrid lesion, 1 (3%) infant was diagnosed with a BC, and 1 (11%) had a CLM in regression.

BPS (n=6, 8%) and hybrid CLM (n=1, 1%)
In 5 (83%) fetuses that showed BPS on prenatal ultrasound, postnatal CT-imaging showed arterial blood supply from the aorta. These infants were subsequently diagnosed with BPS (n=3, 50%), a hybrid lesion (n=1, 17%), and a BPS in one lung with a CPAM type 2 in the other lung (n=1, 17%). In the latter the CPAM was not visible on prenatal ultrasound. In the remaining infant, no arterial blood supply was seen on CT imaging; this infant was diagnosed with CPAM type 2. The one prenatal hybrid lesion was confirmed after birth.

Discussion

In this cohort of fetuses with a CLM, the CVR from 24 weeks' gestation onwards proved to be a reliable predictor of the need for surgical intervention within 2 years after birth. Its predictive value increased with increasing gestational age. Prenatal parameters were not predictive of the need for respiratory support within the first 24 hours after birth. Those who required respiratory support after birth had shown large differences in CVR measurements on prenatal ultrasound, ranging from full regression to a CVR >1.6. Microcystic CPAM on prenatal ultrasound proved to be CLE after birth in almost half of the cases.

Previous research has suggested that a maximum CVR of greater than 0.84[16] or 1.0[17] is a reliable predictor of the risk of respiratory morbidity and the need for surgical intervention, and recommends to have these fetuses delivered at a tertiary care center with pediatric surgical expertise.[18] In agreement with these studies, on average we found a higher CVR in infants who required respiratory support or surgical intervention versus those who did not. However, we also found that even fetuses who show full regression of their CLM are at risk for respiratory distress within 24 hours after birth; some even presented with bilateral pneumothorax. We hypothesize that a pneumothorax may be caused by heterogeneity in the aberrant bronchial tree; this may have led to air trapping, which eventually caused the pneumothorax. This hypothesis warrants further investigation. In agreement with previous research,[19] we showed that the majority of lesions that seemed to have disappeared on prenatal ultrasound were still visible on postnatal CT-imaging. Consequently, regardless of lesion size and prenatal regression, we would recommend to have all fetuses with a CLM delivered at a tertiary care center and admitted for observation for at least 24 hours after birth. When infants

show no respiratory distress during this period, they can be discharged as the possibility of developing acute respiratory distress after this period is low. It should be noted that some children required surgery after the study period, up until the age of 6 years. Therefore, postnatal CT-imaging and prolonged follow-up by a specialized team should be offered to all cases of CLM.

In our study we compared prenatal ultrasound findings with postnatal CT-imaging in most cases instead of with histological evaluation. A previous study in 103 infants who underwent surgical resection of their CLM showed that CT imaging had a concordance rate of 84% with the histological diagnosis of CPAM, and of 90% for the detection of a feeding vessel.[20] Histology is not always available, however, as not all children with CLM undergo surgical resection. In these children, diagnosis on postnatal CT is considered to be the gold standard. Nevertheless, the possible disconcordance between imaging and histological findings should be kept in mind.

Previous studies[20, 21] tried to classify CLMs prenatally according to the postnatal classification guidelines, such as the Stocker criteria.[13] In our study the type of CLM could not be diagnosed based on prenatal assessment of the lesion, particularly because a variety of diagnoses were established after birth in the prenatal microcystic and mixed CPAM groups. We therefore propose to describe the lung lesion according to its ultrasound characteristics; i.e. hyperechogenic, hypoechogenic, or mixed, and to describe where the arterial blood supply derives from (the aorta or the pulmonary arteries). Future parents should be informed that the type of CLM will be determined after postnatal CT-imaging.

From previous literature, CLE is regarded a rare diagnosis (both before and after birth), associated with a higher incidence of respiratory problems compared with other CLMs.[12, 22] In the study by Kunisaki et al., 10% of infants with CLM were diagnosed with CLE; those infants were almost three times as likely to present with respiratory distress after birth as those with other types of CLM.[22] This is in contrast with our findings, where 19% of fetuses with a CLM were diagnosed with CLE after birth, and 80% of these infants remained asymptomatic. They had all presented with a microcystic CPAM on prenatal ultrasound. As CLE is easily distinguishable from other types of CLM on postnatal CT-imaging, we expect that the discrepancy between our findings and those of previous studies is not caused by an inaccurate postnatal diagnosis. Rather, we hypothesize that this discrepancy may be explained by a difference in prenatal versus postnatal inclusion of cases. Previous studies included infants with CLM who had either been diagnosed prenatally, or after birth because of symptoms. CLE may be missed more easily on prenatal ultrasound than other types of CLM, due to very subtle increased echogenicity.[22, 23] Therefore, the proportion of symptomatic infants diagnosed

after birth may be relatively higher than in other types of CLM, and the proportion of asymptomatic infants may appear lower as the CLE in those infants remains undetected. CLE would subsequently be regarded a rare diagnosis, with a higher incidence of respiratory problems. When counseling parents following a prenatal diagnosis of any type of CLM, however, clinicians should focus on the findings in the group of those diagnosed prenatally. In line with our findings, Kunisaki et al. reported that prenatally diagnosed infants with CLE were no more likely to be symptomatic at birth than those with other types of CLM.[22] In case of suspected CLE, counseling should not be more negative than in case of, for example, CPAM type 2.

Conclusion

In fetuses with a CLM, the CVR measured from 24 weeks' onwards is a reliable predictor of the need for surgical intervention within 2 years after birth, but not for the need for respiratory support within 24 hours after birth. We recommend to have all fetuses with a CLM delivered at a tertiary care center and offered postnatal CT-imaging and prolonged follow-up by a specialized team, regardless of the size of their lesion on prenatal ultrasound. The fetuses with a microcystic CPAM on prenatal ultrasound showed a variety of postnatal diagnoses, of which almost half concerned CLE. We propose a prenatal description of the CLM according to its ultrasound characteristics. Future parents should be informed that the type of CLM will be determined after postnatal CT-imaging.

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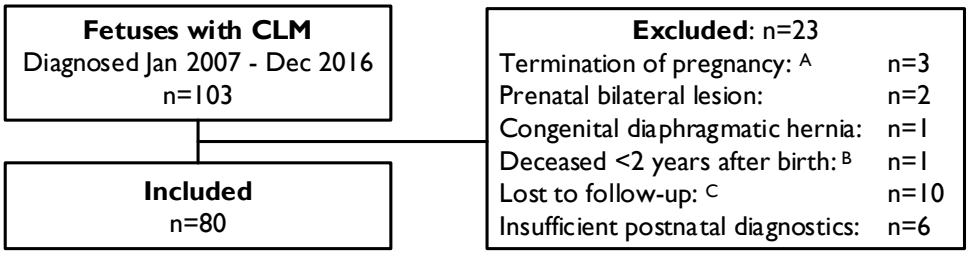
Supplemental material

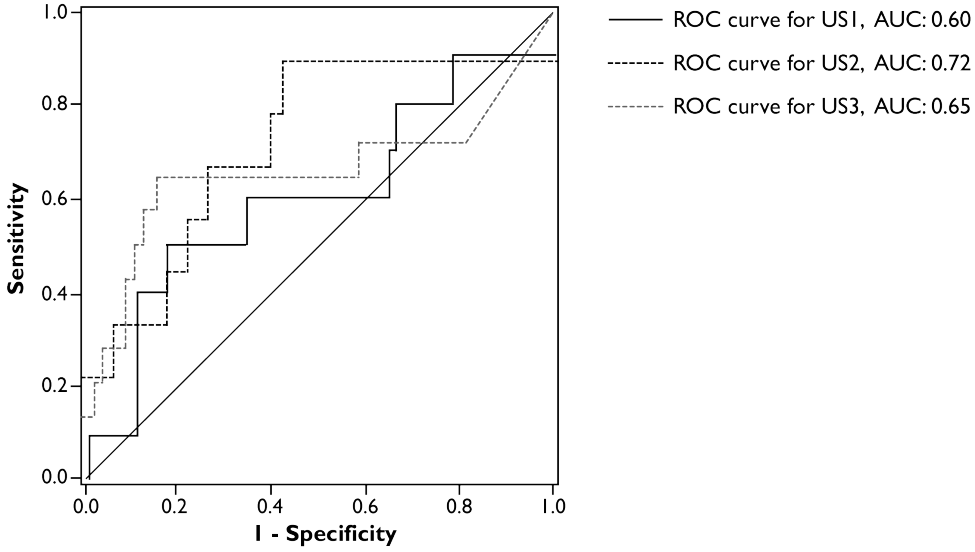
Supplemental table 1 Outcome parameters of ROC curve analyses

	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%

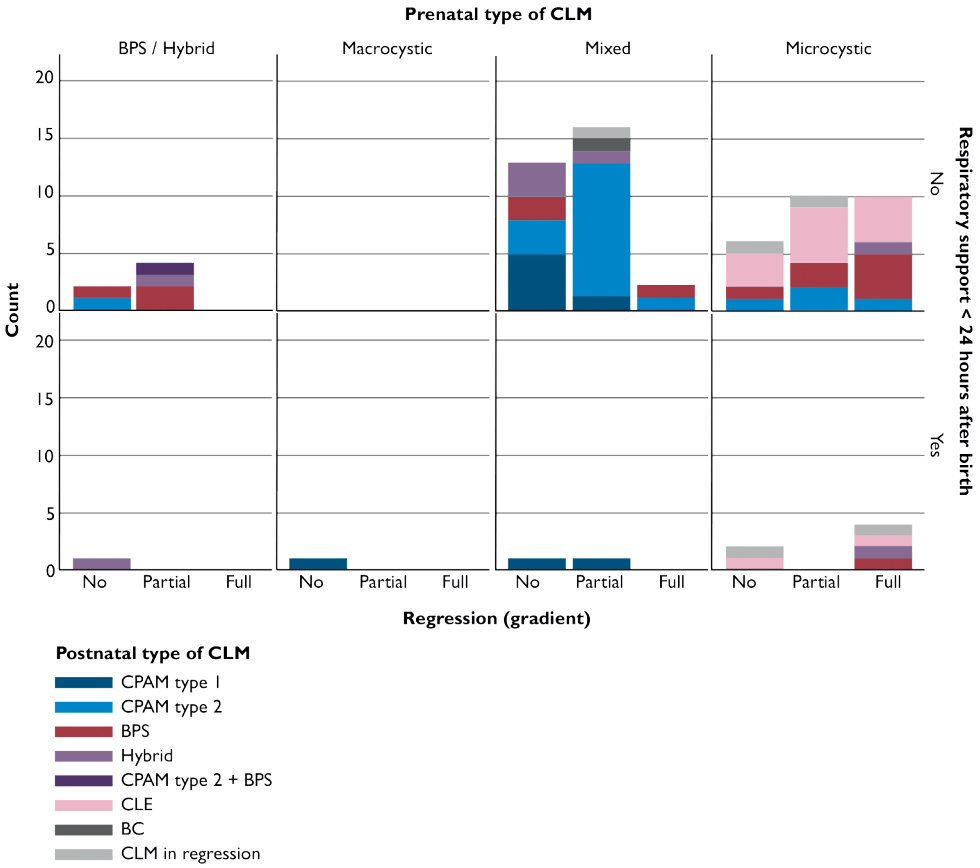
ROC: receiver operating characteristic; AUC: area under the curve; CVR: congenital pulmonary airway malformation volume ratio; US: ultrasound.



Supplemental figure 1 Inclusion flow chart
CLM: congenital lung malformation
[A] Indication: hydrops (n=1), encephalocele (n=1), parental request (n=1). [B] Cause of death: cecum perforation complicated by septic shock and intracerebral hemorrhage. [C] Reasons: refusal (n=4), treated elsewhere (n=3), organizational (n=2), emigrated (n=1).

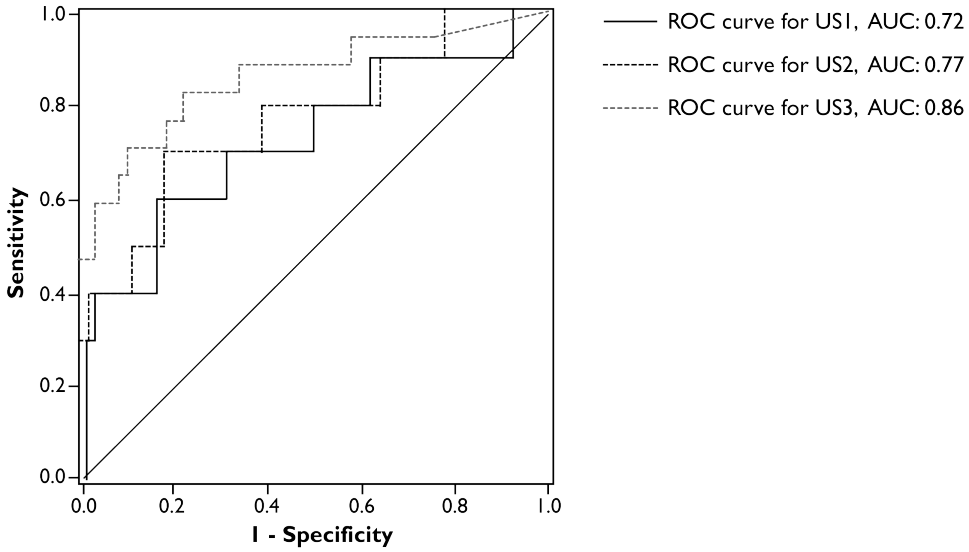


Supplemental figure 2 ROC analyses of the CVR at the different time periods for the need for respiratory support within 24 hours after birth
ROC: receiver operating characteristic; CVR: congenital pulmonary airway malformation volume ratio.



Supplemental figure 3 Prenatal type of CLM, postnatal diagnosis and need for respiratory support in cases with multiple CVR measurements available (n=74)
CLM: congenital lung malformation; BPS: bronchopulmonary sequestration; CPAM: congenital pulmonary airway malformation (type 1: large dominant cyst, optionally surrounded by multiple smaller cysts; type 2: a cluster of cysts); CVR: CPAM volume ratio; CLE: congenital lobar emphysema; BC: bronchogenic cyst.

This figure shows the prenatal type of CLM, stratified for gradient of regression (partial: absolute decrease in lesion area and/or a decrease of at least 0.1 in CVR; full: not visible on the last prenatal ultrasound exam), the need for respiratory support <24 hours after birth, and postnatal diagnosis. Regression of the CLM, either partial or full, was not significantly associated with the need for respiratory support (p=0.44).



Supplemental figure 4 ROC analyses of the CVR at the different time periods for the need for surgical intervention within 2 years after birth

ROC: receiver operating characteristic; CVR: congenital pulmonary airway malformation volume ratio.



9

Lung function, exercise tolerance, and physical growth of children with congenital lung malformations at 8 years of age

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Pediatric Pulmonology 2019; Aug;54(8):1326-1334.

Abstract

Objective

To improve counseling on congenital lung malformations (CLM) by describing long-term outcomes of children either operated on or managed by observation.

Study design

We analyzed lung function (spirometry), exercise tolerance (Bruce treadmill), and physical growth of 8-year-old children with CLM who participated in our longitudinal prospective follow-up program. Data are shown as median SD scores (SDS) with IQR, or estimated marginal means (95% CI) on the basis of general linear models.

Results

Twenty-nine (48%) of the 61 children had required surgery at a median age of 108 (IQR: 8-828) days, and 32 (52%) were managed by observation. In the surgery group, all lung function measurements (except for FVC) were significantly below 0 SDS, with median FEV1 -1.07 (IQR: -1.70 to -0.56), FEV1/FVC -1.49 (-2.62 to -0.33), and FEF25-75% -1.95 (-2.57 to -0.63) (all $p<0.001$). Children in the observation group had normal FEV1 and FVC, whereas FEV1/FVC (-0.81 (-1.65 to -0.14)) and FEF25-75% (-1.14 (-1.71 to -0.22)) were significantly below 0 SDS (both $p<0.001$). Mean exercise tolerance was significantly below 0 SDS in both groups (observation: -0.85 (95% CI: -1.30 to -0.41); surgery: -1.25 (-1.69 to -0.80)); eight (28%) children in the observation group, and ten (40%) in the surgery group scored <-1 SDS. Physical growth was normal in both groups.

Conclusion

Children with CLM may be at risk for reduced lung function and exercise tolerance, especially those who required surgery. As little pulmonary morbidity was found in children with asymptomatic CLM, this study supports a watchful waiting approach in this group.

Introduction

Congenital lung malformations (CLM) are a heterogeneous group of malformations, including congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration, congenital lobar emphysema, bronchogenic cysts, and hybrid forms of these lesions.[1] CLM are increasingly detected prenatally as a result of routine fetal anomaly scanning and improved ultrasound technology. The current estimated incidence is 4.15 per 10 000 births.[2] Children with CLM who develop symptoms, either directly after birth or later in life, undergo surgery. However, the majority of children with CLM remain asymptomatic. The best management strategy – i.e. elective surgical resection or watchful waiting – in these children remains controversial, because of uncertainty about the risk of postoperative complications, the most accurate timing of surgical resection, and the risks of infection and malignancy related with watchful waiting.[3, 4] A previous study at our center showed airflow obstruction in approximately one-third of children with CLM at the ages of 6 and 12 months, both in those who had required surgery and in those who remained asymptomatic.[5] The data on the long-term outcome are scarce, especially in children with asymptomatic CLM.[6-8]

To optimize follow-up and to improve counselling, we primarily aimed to describe pulmonary outcomes (i.e. lung function, exercise tolerance and lower respiratory tract infections (LRTIs)) and physical growth in 8-year-old children with CLM; both in those operated on and those managed by observation. We hypothesized that children with asymptomatic CLM have normal growth and no pulmonary morbidity, and that children who needed surgery have a more complicated clinical course with growth failure and pulmonary morbidity. Secondarily, physical growth, exercise tolerance, and LRTIs were evaluated longitudinally in all children.

Materials and methods

Study population

We analyzed prospectively collected data of live-born children born with CLM between January 1999 and March 2010, and followed in the Erasmus Medical Center-Sophia Children's Hospital Rotterdam. These children had been diagnosed either prenatally or after birth, due to symptoms or coincidentally. The postnatal diagnosis had been made using computed tomography (CT) and/or histology. In our hospital, we advocate a wait-and-see policy in children with asymptomatic CLM; this group is scheduled for CT-imaging approximately 6 months after birth. Those who develop symptoms – such as respiratory distress after birth or recurrent LRTIs – undergo surgical resection, usually after a CT-scan is made. Parents of all surviving children with CLM are invited to enter their child in our longitudinal prospective follow-up program. Since 1999, this program is the standard of care for children with anatomical congenital malformations treated in

our center.[9] Follow-up visits are planned at the ages of 1, 2, 5 and 8 years. The Medical Ethical Review Board waived approval because data obtained during routine care were retrospectively analyzed (MEC-2018-1086).

Variables and definitions

Neonates born <37 weeks' gestation were considered preterm. Those with a birth weight below the 10th centile of Dutch reference curves were considered small for gestational age.[10] Multiple congenital anomalies (MCA) were only documented if they required surgery or multiple follow-up visits. We registered the need for hospitalization within 28 days after birth, including the length of stay (LOS) and the need for and duration of respiratory support (i.e. supplemental oxygen only, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)). Children who had required supplemental oxygen for at least 28 days were diagnosed with chronic lung disease.[11] Spinal and thoracic deformities were assessed during a physical examination at 8 years of age.

Pulmonary outcomes

Lung function

Dynamic lung volumes were measured using spirometry at the age of 8 years. We documented the forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and the forced expiratory flow (FEF) at 25-75% of FVC ($FEF_{25-75\%}$). Standard deviation scores (SDS) were calculated according to the Global Lung Initiative 2012, with -1.64 to +1.64 SDS considered as normal range.[12] In addition, bronchodilator reversibility was reported. Significant reversibility was defined as an increase in FEV1 of >12% compared to the pre-bronchodilator test. Static lung volumes were measured by body plethysmography and expressed in residual volume (RV), total lung capacity (TLC), and RV/TLC. Diffusion capacity was assessed with carbon monoxide diffusion (DLCO) and DLCO corrected for alveolar volume (DLCO/VA). SDS for static lung volumes and diffusion capacity were calculated according to the Utrecht data set.[13]

Exercise tolerance

Exercise tolerance was determined with the Bruce treadmill protocol[14]. Time to maximal effort was assessed at 5 and 8 years, and converted to SDS according to Dutch reference values.[15, 16]

Occurrence of lower respiratory tract infections

At each follow-up visit (1, 2, 5 and 8 years), parents reported whether or not their child had had suffered from an LRTI in the past year. Only LRTIs treated with antibiotics were documented.

Additional imaging

The program does not include routine imaging at 8 years of age yet. Children were, however, referred to the pediatric pulmonologist in a low-threshold setting.

Physical growth

Height and weight were measured at 1, 2, 5 and 8 years of age. We calculated height-for-age (HFA) and weight-for-height (WFH) SDS according to Dutch reference norms; -2 to +2 SDS was considered normal range.[17, 18] Target height SDS was calculated from parental heights.[19] To correct HFA for target height, distance-to-target-height (DTH) SDS was calculated as follows: DTH SDS = HFA SDS – target height SDS.

Statistical analysis

Data are summarized as number (%) or median (interquartile range, IQR), as appropriate. Differences in characteristics between the observation group and the surgery group were evaluated with chi-square or Fisher's exact tests for categorical data, and with Mann-Whitney tests for continuous data. We assessed with Wilcoxon signed-rank tests whether median lung function parameters were below 0 SDS. The courses of exercise tolerance and physical growth over time were evaluated with general linear models. These models included the following independent variables: need for surgery (coded as a time-dependent dichotomous variable: negative before and positive after surgery), the time point (5 and 8 years in case of exercise tolerance; 1, 2, 5 and 8 years in case of physical growth), the interaction effect of the need for surgery and time point, and presence of MCA. To account for within-subject correlations, we used an unstructured error covariance matrix. The results are summarized as estimated marginal means (i.e. the predicted values of the dependent variable, adjusted for covariates in the model) with their 95% confidence intervals (95% CIs). Statistical analyses were performed using IBM SPSS Statistics 24, with a two-sided significance level of 0.05.

Results

Of 79 infants born with CLM between January 1999 and March 2010, 76 (96%) had survived. The three others, who had been diagnosed prenatally, had died within 2 weeks after birth. Two of them had a pneumonectomy because of CPAM in the entire lung, and required ECMO for 5 and 13 days, respectively. Both died because of therapy-resistant pulmonary hypertension. The other infant was diagnosed with bronchopulmonary sequestration and died of cecum perforation complicated by septic shock and intracerebral hemorrhage.

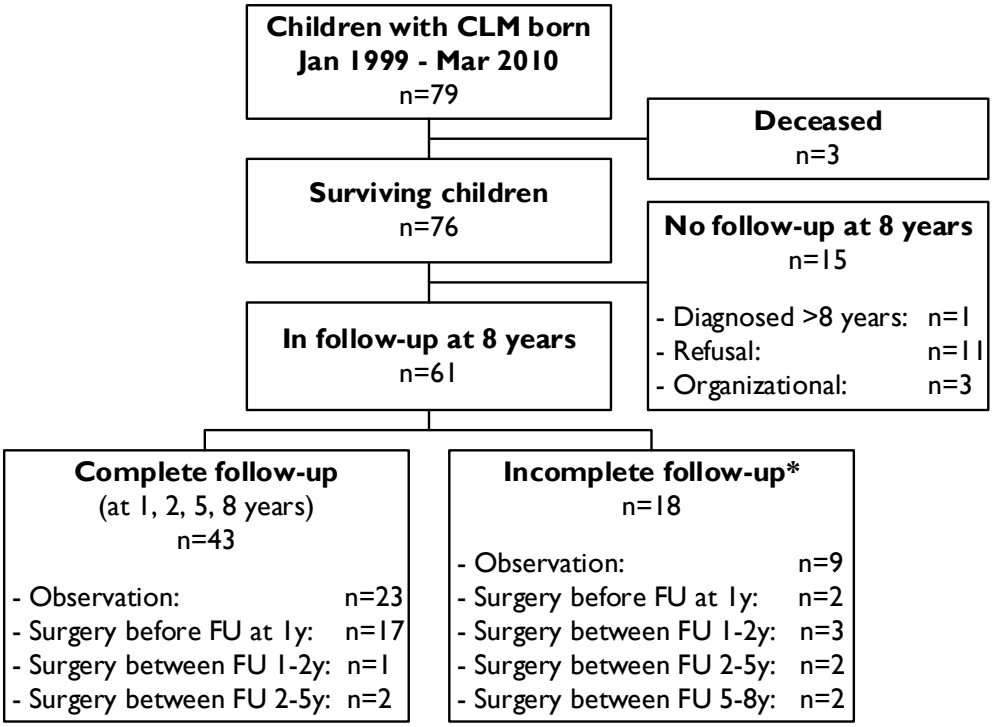

Figure 1 Inclusion flow chart

CLM: congenital lung malformations, FU: follow-up, y: years.

* Reasons for incomplete follow-up: organizational (n=10; seen at 1, 5 and 8y: n=1; seen at 2, 5 and 8y: n=4; seen at 5 and 8y: n=4; seen at 8y: n=1), refusal (n=6; seen at 1, 2 and 8y: n=3; seen at 1, 5 and 8y: n=3), diagnosed >1y (n=1, seen at 2, 5 and 8y), diagnosed >2y (n=1, seen at 5 and 8y).

Sixty-one (80%) children underwent follow-up examination at 8 years of age, of whom 43 (70%) had been seen at all four time points (figure 1). Characteristics of children examined at 8 years and those not examined did not differ significantly, except for the proportion of children not subjected to CT or histology, which was higher in those not examined (supplemental table 1). Supplemental figure 1 provides an overview of the number of children per follow-up time point, categorized according to type of management (i.e. observation or surgery).

Twenty-nine of the 61 (48%) children had undergone surgery at a median age of 108 (IQR: 8-828) days. The indications for surgery were respiratory insufficiency (14/29, 48%), recurrent infections (7/29, 24%), increasing size (3/29, 7%), and miscellaneous (5/29, 17%). One child with an extralobar bronchopulmonary sequestration had undergone embolization of the aberrant artery at 3 years of age because of cardiac insufficiency. This child was included in the surgery group. No features of malignancy

were found in any of the resected specimens. The children in the surgery group had less often been diagnosed prenatally; they had a slightly shorter median gestational age at birth; and they had more often required mechanical ventilation than those in the observation group (table 1).

Table 1 Prenatal, perinatal and postnatal characteristics of children examined at 8 years (n=61)

	n	**Observation group** n=32; 52%	n	**Surgery group** [A] n=29; 48%	***p* value**
Maternal age (years)	31	30.7 (29.0-35.1)	22	29.6 (26.9-35.1)	0.43
Male sex	32	16 (50%)	29	20 (69%)	0.13
Multiple pregnancy	32	-	29	2 (7%)	0.22
Prenatal characteristics					
Prenatal diagnosis	32	29 (91%)	29	18 (62%)	0.01
- Gestational age (weeks) at diagnosis	29	20.4 (19.9-21.7)	15	20.9 (20.1-29.0)	0.15
Perinatal characteristics					
Cesarean section	32	8 (25%)	23	2 (9%)	0.17
Gestational age at birth (weeks)	32	39.6 (28.9-41.0)	25	38.7 (36.5-40.1)	0.02
Preterm birth	32	3 (9%)	29	7 (24%)	0.17
Birth weight (grams)	32	3503 (2878-3879)	26	3070 (2838-3648)	0.13
Small for gestational age	32	3 (9%)	22	1 (5%)	0.64
Apgar score at 5 min	32	9 (9-10)	23	9 (8-10)	0.64
- Apgar score <7 at 5 min	32	2 (6%)	24	2 (8%)	1.00
Umbilical cord pH	29	7.28 (7.26-7.34)	16	7.30 (7.26-7.36)	0.64
Postnatal characteristics					
Type of CLM	32		29		
- CPAM		15 (47%)		13 (45%)	0.87
- Bronchopulmonary sequestration		5 (16%)		8 (28%)	0.26
- Congenital lobar emphysema		4 (13%)		4 (14%)	1.00
- Bronchogenic cyst		-		2 (7%)	0.22
- Hybrid or inconclusive [B]		4 (13%)		2 (7%)	0.67
- CLM in regression		3 (9%)		-	0.24
- Insufficient diagnostics (no CT or histology)		1 (3%)		-	1.00
CT imaging available	32	31 (97%)	29	25 (86%)	0.18
- Age at CT (months)	31	3.0 (0.1-4.5)	25	1.3 (0.1-6.3)	0.84

Table 1 (*continued*)

	n	Observation group n=32; 52%	n	Surgery group [A] n=29; 48%	*p* value
Localization of CLM	32		29		
- Left upper lobe		5 (16%)		3 (10%)	0.71
- Left lower lobe		7 (22%)		8 (28%)	0.61
- Right upper lobe		4 (13%)		-	0.11
- Right middle lobe		1 (3%)		1 (3%)	1.00
- Right lower lobe		13 (41%)		8 (28%)	0.28
- Multilobar		2 (6%)		4 (14%)	0.41
- Mediastinal		-		3 (10%)	0.10
- Extralobar		-		2 (7%)	0.22
Multiple congenital anomalies [C]	32	6 (19%)	27	5 (17%)	0.88
Hospitalized ≤28 days after birth	32	32 (100%)	27	24 (89%)	0.09
- Duration (days)	32	4 (2-8)	23	14 (3-29)	0.003
- Respiratory support during hospitalization	32		24		
- None		21 (66%)		7 (29%)	0.01
- Supplemental oxygen only		8 (25%)		4 (17%)	0.45
- Mechanical ventilation		3 (9%)		10 (42%)	0.01
- ECMO		-		3 (13%)	0.07
- Chronic lung disease	32	-	27	3 (11%)	0.09

Data presented as median (interquartile range) or n (%). CLM: congenital lung malformation; CPAM: congenital pulmonary airway malformation; CT: computed tomography; ECMO: extracorporeal membrane oxygenation; n/a: not applicable. [A] Thoracotomy (n=20); thoracoscopy (n=6); laparotomy (n=1); embolization (n=1); unknown (n=1). [B] CPAM and/or congenital lobar emphysema (n=3); CPAM and/or bronchogenic cyst (n=3). [C] Ventricular septal defect (n=2); atrial septal defect (n=2); tetralogy of Fallot (n=1); patent ductus arteriosus and duplicated renal collecting system (n=1); laryngeal cyst (n=1); Filamin A deficiency (n=1); congenital diaphragmatic hernia (n=1); bladder exstrophy and anal atresia and duplicated renal collecting system (n=1); bilateral ovarian cysts (n=1).

Spinal and thoracic deformities were assessed in 56 (92%) children at 8 years of age. None of them had scoliosis. One child in the observation group had pectus excavatum (1/28; 4%) versus three children in the surgery group (3/28; 11%). These three children had all undergone thoracotomy.

Pulmonary outcomes

Lung function

Reliable spirometry tests at 8 years of age were obtained in 57/61 (93%) children. Spirometry results per diagnosis are shown in figure 2. Overall, children in the observation group (n=31) had median FEV_1 SDS (-0.37 (IQR: -0.94 to 0.49)) and FVC SDS (0.10 (-0.59 to 0.74)) comparable to reference norms, whereas median FEV_1/FVC SDS (-0.81 (-1.65 to -0.14)) and $FEF_{25-75\%}$ SDS (-1.14 (-1.71 to -0.22)) were significantly below 0 (both p<0.001). Four (13%) children scored FEV_1 <-1.64 SDS, two (6%) scored FVC <-1.64 SDS, and FEV_1/FVC and $FEF_{25-75\%}$ were <-1.64 SDS in eight (26%) children.

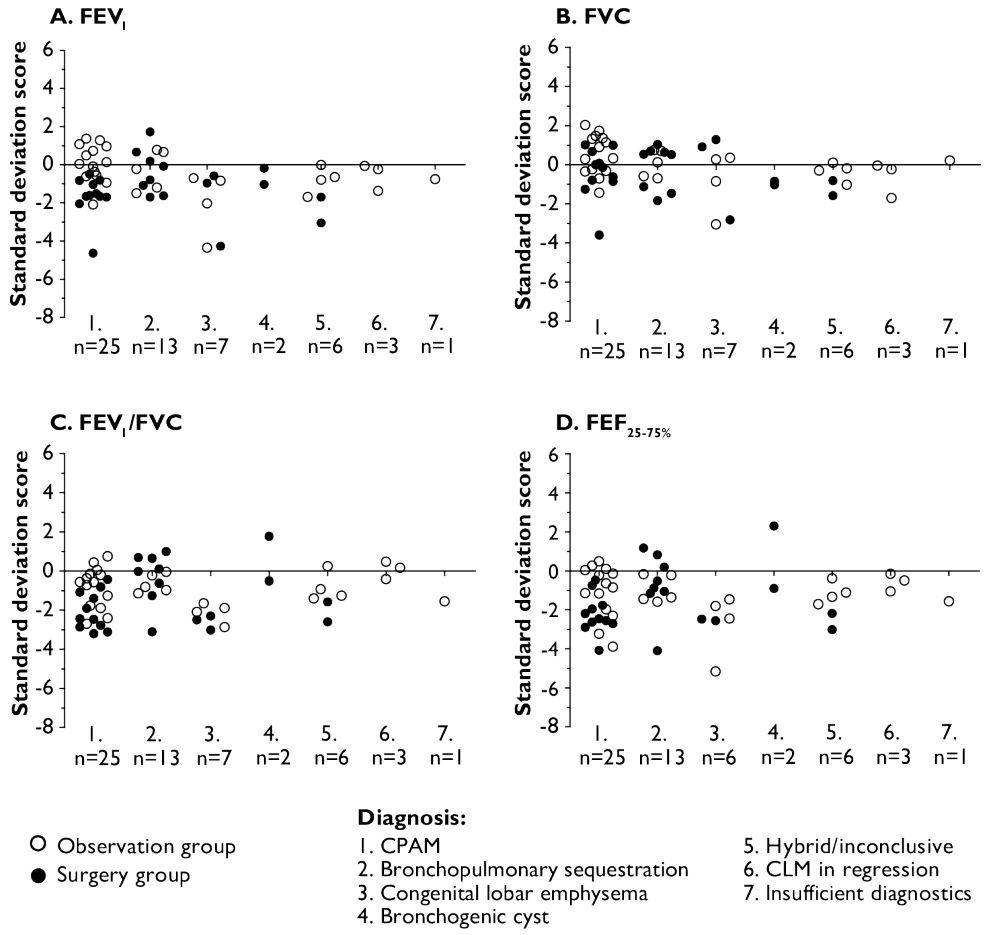

Figure 2 Scatter plots showing lung functions at 8 years of age in the observation group and in the surgery group, per diagnosis

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25-75% of FVC; CPAM: congenital pulmonary airway malformation; CLM: congenital lung malformation.

In the surgery group (n=26), median FVC SDS was comparable to reference norms (-0.39 (IQR: -1.16 to 0.68)). The other lung function parameters were significantly below 0 SDS, with median FEV_1 -1.07 (-1.70 to -0.56), FEV_1/FVC -1.49 (-2.62 to -0.33) and $FEF_{25-75\%}$ -1.95 (-2.57 to -0.63) (all p<0.001). Nine (35%) children scored FEV_1 <-1.64 SDS, three (12%) scored FVC <-1.64 SD, FEV_1/FVC was <-1.64 SDS in 12 (46%) children, and 14 (56%) scored $FEF_{25-75\%}$ <-1.64 SDS. Compared with children in the observation group, those in the surgery group had lower median FEV_1 SDS (p=0.007), and a higher proportion scored $FEF_{25-75\%}$ <-1.64 SDS (p=0.02); the other parameters did not differ significantly.

Bronchodilator reversibility was tested in 38 children. Two of 19 (11%) children in the observation group and 2/19 (11%) in the surgery group showed significant reversibility. One of these four children had been prescribed inhaled corticosteroids; the others were asymptomatic.

Body plethysmography was performed in 41/61 (67%) children. In the observation group (n=20), median static lung volumes (SDS) were comparable to reference norms (RV 0.15 (IQR: -0.33 to 0.40); TLC 0.13 (-1.12 to 0.58); RV/TLC 0.17 (-0.34 to 0.78)). In the surgery group (n=21), median RV (-0.23 (-1.34 to 0.13)) and RV/TLC (-0.20 (-1.21 to 1.01)) were comparable to reference norms, whereas median TLC was significantly below 0 (-0.44 (-1.35 to 0.19), p=0.047). Body plethysmography parameters did not differ significantly between both groups.

Diffusion capacity was assessed in 37/61 (61%) children. In both groups, median DLCO and DLCO/VA SDS were comparable to reference norms (observation group (n=20): 0.05 (IQR: -1.03 to 0.54) and 0.07 (-0.50 to 0.54), respectively; surgery group (n=17): 0.05 (-0.41 to 0.52) and -0.16 (-0.69 to 0.35), respectively). Diffusion capacity did not differ significantly between the observation group and the surgery group.

Exercise tolerance

Exercise tolerance had been assessed in 44/57 (77%) children at 5 years and in 54/61 (89%) at 8 years of age. Forty-three children were seen at both time points. At 5 years, the estimated marginal mean exercise tolerance SDS of children in the observation group (n=25; -0.13 (95% CI: -0.56 to 0.30)) did not differ significantly from 0 SDS. Those in the surgery group (n=19) scored significantly below 0 SDS (-0.56 (-1.05 to -0.07)). At 8 years, both groups scored significantly below 0 SDS (observation group (n=29): -0.85 (-1.30 to -0.41); surgery group (n=25): -1.25 (-1.69 to -0.80)). Eight (28%) children in the observation group and 10 (40%) in the surgery group scored <-1 SDS, of whom two children in the observation group and three in the surgery group scored <-2 SDS.

Overall, the general linear model analysis showed a significant decrease in exercise tolerance SDS from 5 to 8 years of age of -0.70 (95% CI: -1.01 to -0.40). Children in the surgery group had significantly lower exercise tolerance SDS than those in the observation group (mean difference: 0.49 (0.03 to 0.95)).

Occurrence of lower respiratory tract infections

LRTIs during the past year had been reported for 2/50 (4%) children at 1 year follow-up, in 4/51 (8%) at 2 years, for 7/57 (12%) at 5 years, and for 3/61 (5%) children at 8 years. Of 61 children in follow-up, 14 (23%) had suffered at least one LRTI (supplemental figure 2). Three of them had an LRTI after surgical resection; four underwent surgical resection because of the infection; and seven had been managed by observation despite having had an LRTI.

Additional imaging

In 37 of 61 (61%) children in follow-up at 8 years, additional imaging had been performed after the initial diagnostic CT-scan, at a median age of 8.4 years (range: 1.2-15.4 years). Additional imaging had been performed mostly because of respiratory symptoms (n=19, 51%), including coughing, fatigue or deteriorating lung function, or because previous imaging had been inconclusive with respect to the type of CLM (n=5, 14%). Eighteen of them were managed by watchful waiting (observation group), 18 had undergone surgery prior to the imaging, and one child underwent surgical resection after additional imaging.

Of the 37 children who underwent imaging, CT-imaging was performed in 21 (57%) children, 14 (38%) children were subjected to X-ray, and two (5%) children underwent magnetic resonance imaging. Of the 23 children who had underwent CT or magnetic resonance imaging, gas trapping was reported in 10 (43%).

Physical growth

Physical growth data of all children in follow-up at 8 years are shown in figure 3. Estimated marginal mean HFA, DTH and WFH SDS were within reference norms at 1, 2, 5 and 8 years in both the observation group and the surgery group. Only WFH SDS in the surgery group at 2 years (-0.49 (95% CI: -0.95 to -0.03)) was significantly below 0 SDS.

Overall, the general linear model analysis showed a significant decrease of HFA SDS (-0.26 (-0.46 to -0.07)) and DTH SDS (-0.26 (-0.46 to -0.06)) between 2 and 5 years, and a significant increase of WFH SDS (0.41 (0.10 to 0.71)) between 2 and 8 years. Neither the presence of MCA nor the need for surgery affected any physical growth parameter.

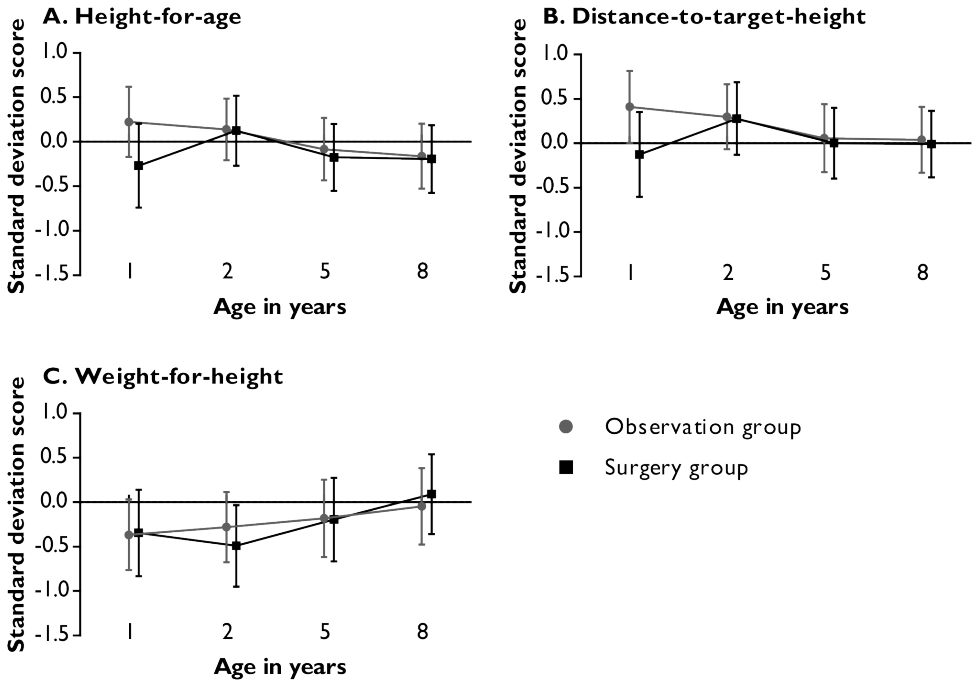

Figure 3 Line charts showing physical growth parameters measured at ages 1, 2, 5 and 8 years

Symbols represent estimated marginal means with 95% confidence intervals, based on a general linear model that includes age, need for surgery (coded as time-dependent dichotomous variable), the interaction effect of need for surgery and time point, and the presence of multiple congenital anomalies as explanatory variables.

Discussion

To our knowledge, this is the first study to evaluate lung function, exercise tolerance and physical growth in 8-year-old children with either observationally or surgically managed CLM. As we hypothesized, most children with asymptomatic CLM had normal lung function parameters, exercise tolerance, and physical growth. Those who had required surgery had worse lung function and exercise tolerance than healthy children, but, in contrast to what we expected, showed normal physical growth.

The optimal management strategy in asymptomatic CLM remains debatable.[4] In this study, more than half of the children with CLM did not require surgical resection, which is consistent with a previous study that advocated a watchful waiting approach.[6] When only looking at the infants who had been diagnosed prenatally, it appears that approximately two-thirds (i.e. 29/47, 62%) could be managed observationally. Children in the observation group showed normal physical growth, and most of them had normal

lung function parameters and exercise tolerance at 8 years of age, which supports a watchful waiting approach in asymptomatic CLM. About a quarter of children in this group did show reduced lung function parameters and/or exercise tolerance, however, and clinicians and parents should be aware of this. Several factors could have negatively influenced pulmonary outcomes, such as parental smoking and presence of asthma. Parents should be carefully counselled and encouraged to stimulate physical activity and sport participation of their children.

Approximately half of the children in the surgery group had abnormal lung function parameters (except for FVC, which was abnormal in only 12%), and mean exercise tolerance fell below -1 SD at 8 years of age. In contrast, a previous study showed that over 75% of 21 children who had undergone lobectomy for CLM had normal lung function at a median age of 6 years (range 3-16).[20] Most of these children, however, had been diagnosed prenatally and underwent surgical resection regardless of having symptoms. In our study, the majority of these children would have been included in the observation group. We, therefore, assume that the pulmonary morbidity we found in our surgery group was caused by the severity of the CLM, rather than by the surgery itself. In other words, these malformations may not be just isolated or localized defects, and weaknesses might occur in adjacent lung sections. In addition, while we included children who underwent surgery in the first decade of this century, the 21 children in the previous study underwent surgery between 2005 and 2016, when medical technologies – including surgical techniques, ventilation methods, and use of ECMO – had advanced.

At each follow-up time point, 4-12% of parents reported that their child had suffered from an LRTI during the past year. This is higher than the incidence reported in healthy European children (i.e. 14.5 per 10 000 children per year).[21] Two recent studies evaluated data of children with CLM who had been diagnosed prenatally; in both studies, 9% of children required surgery because of respiratory infections.[6, 22] In our study, LRTIs in the observation group did not always lead to surgical resection, for example because children recovered well from a single LRTI or because no imaging data were available to confirm that the LRTI had been located in the same lobe as the CLM. LRTIs have also been reported in children with CLM in regression or after surgery. Hence, resection does not necessarily eliminate LRTIs; previous research even reported a paradoxical increase of pulmonary infections following resection of CLM,[7] and a high prevalence of recurrent LRTIs (i.e. 19%) in 7-year-olds who had undergone early surgery regardless of having symptoms.[23]

Strengths of our study include the data collection from a longitudinal prospective follow-up program, the high proportion (80%) of children that entered this program,

the length of follow-up of both observationally and surgically managed children, and the standardized assessments during follow-up. Several limitations need to be addressed. First, we included children born from 1999 onwards, whereas the 20-week fetal anomaly scan was introduced in the Netherlands only in 2007. This has probably led to an underestimation of the number of children in the observation group. Second, there was selection bias of children in the surgery group: as only symptomatic children underwent surgery, it is no surprise that this group showed more morbidity. In some children, symptoms even led to the diagnosis of CLM. Third, our study does not answer the question whether early surgery in all children with CLM, including asymptomatic ones, would have resulted in everyone having a normal lung function and exercise tolerance or whether it would have worsened pulmonary outcomes. To find out whether surgical treatment could be superior to observation management in children with asymptomatic CLM, a randomized controlled trial or case-control study could be carried out to evaluate long-term outcomes in asymptomatic children who either do or do not undergo surgery. Fourth, LRTIs were parent-reported and we were unable to include data on specific pathogens or on the location of the LRTI. To limit recall bias, we asked parents to report LRTIs that had occurred during the 12 months preceding the follow-up visit; hence, we have no data on LRTIs for ages 2-4 years and 5-7 years. Last, the patient samples were too small and the follow-up period was not long enough to evaluate the risk of malignancy in CLM, particularly CPAM.

In conclusion, children with CLM may be at risk for reduced lung function and exercise tolerance, especially those who required surgery. This study does not give a clear answer regarding the optimal management strategy in children with asymptomatic CLM. Still, as little pulmonary morbidity was found in these children, this study supports a watchful waiting approach in this group. Continued follow-up until adulthood is recommended to evaluate the risk of malignancy in both symptomatic and asymptomatic CLM.

Acknowledgements

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Supplemental material

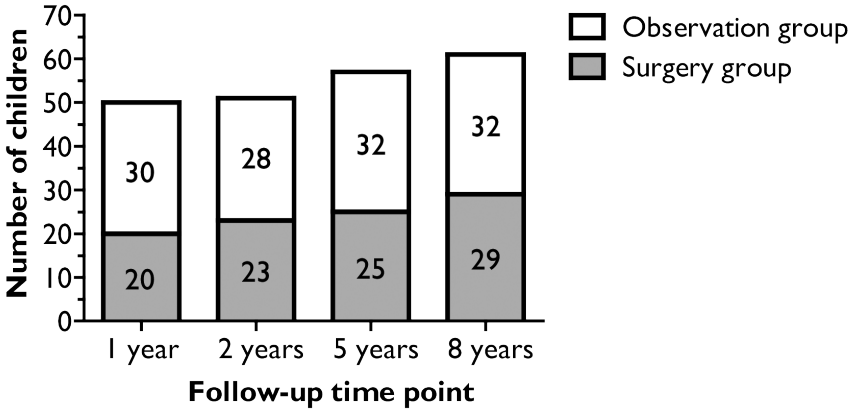
Supplemental table 1 Characteristics of children examined at 8 years versus those who were not examined

	n	In follow-up at 8 years n=61	n	Not in follow-up at 8 years n=15	*p* value
Maternal age (years)	53	30.3 (27.7-35.1)	14	28.9 (26.9-33.9)	0.40
Male sex	61	36 (59%)	15	9 (60%)	0.95
Multiple pregnancy	61	2 (3%)	15	1 (7%)	0.49
Prenatal characteristics					
Prenatal diagnosis	61	47 (77%)	15	12 (80%)	1.00
- Gestational age (weeks) at diagnosis	43	20.6 (20.0-21.9)	11	20.6 (20.3-21.7)	1.00
Perinatal characteristics					
Cesarean section	55	10 (18%)	15	1 (7%)	0.44
- Gestational age at birth (weeks)	57	39.3 (37.4-40.5)	15	38.6 (38.0-40.4)	0.58
Preterm birth	61	10 (16%)	15	2 (13%)	1.00
Birth weight (grams)	58	3283 (2855-3821)	15	3170 (2800-3585)	0.42
Small for gestational age	54	4 (7%)	14	2 (14%)	0.60
Apgar score at 5 min	55	9 (9-10)	14	9 (8-10)	0.51
- Apgar score <7 at 5 min	56	4 (7%)	14	1 (7%)	1.00
Umbilical cord pH	45	7.29 (7.26-7.34)	9	7.27 (7.21-7.31)	0.25
Postnatal characteristics					
Type of CLM	61		15		
- CPAM		28 (46%)		5 (36%)	0.38
- Bronchopulmonary sequestration		13 (21%)		2 (14%)	0.72
- Congenital lobar emphysema		8 (13%)		1 (7%)	0.68
- Bronchogenic cyst		2 (3%)		2 (14%)	0.17
- Hybrid or inconclusive [A]		6 (10%)		1 (7%)	1.00
- CLM in regression		3 (5%)		-	1.00
- Insufficient diagnostics (no CT or histology)		1 (2%)		4 (27%)	0.01
Multiple congenital anomalies [B]	61	11 (18%)	14	1 (7%)	0.44

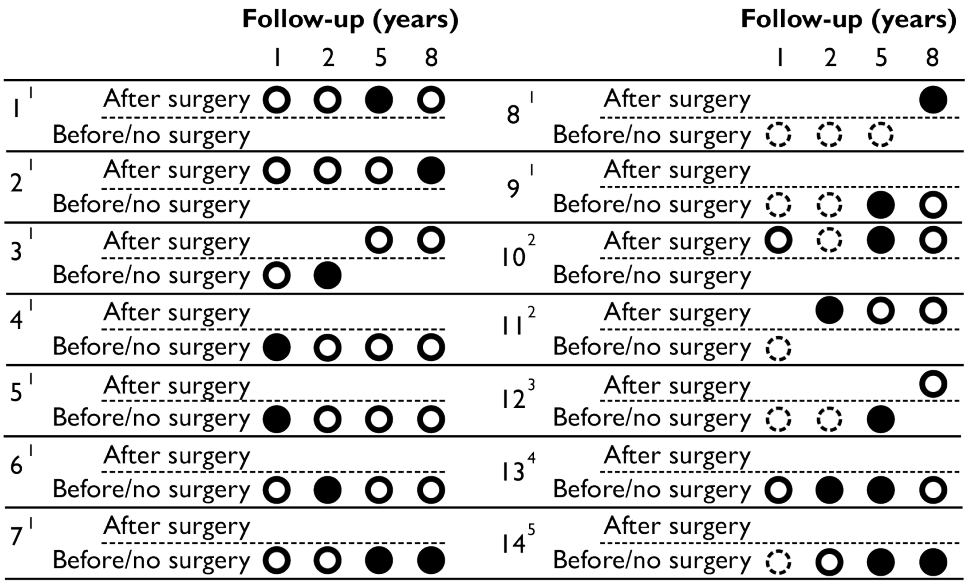
Supplemental table 1 (continued)

	n	In follow-up at 8 years n=61	n	Not in follow-up at 8 years n=15	*p* value
Hospitalized ≤ 28 days after birth	59	56 (95%)	14	14 (100%)	1.00
Duration (days)	55	5 (2-16)	13	2 (2-5)	0.06
Respiratory support during hospitalization	56		14		
- None		28 (50%)		11 (79%)	0.05
- Supplemental oxygen only		12 (21%)		1 (7%)	0.44
- Mechanical ventilation		13 (23%)		2 (14%)	0.72
- ECMO		3 (5%)		-	1.00
Chronic lung disease	59	3 (5%)	15	2 (13%)	0.27
Surgical characteristics					
Surgical intervention	61	29 (48%)	14	3 (21%)	0.08
Indication for surgery	28		3		
- Respiratory insufficiency		14 (48%)		3 (100%)	0.23
- Recurrent infections		7 (24%)		-	1.00
- Increasing size		3 (10%)		-	1.00
- Volume overload		2 (7%)		-	1.00
- Unclear		3 (10%)		-	1.00
Median age at surgery (years) [C]	29	0.3 (0.0-7.9)	3	0.1 (0.0-0.9)	0.76

Data presented as median (interquartile range) or n (%), [C] except for 'median age at surgery', which is presented as median (range). CLM: congenital lung malformation; CPAM: congenital pulmonary airway malformation; CT: computed tomography. [A] Hybrid or inconclusive diagnosis: CPAM and/or congenital lobar emphysema (n=3), CPAM and/or bronchopulmonary sequestration (n=4). [B] Ventricular septal defect (n=2); atrial septal defect (n=2); tetralogy of Fallot (n=1); patent ductus arteriosus and duplicated renal collecting system (n=1); laryngeal cyst (n=1); Filamin A deficiency (n=1); congenital diaphragmatic hernia (n=1); bladder exstrophy and anal atresia and duplicated renal collecting system (n=1); bilateral ovarian cysts (n=1); Coffin Siris syndrome with an atrial septal defect and recurrent urolithiasis (n=1).



Supplemental figure 1 Histogram showing the number of children per follow-up time point, categorized according to type of management (observation or surgery)



Supplemental figure 2 Lower respiratory tract infections (LRTIs) in the past year, reported at ages 1, 2, 5 and 8 years of children who had endured at least one LRTI (n=14).

Numbers 1 to 14 represent different children. CPAM: congenital pulmonary airway malformation; CLM: congenital lung malformation.

DISCUSSION AND SUMMARY



10

General discussion

What have we learned?

Aims and main findings

Every day, more than 370 000 newborns enter the world.[1] In general, chances of surviving and thriving are largely dependent on the place where you are born.[2] Being diagnosed with a structural congenital anomaly adds some other factors that could affect outcome. Even in Western Europe, death due to structural congenital anomalies is highly listed in health statistics on infant mortality.[3] In surviving children, long-term outcome – including physical growth and development – may be affected. This thesis focuses on these outcomes for children born with an abdominal wall defect (AWD) or a congenital lung malformation (CLM).

In Western Europe, AWD and CLM are usually diagnosed prenatally at the 20-week anomaly scan,[4, 5] or even as early as in the first trimester.[6] This early diagnosis offers the opportunity to counsel parents long before the estimated due date, and well before the legal upper limit for termination of pregnancy (i.e. 24 weeks' gestation in the Netherlands). A prenatal diagnosis of a congenital anomaly is usually very distressing for expecting parents. Early counseling may help reduce feelings of anxiety and stress. They can make an informed decision regarding continuation of the pregnancy, and eventually prepare themselves for the birth of a child requiring extra care.

In live-born children with an AWD or a CLM, long-term problems are probably not as evident as in other congenital anomalies, such as spina bifida or genetic syndromes. Most of these children are able to visit the outpatient clinic and to fulfill standardized physical and neurodevelopmental assessments. Nonetheless, many of them have experienced feeding difficulties, respiratory problems and infections, which put them at risk for long-term impairments.

The research presented in this thesis aims to provide caregivers with a general overview of what parents who are expecting a child with an AWD or a CLM can expect – from the prenatal period up to school age. We asked ourselves two key questions:

- Can we identify prenatal characteristics that contribute to the prediction of postnatal morbidity?
- What kind of long-term morbidity is seen in these children?

In the following section, our main findings are placed into a broader perspective, and recommendations for clinical practice and future research will be discussed. The chapter is concluded with a summary on what to tell parents.

Can we identify prenatal characteristics that contribute to the prediction of postnatal morbidity?

The 20-week anomaly scan, introduced as standard care in the Netherlands in 2007, has led to increased prenatal diagnosis of AWD and CLM.[5, 7] Besides prenatal detection, we showed that specific ultrasound measures can contribute to the prediction of postnatal morbidity in some, but not all of these cases.

In fetuses with gastroschisis, neither two-dimensional (2D) nor three-dimensional (3D) ultrasound markers could reliably distinguish between simple and complex gastroschisis (**chapters 2 and 3**). In those with omphalocele, we were able to reliably predict the type of postnatal surgery and survival (**chapter 5**). In fetuses with CLM, we were able to predict the need for surgery within 2 years after birth, but not the need for respiratory support within 24 hours (**chapter 8**).

Gastroschisis

The clinical course of infants with gastroschisis largely depends on the presence of additional intestinal defects. This is why Molik and colleagues proposed to categorize these infants into having either 'simple' or 'complex' gastroschisis – with the latter occurring in approximately 17%.[8, 9] This risk categorization has now been widely accepted in both research on hospital outcome and in clinical care.

The difference between simple and complex gastroschisis is usually easy to see at primary postnatal evaluation, although it can be difficult when the intestines are extensively matted together. On prenatal ultrasound, it is – in any case – very difficult to distinguish complex from simple gastroschisis. Over the last few decades, numerous efforts have been made to predict complex gastroschisis prenatally, using 2D ultrasound. In a recent meta-analysis, intra-abdominal bowel dilatation seemed to be the most promising predictor of intestinal atresia, but with a low positive predictive value of only 22%.[10] The studies included in this meta-analysis, however, used different thresholds of bowel dilatation, ranging from >6 to >18 mm; some studies did not even state a threshold.[10] The added value of such a meta-analysis to clinical practice may therefore be questionable. This inspired us to evaluate the use of gestational-age corrected thresholds for bowel dilatation in the prediction of complex gastroschisis (chapter 3). We showed that extra-abdominal bowel dilatation at 30 weeks' gestation, but not at the final ultrasound prior to delivery, was significantly associated with complex gastroschisis. Its positive predictive value was low, however; only 40% of

fetuses with extra-abdominal bowel dilatation at 30 weeks' gestation appeared to have complex gastroschisis at birth.

Although the added value of 3D to 2D ultrasound in the fields of obstetrics and prenatal medicine was already recognized in the previous century,[11] our study was the first to evaluate the use of 3D ultrasound in fetal gastroschisis (chapter 2). We hypothesized that 3D ultrasound – rather than 2D ultrasound – would be more accurate in measuring fetal stomach volume and thus predicting complex gastroschisis. Furthermore, the hypothesis arose that stomach-bladder distance, accurately measured using 3D ultrasound, may predict complex gastroschisis. This hypothesis was based on a study using magnetic resonance imaging (MRI) in 24 fetuses with gastroschisis that described extensive stomach-bladder contact in all fetuses with simple gastroschisis, but not in those with intestinal stenosis; their abdominal cavity was filled with dilated bowel loops.[12] Unfortunately, our study showed that neither stomach volume nor stomach-bladder distance could predict complex gastroschisis.

As intestinal and stomach dilatation throughout gestation have been extensively studied without leading to a clear ultrasound predictor for complex gastroschisis,[10] we may need to think about alternative ways to study complex gastroschisis prenatally. The first step should be to study the onset of complex gastroschisis, as this is not well understood. Intestinal atresia, perforation or necrosis are most likely the result of obstruction at the umbilical ring or a volvulus of the eviscerated intestines,[13] which may occasionally lead to necrosis of the complete gut with dismal outcome. Parents opting for termination of pregnancy or whose pregnancy results in intrauterine death, should always be offered autopsy with special attention to intestinal malrotation and volvulus. The autopsy findings may provide further insight into the onset and development of complex gastroschisis. In continuing pregnancies, MRI throughout gestation may be a promising technique to study the onset of complex gastroschisis. The MRI study of Brugger and Prayer resulted in very clear images of the development of gastroschisis during gestation. The three fetuses with bowel dilatation appeared to have intestinal stenosis without atresia.[12] It is yet unclear what complex gastroschisis looks like on prenatal MRI, and whether this could be distinguished from simple gastroschisis.

Moreover, we must keep in mind that it is in fact not complex gastroschisis that we would like to predict, but rather the complexity of the child's hospital course – which eventually influences long-term morbidity, growth, and development. The complexity of the child's hospital course includes chances of complications, the duration of parenteral nutrition, and the length of hospital stay. These factors are most likely determined by the extent of intestinal damage, which may be related to the exposure to amniotic fluid. In light of this, we may have to look further than imaging techniques

alone. It would be interesting to identify markers in the amniotic fluid or, less invasive, in maternal serum that correlate with the duration of parenteral nutrition and the length of hospital stay.

A previous study in 30 fetuses with gastroschisis found a weak correlation between lipase concentration in the amniotic fluid and the duration of hemodynamic support.[14] None of the biochemical substances that were assessed (i.e. ferritin, total proteins, and digestive compounds) correlated with the duration of parenteral nutrition or the length of hospital stay.[14] Another marker that may be interesting to look at, is alpha-fetoprotein (AFP). Historically, before the widespread use of prenatal ultrasound, gastroschisis was suspected in case of elevated AFP levels in the amniotic fluid[15, 16] or in maternal serum.[17, 18] AFP is produced by the fetal liver; maternal serum levels of AFP increase with increasing gestational age.[19] Elevated levels in pregnancies with gastroschisis are thought to be caused by direct diffusion through the exposed intestines into the amniotic fluid.[17] In cases with complex gastroschisis, disturbance of the normal passage of amniotic fluid, gastric juice, and/or bile might prevent normal absorption or degradation of AFP, leading to even higher levels of maternal serum AFP. Evidence to support this hypothesis is lacking.

In addition to AFP, future research on markers in maternal serum could focus on specific T-cells. Recently, increased levels of pro-inflammatory CD4+ T-cells that originated from the fetal intestine were found in the cord blood of neonates with gastroschisis.[20] The authors hypothesized that these cells play a role in fetal immune activation, caused by exposure of the intestinal serosa to amniotic fluid, or by luminal insults resulting in activation of mucosal immune cells.[20] It has not been established yet whether these measurements correlate with postnatal outcome, and whether these cells can already be detected in maternal blood during pregnancy.

Omphalocele

When discussing outcomes in omphalocele, it is important to be aware of the difference between fetuses and live-born neonates with omphalocele; or, in other words, the difference between the prenatal and postnatal frames of reference. Previous studies on live-born neonates reported survival rates of 70-80%,[21, 22] which increased to at least 90% for those with isolated or minor omphalocele.[21, 22] These rates seem quite high, but ignore the 'hidden mortality' of omphalocele during the prenatal period. Our finding that only 40% of fetuses with omphalocele were born alive (chapter 6) may still be too optimistic; in a more recent Dutch cohort of fetuses with omphalocele diagnosed between 2010 and 2013, only 20% was born alive.[7]

This discrepancy may be explained by the difference in the years of inclusion; the routine 20-week fetal anomaly scan was introduced in the Netherlands only in 2007, and ultrasound quality has improved significantly over the years. Although our prenatal detection rate of 87% was relatively high, we may have missed additional anomalies, possibly leading to a lower rate of parents opting for termination of pregnancy. A previous study at our center between 1991 and 2004 showed that over one third of fetuses with isolated omphalocele turned out to have additional anomalies after birth.[23] In line with this finding, the rate of fetuses diagnosed with additional anomalies was 56% in our study versus 83% in the cohort diagnosed between 2010 and 2013.[7] In both studies, more than half of the fetuses diagnosed with additional anomalies had a lethal prognosis, and 65-70% of parents opted for termination of pregnancy when additional anomalies were detected. The termination of pregnancy rate was, therefore, much higher in the latter study, which contributed to the lower proportion of live-born neonates. The difference between prenatal and postnatal frames of reference may thus well become even bigger with advances in prenatal ultrasound; increased detection of severe additional anomalies could lead to increased termination of pregnancy rates, which would subsequently result in lower rates of prenatal survival, and higher rates of survival in live-born neonates. A multidisciplinary approach in parental counseling is very important; pediatric surgeons and pediatricians may be more optimistic about survival rates than are obstetricians and prenatal specialists.

Besides the presence of additional anomalies, the extent of postnatal morbidity is largely determined by the size of the omphalocele, and whether or not the defect can be closed primarily (chapter 5). Our findings of the highly predictive value – with sensitivity and specificity around 90% – of the prenatal ratio between omphalocele circumference and abdominal circumference (OC/AC-ratio) for type of surgical closure, are in line with those of a previous study that included only one measurement per patient.[24] The finding that the OC/AC-ratio appeared not only predictive of type of surgical closure but also of 1-year survival is not very surprising, as a higher degree of visceroabdominal disproportion is associated with a higher probability of respiratory problems, and eventually lower survival.[25]

Measuring the OC/AC-ratio at three time periods during gestation resulted in different cut-offs per time period, as the OC/AC-ratio decreased with increasing gestational age (chapter 5). An omphalocele can appear as giant during the first trimester, but relatively decrease in size during gestation. Repeated measurements throughout gestation are therefore recommended. In addition to the presence of additional anomalies and the presence of liver herniation, these cut-offs provide helpful information when counseling parents. Parents should be informed that both type of closure and survival can be more accurately predicted by measurements in the third trimester.

As a constant cut-off throughout gestation would be easier to implement in clinical practice, a previous study tried to correct for gestational age by using fetal growth parameters that remained relatively constant throughout gestation.[26] The ratios in that study, however, resulted in lower predictive values for the type of closure than those we found. Future research may investigate whether certain algorithms could result in a constant cut-off of the OC/AC-ratio throughout gestation, without affecting its predictive value.

Another challenge that remains is that of categorization of the size of the omphalocele after birth. While the OC/AC-ratio measured in fetuses reflects the extent of visceroabdominal disproportion on a continuous scale, live-born neonates are categorized into having either a minor or giant omphalocele based on the diameter of the defect. This categorization is convenient for clinical and research purposes, but there is room for improvement. The most commonly used definition of giant omphalocele – a defect of ≥5 cm with liver protruding[27] – seems simple, but does not sufficiently take into account the extent of visceroabdominal disproportion. For example, many clinicians would perceive a defect of 4.8 cm with an entire liver lobe protruding seen in a neonate born preterm or small for gestational age as more 'giant' than a defect of 5 cm with only a slip of the liver entering the sac seen in a term neonate. As nowadays over 90% of omphaloceles are diagnosed prenatally,[4] we would suggest to categorize neonates into having a minor or giant omphalocele according to the final OC/AC-ratio prior to delivery. Not only would this provide a more accurate idea of the extent of visceroabdominal disproportion, it would also bridge the gap between prenatal and postnatal definitions. Based on our findings (chapter 5), we would suggest to use a cut-off of 0.63 of the OC/AC-ratio between 30-38 weeks' gestation; all infants without liver herniation at the final ultrasound prior to birth can be regarded as having a minor omphalocele.

Congenital lung malformations

In contrast to neonates with AWD, the majority of neonates diagnosed with a CLM do not develop symptoms after birth. There may well be a substantial proportion of adults who are unaware of having a CLM, as they were born prior to the introduction of the 20-week fetal anomaly scan, and never developed any symptoms. While the increased prenatal detection of CLM nowadays has led to improved care of symptomatic neonates, it can also place clinicians and parents in a difficult position as the optimal management of asymptomatic CLM is yet to be determined. Parental counseling is therefore less straightforward than it is in case of an AWD.

Diagnosing the specific type of CLM in a fetus remains difficult (chapter 8). This is illustrated by our finding that all cases of congenital lobar emphysema (CLE) had presented as a microcystic congenital pulmonary airway malformation (CPAM) on prenatal ultrasound. We would not recommend to perform routine fetal MRI, as findings on fetal MRI have been found to resemble ultrasound features.[28] Instead, we propose to describe the lesion prenatally according to its ultrasound appearance (i.e. hyperechoic, hypoechoic, or mixed), and to the origin of arterial blood supply (the aorta or the pulmonary arteries). Future parents should be informed that the specific type of CLM will be determined after postnatal CT-imaging.

There is a persistent belief among clinicians that CLE is very difficult to detect prenatally, and that this type of CLM is associated with higher incidence of neonatal respiratory distress than other types of CLM.[29, 30] This is in contrast to the findings in our study; 19% of all prenatally detected CLM concerned CLE after birth, and 80% of infants with CLE remained asymptomatic and did not need surgical intervention. This increased detection rate of asymptomatic CLE may be explained by the introduction of the 20-week fetal anomaly scan. Clinicians should be aware of our findings when counseling parents; infants with CLE do not necessarily have worse outcomes than those with other types of CLM.

Our findings of a higher CPAM volume ratio (CVR) in fetuses who after delivery required respiratory support within 24 hours or surgery within 2 years (chapter 8), are in agreement with those of previous studies.[31, 32] Although we were able to reliably predict the need for surgery from 24 weeks' gestation onwards, we were unable to predict the need for respiratory support. This was partly due to the fact that even in the group who had shown full regression of their CLM on prenatal ultrasound, one quarter still required respiratory support within 24 hours after birth – some even presented with bilateral pneumothorax. It is unclear how some lesions spontaneously shrink or even become invisible during pregnancy. In comparison with our findings, previous literature showed that most of these lesions are still visible on postnatal CT-imaging.[33, 34] As we were unable to predict the need for respiratory support, we would recommend to have all fetuses with a CLM delivered in a tertiary care center, regardless of lesion size and prenatal regression. We hypothesize that the unusual occurrence of bilateral pneumothorax may be caused by heterogeneity in the aberrant bronchial tree; this may have led to air trapping, which then eventually caused the pneumothorax. This hypothesis needs further investigation.

Our cut-offs for predicting the need for surgery may eventually become redundant; if future research proves a beneficial effect of early surgery on outcome in asymptomatic CLM, all children will be operated on. This will probably take a while, however, and in

the meantime our cut-offs provide clinicians and parents with a reliable and valuable estimation of the child's need for surgery.

What kind of long-term morbidity is seen in these children?

In general, the extent of short-term and long-term morbidity in these children is mainly determined by the severity of illness, including gastrointestinal and respiratory problems, and by the possibilities for adequate sensory stimulation. Sensory stimulation can be inadequate in hospitalized children; they are exposed to inevitable, but painful medical procedures, high levels of noise and light, and disruption of sleep.[35, 36] Furthermore, hospitalized children do not receive the same interaction and stimulation as healthy children generally receive in the home environment; for example, interaction and stimulation may be negatively affected by a poor nutritional status and failure to thrive, limited freedom of movement, or impaired emotional well-being of either the child, its parents, or both.

We found that most children born with an AWD or a CLM grow normally during infancy and childhood, respectively (**chapters 3**, **6**, and **9**). During the first two years of life, infants born with gastroschisis or omphalocele appeared to be at risk for motor function delay (**chapter 3** and **6**). At school age, parent-reported outcomes of children born with gastroschisis or omphalocele were mainly reassuring. Clinicians and parents should, however, be aware of the higher risk of cognitive problems (**chapter 4** and **7**). In children born with CLM, we focused on pulmonary outcomes. Most of the children with asymptomatic CLM proved to have normal lung function and exercise tolerance. Half of those who had required surgery showed abnormal lung function and exercise tolerance (**chapter 9**).

Gastroschisis

Our observation that height and weight of children born with gastroschisis are within normal range, despite low birth weights (chapter 3), is in line with previous literature.[37, 38] That we did not find any differences in physical growth between simple and complex gastroschisis is in contrast to the two studies that took into account the type of gastroschisis.[38, 39] Apart from these studies, previous literature on physical growth did not differentiate between simple and complex gastroschisis, and strong conclusions with regards to a potential difference cannot be made yet. A possible explanation for the favorable growth of those with complex gastroschisis in our cohort may be the close monitoring in our follow-up program, and the intestinal rehabilitation program for those with intestinal failure; this finding underlines the importance of adequate follow-up.

Both mental and motor development in infants with gastroschisis have previously been reported as favorable, with a low incidence of adverse developmental outcome.[37, 39-43] However, no previous study distinguished between simple and complex gastroschisis. Our finding that infants with simple gastroschisis have normal mental and motor development – whereas those with complex gastroschisis are at risk of motor function delay – may be explained by the higher morbidity in the latter group (chapter 3). Previous studies in other groups of patients also showed a relation between the extent of morbidity in critically ill children, and neurodevelopmental functioning later in life.[44, 45] Feeding difficulties, complications such as sepsis, painful procedures, and prolonged hospital stay may lead to impaired sensory stimulation, emotional deprivation, and altered parent-child interaction. These could all interfere with adequate motor function development. In addition to early start of pediatric physical therapy, we recommend to offer parents not only practical and emotional support, but also teach them how to stimulate their child's development. Several interventions that support parents' presence and involvement in their child's care during hospitalization have shown to be beneficial to parents' emotional well-being and child development.[46-49] Furthermore, the implementation of home parenteral nutrition – and thus a reduced length of hospitalization – may help improve the child's motor development. Parents should be trained and supported to ensure that they are confident and competent in all aspects of their child's care at home.

In line with previous studies,[41, 50, 51] we found that parents of children with gastroschisis more often reported cognitive problems in their child at school age; other outcomes were similar to those of healthy children (chapter 4). We may have even underestimated the prevalence of cognitive problems because of selection bias; the response rate was relatively low, particularly in those with a low socioeconomic status. Previous research suggests that the cognitive problems in children with gastroschisis mainly relate to executive functioning[50] or working memory.[41, 51] It remains unclear what causes cognitive problems in these children, and – more importantly – what could be done to prevent them.

Interestingly, children who had experienced neonatal intestinal failure and children whose parents experienced increased vulnerability were more often reported to have cognitive problems. An explanation of the latter association could be that parents who perceive their child as highly vulnerable may report more problems, despite normal outcome at objective assessments. Previous studies also have associated increased parent-perceived vulnerability with adverse parent-reported outcome, including behavioral problems,[52] poorer emotional adjustment,[53] and impaired health status.[54] Early parental counseling and support may positively affect the child's outcome as perceived by parents.

In addition, neonatal intestinal failure may have acted as a confounder, by influencing both perceived vulnerability and cognitive functioning. If children need medical care for a relatively long period, for example because of intestinal failure, parents are usually trained to perform certain medical procedures (e.g. dressing changes, care of infusion pumps, central line care, colostomy care). Possible distress of either the child, its parents or both could negatively affect the attachment style, and may eventually result in insecure attachment or even attachment disorders.[55, 56] Previous research has linked attachment problems or relational trauma to dysregulation of the right brain,[57] which may impact cognitive functioning. Although very little is known on cognitive functioning in children who experienced neonatal intestinal failure, they seem to be at significant risk for delayed cognitive development.[58] Future research may look into the attachment style of these children and their parents, and see whether this style plays a role in the child's cognitive functioning. We recommend to routinely offer psychosocial support to all parents who are expecting a child with a congenital anomaly as this may have a positive impact on attachment style. Psychosocial support, for example by a nurse practitioner or medical social worker, should be part of standard, multidisciplinary care; not only after birth, but also during pregnancy in case of a prenatal diagnosis. In addition, the follow-up of children with gastroschisis and neonatal intestinal failure should be extended to school age, with special attention to cognitive problems and attachment style.

Certain remarks must be made. First, we do not know whether the children in our group would also have had normal outcome at objective assessments at school age. They may well have shown cognitive problems also on a more objective measure; a significant proportion attended special education. Second, some factors associated with the risk of gastroschisis itself may also negatively affect the child's cognitive functioning. Examples are young maternal age, alcohol and illicit drug use during pregnancy, and low socioeconomic status.[59, 60] Finally, even if objective assessments show normal outcome, parents should be taken seriously if they feel that their child has a problem; it indicates that either the child, its parents, or both, need more support. Moreover, objective assessments might not always be accurate enough; specific neurodevelopmental impairments can be difficult to pick up by a global outcome measure.[61]

Omphalocele

The relatively high proportions of children with low height and weight we found in 2-year-olds with omphalocele (chapter 6) are similar to those reported previously among children aged 1-10 years.[62] Other studies on physical growth did not distinguish between gastroschisis and omphalocele.[63-65] Considering our finding of normal physical growth in infants with gastroschisis, these studies may have overestimated height and

weight. Still, they reported suboptimal growth during infancy.[63, 64] As infants with omphalocele seem to be at greater risk of failure to thrive than those with gastroschisis, we assume that work of breathing may have been an important determinant of poor growth; respiratory problems, including pulmonary hypoplasia, are more common in infants with omphalocele than in those with gastroschisis.[66] The fact that growth seemed to be more affected in infants with a giant omphalocele than in those with a minor omphalocele supports this assumption. Close monitoring of growth is recommended, with early nutritional intervention if necessary. Indirect calorimetry can be helpful to determine energy requirements and to avoid underfeeding and overfeeding in critically ill children.[67] Work of breathing should be supported as much as possible, by optimization of respiratory conditions, and with low thresholds for supplemental oxygen.

Previous studies on neurodevelopment that did not distinguish between different types of non-cardiac structural anomalies reported high prevalences of neurodevelopmental problems.[68-70] In contrast, the studies that included infants with AWD showed normal mental and motor development in infancy.[63, 64] As gastroschisis and omphalocele are two different entities, however, outcomes should always be evaluated separately, even though this negatively affects sample sizes. Similar to our results (chapter 6), the studies that included only infants with omphalocele reported motor function delay.[51, 71] Especially infants with a giant omphalocele appear to be at risk of impaired motor function, which could be explained by the same factors that may play a role in motor function delay in infants with complex gastroschisis. In addition, the ventral hernia and altered trunk stability presumably contributed to impaired motor development in infancy.

We expect that most children with motor function delay will catch up on it during childhood; the right conditions for normal development seem to be present, and a previous study reported normal motor function in eight children with a giant omphalocele aged 3.5-12 years.[72] In line with this finding, our study showed that over 80% of parents reported normal motor function at school age. Other parent-reported outcomes at school age were also mainly reassuring. Follow-up of children with an isolated, minor omphalocele can therefore be limited to 2 years of age. As cognitive problems were reported more frequently in children with either a giant omphalocele or multiple congenital anomalies, we recommend these children are followed until reaching school age and beyond. That way, we can offer timely intervention if needed, and it may help to point out specific features and possible causes of these problems. Remarkably, all three children with Beckwith-Wiedemann Syndrome in our study were reported to have cognitive problems (e.g. concentration or language difficulties), whereas previous literature reported normal intelligence in these children.[73, 74]

Unfortunately, our sample size was too small to allow further investigation of this finding.

Congenital lung malformations

Our findings of normal physical growth during childhood (chapter 9) are in line with those of a previous study in 79 children with CLM who did not undergo surgery.[75] We showed similar growth in children either operated on or not. In contrast to our findings of decreased lung function and exercise tolerance in half of the children in the surgery group, a previous study showed normal lung function in over 75% of children who had undergone surgery.[76] The difference with our study may be explained by selection bias: most children included in that study had been diagnosed prenatally, and had undergone surgery regardless of having symptoms.[76] In our study, the majority of these children would have been included in the observation group, of which 75% had normal lung function and exercise tolerance. We assume that the impaired lung function and exercise tolerance we found in the surgery group is caused by the severity of the CLM, rather than by the surgery itself.

As one-quarter of children with asymptomatic CLM showed airflow obstruction and decreased exercise tolerance, there seems to be room for improvement. Some clinicians prefer early surgery in asymptomatic children, because of the possibility of compensatory lung growth, and because surgery is technically easier when the child has not yet suffered from lower respiratory tract infections (LRTIs).[77, 78] Then again, general anesthesia in early life, and possible surgical complications may in fact worsen not only the child's pulmonary outcomes, but also its general neurodevelopment.[79] As of yet, we know neither whether early surgery in asymptomatic CLM would result in better pulmonary outcomes, nor whether this would negatively affect their neurodevelopment.

Our finding that children with CLM appeared to be at higher risk of developing LRTIs mirrors that of previous studies.[80, 81] Currently, it is recommended that all children with a CLM who are suspected of having an LRTI should be referred for chest x-ray imaging in a low-threshold setting. If recurrent infections are located in the same lobe as the CLM, these children usually undergo surgical resection. Although this seems to be a logical solution, resection does not necessarily eliminate LRTIs. Previous research even reported a paradoxical increase of pulmonary infections after resection of symptomatic CLM,[75] and a high prevalence of recurrent LRTIs (i.e. 19%) in 7-year-olds who had undergone early surgery regardless of having symptoms.[82] Surgical resection of the CLM because of recurrent LRTIs is therefore questionable, and we do not know whether early surgery in asymptomatic CLM would result in a lower prevalence of LRTIs.

The potential risk of malignant transformation is probably the most important reason to advocate surgery in children with asymptomatic CLM.[77] A recent systematic review provided an overview of malignant transformation of CLM. The authors reported 168 lung tumors associated with CLM, of which 76 involved children, and 92 involved adults.[83] No limits were set to the birth year of the population, and only four of these cases had been diagnosed prenatally. It is very difficult to determine the true risk of malignant transformation in asymptomatic CLM, as a large number of these patients may be undiagnosed. Some clinicians argue that the risk is not high enough to subject a child without any symptoms to major surgery,[84] whereas others would say that this argument does not hold water as the risk is yet to be determined. Clinicians should at least be aware of the potential risk of malignant transformation. Continued monitoring until adulthood and beyond may be considered, but this concept needs to be further explored. International consensus is needed regarding the frequency and method of monitoring, and data should be collected in a standardized way. Advances in molecular biology may help in identifying genetic mutations that can reliably distinguish between 'normal' CPAM and malignant tissue.

In summary, there is not enough evidence to draw conclusions regarding the optimal management of children with asymptomatic CLM. Compared with healthy children, these children seem to be at increased risk for reduced lung function and exercise tolerance, for developing LRTIs, and probably even for malignant transformation of their CLM. It is not clear whether early surgery in children with asymptomatic CLM would improve or deteriorate their outcomes. In addition, the effects of early surgery or watchful waiting on parents' and treating physicians' psychological wellbeing have not been studied yet. Either approach could increase stress and anxiety, for obvious reasons. Ideally, a multicenter case-control study or a randomized controlled trial should be carried out to provide answers, and to create a risk assessment tool to assist clinicians in identifying children who are at risk of adverse outcome. In the meantime, we would recommend involving parents in the decision-making process. Parents should be counseled on the pros and cons of early surgery versus watchful waiting in asymptomatic CLM in a standardized matter. This could, for example, be done by an educational video on a webpage or by an app. This also fits well within the family-centered approach to care.

Limitations

One of the major limitations of our research concerns the sample sizes. Although our sample sizes were relatively large for such rare diseases, they were generally not large enough to allow for multivariable regression analyses to find predictors of impaired outcome, and we could not distinguish between type of gastroschisis, omphalocele, or

CLM in our studies on outcomes at school age. Because these anomalies are rare, this issue can only be solved by extending the years of inclusion or by including children from multiple centers. Extending the years of inclusion would not be the first choice; a very long inclusion period is needed to include a sufficient number of children, whilst health care is rapidly changing over time. Multicenter research bypasses this problem, but adds the problem of possible heterogeneity in clinical practice. There is thus need for standardized treatment protocols and guidelines for follow-up for these rare diseases. Development of protocols and guidelines may be facilitated by the European Reference Network on inherited and congenital anomalies (ERNICA); subsequent execution of large clinical studies would be a promising step towards better understanding and treatment options of rare diseases.

Second, selection bias may have influenced our findings. The decision of parents to participate in our follow-up program may correlate with social, educational, and health circumstances. These circumstances may again correlate with physical growth, neurodevelopment, and other outcomes assessed. Moreover, the decision to participate in subsequent follow-up could be related to the outcome of previous follow-up assessments. For example, parents of children with motor function delay at 12 months of age may be more motivated to visit the outpatient clinic at 24 months, and vice versa. The opposite may also be true.

Third, outcomes during infancy do not always adequately predict daily functioning later in life.[85] Subtle problems may become evident only later in childhood when demands on cognitive functioning increase (i.e. children 'grow into their deficit').[86] Moreover, as infants with AWD or CLM normally do not have severe neurologic injury, environmental factors may be crucial for their long-term quality of life and school functioning. We investigated these long-term outcomes in school-aged children with AWD by using parent-reported questionnaires. It should be noted, however, that parents' internal standards may have shifted after having seen their child's critical state after birth. This response shift may lead to overestimation of their child's abilities, and thus to an underestimation of problems.[87] It would be interesting to see whether other outcome measures, such as elaborate neuropsychological assessments, child-self reports or teacher-reports, would lead to different conclusions regarding the outcome of these children. But then again, what to do when neuropsychological assessments detect problems that do not seem to bother the child or its parents? What should be regarded as relevant? In the end, happiness and good quality of life probably matter most, more than objective measures of motor function or academic achievements.

Recommendations for clinical practice

The research presented in this thesis provides an overview of what parents who are expecting a child with an AWD or CLM can expect – from the prenatal period up to school age. Our findings underline the necessity of a multidisciplinary, standardized approach in parental counseling with long-term follow-up. Psychosocial support, for example by a nurse practitioner or medical social worker, should be part of routine care – both before and after the delivery. We recommend to strive more towards a family-centered approach to care. Parents should be offered not only practical and emotional support, but also be taught how to stimulate their child's development. We recommend involving parents in the decision-making process concerning their child's treatment policy, especially in case of asymptomatic CLM.

Based on the insights of this thesis, and in light of the considerations discussed above, we present the following specific recommendations for clinical care:

Gastroschisis

- Parents opting for termination of pregnancy or whose pregnancy results in intrauterine death, should always be offered autopsy of the child with special attention to intestinal malrotation and volvulus.
- Follow-up of children with simple gastroschisis without intestinal failure can be limited to 2 years of age, considering their favorable outcome.
- Follow-up of children with neonatal intestinal failure should be extended to school age, with special attention to cognitive problems and attachment style.

Omphalocele

- It is important to be aware of the difference between the prenatal and postnatal frames of reference; because of the 'hidden mortality' of omphalocele, obstetricians and prenatal specialists may be less optimistic about survival rates than pediatric surgeons and pediatricians.
- The OC/AC-ratio and the fetal liver position should be used to predict postnatal type of surgery and survival. We recommend repeated measurements of the OC/AC-ratio throughout gestation as different cut-offs apply for each time period. The OC/AC-ratio at 30-38 weeks' gestation is most predictive of outcome.
- Postnatal categorization of minor and giant omphalocele should be based on the final OC/AC-ratio prior to birth. We suggest to use a cut-off of 0.63 between 30-38 weeks' gestation; all infants without liver herniation at the final ultrasound prior to birth can be regarded as having a minor omphalocele.

- Physical growth should be monitored closely, with early nutritional intervention if necessary. Indirect calorimetry may be helpful to determine energy requirements. Thresholds for supplemental oxygen should be low.
- Follow-up of children with an isolated, minor omphalocele can be limited to 2 years of age, as their outcome is usually favorable.
- Follow-up of children with a giant omphalocele or multiple congenital anomalies should be extended to school age, with special attention to cognitive problems.

Congenital lung malformations

- A prenatal diagnosis of CLM should be descriptive, according to ultrasound appearance (i.e. hyperechoic, hypoechoic, or mixed) and the origin of arterial blood supply (the aorta or the pulmonary arteries). Future parents should be informed that the specific type of CLM will be determined after postnatal CT-imaging.
- Infants with CLE do not necessarily have worse outcomes than those with other types of CLM; clinicians should be aware of this when counseling parents.
- The CVR from 24 weeks' onwards should be used to predict the need for surgical intervention within 2 years after birth. The CVR is not a reliable predictor of the need for respiratory support within 24 hours after birth.
- All fetuses with a CLM should be delivered at a tertiary care center, regardless of lesion size and prenatal regression.
- Postnatal CT-imaging should be offered to all infants born with CLM.
- Parents of children with asymptomatic CLM should be involved in the decision-making process concerning their child's treatment strategy. They should be counseled in a standardized way on the pros and cons of early surgery versus watchful waiting, for example by an educational video on a webpage or by an app.
- Continued follow-up until adulthood and beyond may be considered to evaluate the risk of malignancy. This concept needs to be further explored.

Future research directions

A subject that requires further study, is that of prenatal counseling itself. A systematic review in 2016 reported that prenatal counseling reduced parental anxiety.[88] This was assessed in only three studies, however, and the authors concluded that there is very little evidence of the effectiveness of counseling in relation to other psychological outcomes.[88] Additionally, most of the studies focused on the mothers' experiences or did not mention the parent's gender. Future research may investigate potential differences in needs and experiences between mothers and fathers. In line with this, further research should investigate the effect of routine psychosocial support. Previous literature has illustrated the overwhelming effect on future parents of a prenatal

diagnosis of a congenital anomaly.[88, 89] We hypothesize that routine psychosocial support during pregnancy and after the delivery may contribute to better coping, less anxiety, and secure attachment between parents and their child. On the long-term, this may even lower the chances of behavioral and learning difficulties. We acknowledge that these hypotheses are speculative.

Along with the fact that most children born with an AWD or a CLM nowadays survive into adulthood, additional important issues emerge. In particular, data on reproductive potential are still very limited, despite the existence of evident risk factors that could impair fertility or pregnancy outcome. In males born with an AWD, fertility could be impaired by prenatal evisceration of the testes, or on account of undescended testes, which is relatively often seen in these boys.[90, 91] In females born with an AWD, the defect itself could impact abdominal capacity. In addition, fertility could be affected by postoperative adhesions; the incidence of adhesive small bowel obstruction after 10 years is estimated as frequent as 37% in gastroschisis, and 15% in omphalocele.[92] Normal vaginal delivery after an uncomplicated pregnancy has been described in a few women previously affected by an AWD,[93] but true incidences of infertility and normal pregnancy outcome are not known yet. A family history of fertility problems may add to the risk of subfertility in patients with omphalocele and Beckwith-Wiedemann Syndrome, of whom a significant proportion (i.e. 9-40%) is conceived by assisted reproductive technology.[94, 95]

In adults with a CLM, incidences of fertility problems and pregnancy outcomes have not yet been reported. Considering the fact that these patients usually do not need abdominal surgery, we expect that fertility will be unaffected. Pregnancy outcome, however, might be affected by impaired lung function and reduced exercise tolerance. Females with a CLM may have lower reserves to cope with the physiological changes during pregnancy, such as increased cardiac output, the significant increase in oxygen demand, and the subjective feeling of breathlessness.[96]

In addition to the general recommendations described above, the results reported in this thesis have raised new questions. We have the following specific recommendations for future research:

Gastroschisis

- Future research should aim to gain insight into the timing and development of complex gastroschisis, possibly by using autopsy data and/or MRI. In line with this, it would be interesting to investigate certain markers of complex gastroschisis in the amniotic fluid or, less invasive, in maternal serum that may correlate with the duration of parenteral nutrition and hospitalization.

- Future research should look into the mechanisms behind the associations between parent-reported cognitive problems at school age, and neonatal intestinal failure, increased parent-perceived vulnerability, and attachment style.

Omphalocele

- Future research should investigate whether certain algorithms could result in a constant cut-off of the OC/AC-ratio throughout gestation for type of postnatal closure, without affecting its predictive value.
- Future research should look into the mechanism behind parent-reported cognitive problems at school age in children with either a giant omphalocele or multiple congenital anomalies.

Congenital lung malformations

- Further research should investigate CLM that seem to disappear prenatally; most lesions are still visible on CT-imaging after birth. In line with this, it would be interesting to investigate possible mechanisms behind the rather unusual occurrence of bilateral pneumothorax in some of these cases.
- A multicenter case-control study or a randomized controlled trial should be carried out to provide answers regarding the optimal management strategy of asymptomatic CLM, and to create a risk assessment tool to assist clinicians in identifying children who are at risk of adverse outcome.
- With advances in molecular biology, future research may try to identify genetic mutations that can reliably distinguish between 'normal' CPAM and malignant tissue.

What to tell parents? Take home messages

Gastroschisis

- The majority of children with gastroschisis have simple gastroschisis; approximately 17% has complex gastroschisis.
- Complex gastroschisis means that gastroschisis is complicated by intestinal atresia, volvulus, necrosis and/or perforation.
- Most children do not have additional structural congenital anomalies; amniocentesis is usually not needed.
- While the difference between simple and complex gastroschisis is usually easy to see at primary postnatal evaluation, it is very difficult to distinguish complex from simple gastroschisis on prenatal ultrasound. The presence of bowel dilatation does not necessarily mean that the child has complex gastroschisis, and absence of bowel dilatation does not necessarily mean that the child has simple gastroschisis.
- Infants with gastroschisis can be delivered vaginally from 37 weeks' onwards, unless obstetric reasons require otherwise.
- Most live-born infants with gastroschisis survive.
- Surgery is required shortly after birth, by means of primary closure when possible or by placing a silastic silo to allow gradual reduction into the abdominal cavity prior to definite closure.
- Hospital outcome largely depends on the type of gastroschisis; median durations of time to full enteral feeding and hospitalization are less than 2 months in infants with simple gastroschisis, and close to 6 months in those with complex gastroschisis.
- Physical growth is within normal range. Neurodevelopment at 2 years of age is generally normal in infants with simple gastroschisis; those with complex gastroschisis may be at risk for delayed development, with motor function being most affected. We expect that most of them will catch up on this during childhood, provided that they receive adequate follow-up and timely intervention if needed.
- Parent-reported outcomes at school age are comparable with those of healthy children, except for cognitive problems, which seem to be more prevalent in children with gastroschisis.

Omphalocele

- Approximately 75-80% of fetuses with omphalocele present with chromosomal abnormalities and/or additional congenital anomalies; amniocentesis is recommended.
- One-third of all fetuses with an omphalocele have a lethal additional anomaly, none of these fetuses survive. The survival rate in those with a non-lethal additional anomaly is around 20%, depending on the type of anomaly.
- The survival in fetuses with an isolated omphalocele varies between 32% and 75%, depending on the size of the omphalocele, and on whether the liver is herniated or not.
- Most infants with minor omphalocele undergo primary closure within 48 hours after birth. Those with giant omphalocele usually require an initial period of epithelialization of the omphalocele before definitive surgical closure is performed. Closure is usually planned before the age of 1 year.
- The type of postnatal surgical closure and the chance of 1-year survival can be predicted prenatally, using the fetal liver position and the OC/AC-ratio. Predictive values increase with increasing gestational age.
- Infants with omphalocele can be delivered vaginally, unless obstetric reasons require otherwise.
- The 2-year survival rate in live-born infants with a prenatally diagnosed, isolated, minor omphalocele, is approximately 80-90%. The survival rate in those with giant omphalocele is somewhat lower, mostly because of the risk of respiratory problems (e.g. pulmonary hypoplasia, CLD). Approximately 60-70% of these infants survive.
- Hospital outcome largely depends on the type of omphalocele; median durations of time to full enteral feeding and hospitalization are approximately 1 week in children with a minor omphalocele. Those with a giant omphalocele require around 3 weeks to reach full enteral feeding, and need to stay in hospital for approximately 7 weeks.
- Infants with omphalocele seem to be at risk for failure to thrive. Mental development is generally normal at 2 years of age. Those with a giant omphalocele are at risk for impaired motor function. We expect that most children with an isolated omphalocele will catch up during childhood, provided that they receive adequate follow-up and timely intervention if needed.
- Parent-reported outcomes at school age are comparable with those of healthy children. Children with a giant omphalocele or multiple congenital anomalies are more often reported to have cognitive problems.

Congenital lung malformations

- CLM compromise a group of anomalies that are categorized by the size of the cysts, and by the presence or absence of blood supply from the aorta. The prenatal appearance of the lesion does not always correspond with that after birth.
- The prognosis is usually good. Problems during pregnancy, such as hydrops, severe mediastinal shift or polyhydramnios, are rare, but when present strongly worsen the child's prognosis.
- The size of the CLM can either increase, decrease, or remain stable throughout pregnancy. Some CLM seem to disappear, but most of these lesions are still visible on CT-imaging after birth.
- Prenatal disappearance of the lesion does not necessarily mean that the child does not develop symptoms after birth.
- It is difficult to prenatally predict the need for respiratory support after birth. In most cases, respiratory support directly after birth is not needed.
- The need for surgery within 2 years after birth can be predicted prenatally, using the CVR.
- Approximately 50% of the children who need respiratory support will need surgical intervention before the age of 2 years. Of those who initially do not need respiratory support, approximately 15% will eventually need surgery.
- Most neonates can be discharged home within 1 week after birth.
- CT-imaging is performed in all infants born with CLM, around the age of 6 months.
- The optimal management of asymptomatic CLM is still being debated. Some clinicians prefer early surgery, whereas others advocate a watchful waiting approach.
- Physical growth is within normal range.
- Children with a CLM are at risk for reduced lung function and exercise tolerance, especially those who require surgery because of symptoms. It is important to stimulate physical activity and sport participation.
- Recurrent LRTIs may occur. We do not know whether surgical resection of the CLM will solve this problem.
- The current literature suggests that the risk of malignant transformation of the CLM is small, but not negligible. Therefore, continued follow-up may be considered until adulthood and beyond.

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11

Summary

Introduction

Prenatal detection of a congenital anomaly offers the possibility of early parental counseling and of optimizing postnatal care. When counseling expectant parents, it is important to know how to interpret certain prenatal characteristics, and to be aware of the implications of the anomaly in terms of survival, hospital outcome, and long-term consequences.

Prenatal detection rates of abdominal wall defects (AWD; i.e. gastroschisis or omphalocele) and congenital lung malformations (CLM) are relatively high, but not so much is known on the long-term outcome of children born with either of these anomalies.

This thesis aims to improve the knowledge on prenatal characteristics and long-term outcome of AWD and CLM, with the ultimate aim to optimize parental counselling and postnatal follow-up. Most of the presented studies made use of data from the longitudinal multidisciplinary follow-up program at the Erasmus MC-Sophia Children's Hospital.

We asked ourselves two general key questions:

- Can we identify prenatal characteristics that contribute to the prediction of postnatal morbidity?
- What kind of long-term morbidity is seen in these children?

The research described in this thesis is divided into three parts: gastroschisis, omphalocele, and congenital lung malformations.

Gastroschisis

Can we identify prenatal 2D or 3D ultrasound markers of complex gastroschisis?

Chapter 2 describes the findings of a longitudinal, prospective cohort study, in which we investigated whether prenatal three-dimensional (3D) ultrasound could distinguish complex gastroschisis from simple gastroschisis. A previous study using magnetic resonance imaging showed stomach-bladder contact in all fetuses with gastroschisis in the third trimester, except for those with intestinal stenosis; their abdominal cavity was filled with dilated bowel loops. We hypothesized that complex gastroschisis would lead to stomach dilatation – which is difficult to measure using two-dimensional ultrasound – and to an increased stomach-bladder distance. We assessed the fetal stomach volume

and stomach-bladder distance throughout gestation. With advancing gestational age, the stomach volume increased, and the stomach-bladder distance decreased. The developmental changes in stomach volume and stomach bladder distance did not differ between fetuses with simple and complex gastroschisis.

In **chapter 3** we evaluated the association between gestational-age corrected two-dimensional (2D) ultrasound markers and complex gastroschisis. We determined the presence of either gastric dilatation or bowel dilatation using gestational-age specific reference norms, both at 30 weeks' gestation and at the last ultrasound examination prior to delivery. Only extra-abdominal bowel dilatation at 30 weeks' gestation was found to be associated with complex gastroschisis, but its positive predictive value was low.

We conclude that neither 2D nor 3D ultrasound measures can reliably distinguish complex gastroschisis from simple gastroschisis.

How do infants with either simple or complex gastroschisis grow up in terms of physical growth, mental development, and motor development?

In **chapter 3**, we evaluated the physical growth and neurodevelopment of 61 infants with either simple or complex gastroschisis at 12 and 24 months of age. At 24 months, only 8% scored below Dutch reference norms for weight, and all had normal height. Both mental and motor development were normal in over 80% of infants with simple gastroschisis, and in half of those with complex gastroschisis – with motor function being most affected.

We conclude that most infants with gastroschisis show encouraging physical growth and neurodevelopment. Infants with complex gastroschisis may be at increased risk for motor function delay; they should be monitored more closely, and offered timely pediatric physical therapy.

How do parents rate their child's motor function, cognition, health status, quality of life and behavior at school age?

Chapter 4 describes daily functioning in 31 children with gastroschisis at school age (i.e. 4-17 years). We evaluated parent-reported outcomes using paper questionnaires. Parent-perceived vulnerability and motor function were compared with Dutch reference data. Data on cognition, health status, quality of life, and behavior were

compared with those of healthy controls matched for age, gender, and maternal education level. Three-quarters of parents reported that their child had normal motor function, and scores on health status, quality of life, and behavior were similar to those of matched controls. Cognitive problems were reported in 43% of children with gastroschisis (versus 11% of matched controls). Neonatal intestinal failure and increased parent-perceived vulnerability were associated with cognitive problems.

We conclude that parent-reported outcomes of children with gastroschisis at school age are mainly reassuring. Clinicians and parents should be aware of the higher risk of cognitive problems. We recommend multidisciplinary follow-up at school age of children with neonatal intestinal failure.

Omphalocele

How does the prenatal frame of reference differ from that after birth?

Comparison between the prenatal frame of reference of omphalocele (i.e., survival of fetuses) with that after birth (i.e., survival of live born neonates) was studied in **chapter 6**. The prenatal frame of reference was considerably worse than that after birth. Fifty (40%) of the 126 fetuses diagnosed with omphalocele were live born, and only 35 (28%) survived at least 2 years. Additional structural or chromosomal anomalies – mainly lethal – were found in more than half of the fetuses, which led to high rates of termination of pregnancy and intrauterine death. In contrast, the 2-year survival rate in live born neonates was 75%.

We conclude that the prenatal frame of reference differs considerably from that after birth; the 2-year survival rate in prenatally diagnosed omphalocele is almost three times as low as that in live born neonates. A multidisciplinary approach in parental counselling is therefore recommended.

Can we prenatally predict the type of surgical closure in fetuses with either isolated or non-isolated omphalocele?

Chapter 5 describes the predictive value of the ratio between omphalocele circumference (OC) and abdominal circumference (AC) for type of surgical closure and survival in 63 fetuses with omphalocele. The OC/AC-ratio and liver position were determined at three time periods during gestation (11-16, 17-26, and 30-38 weeks). As the OC/AC-ratio decreased with increasing gestational age, different cut-offs for

predicting type of closure were calculated for each time period. Each cut-off had high sensitivity and specificity (around 90%). The omphalocele was closed primarily in all 32 fetuses without liver herniation. Overall, of 37 infants whose defect was closed primarily, 36 (97%) survived.

We conclude that the type of surgical closure and survival in fetuses with omphalocele can be predicted prenatally, using different cut-offs of the OC/AC-ratio throughout gestation combined with the position of the liver.

How do infants with either minor or giant omphalocele grow up in terms of physical growth, mental development, and motor development?

We assessed physical growth and neurodevelopment in 42 infants with minor or giant omphalocele in **chapter 6**. At 24 months of age, height was below Dutch reference norms in 8% of infants with minor omphalocele, and in 30% of those with giant omphalocele. Weight was lower than the norm in 16% of infants with minor omphalocele, and in 40% of those with giant omphalocele. Mental development was normal in both groups. Motor development was delayed in 21% of infants with minor omphalocele, and in 82% of infants with giant omphalocele.

We conclude that infants with omphalocele seem to be at greater risk of failure to thrive. They have normal mental development. Infants with giant omphalocele often have delayed motor development. We recommend timely referral to pediatric physical therapy, and prolonged follow-up in these children.

How do parents rate their child's motor function, cognition, health status, quality of life and behavior at school age?

Chapter 7 describes daily functioning of 31 children with omphalocele at school age (i.e. 4-17 years). We evaluated parent-reported outcomes using paper questionnaires. Motor function was compared with Dutch reference data. We compared cognition, health status, quality of life, and behavior with those of healthy controls matched for age, gender, and maternal education level. Over 80% of parents reported normal motor function, and scores on cognition, health status, quality of life, and behavior were similar to those of matched controls. Cognitive problems were reported in 26% of children with omphalocele (versus 9% of matched controls). Giant omphalocele and multiple congenital anomalies were most prominently associated with cognitive problems.

We conclude that parent-reported outcomes of children with omphalocele at school age are reassuring. Children with isolated, minor omphalocele probably do not need extensive long-term follow-up. Those with giant omphalocele or multiple congenital anomalies may be at risk for cognitive problems at school age; we recommend long-term follow-up to ensure that timely intervention can be offered if needed.

Congenital lung malformations

How does the prenatal appearance of CLM correspond with that after birth?

In **chapter 8**, we assessed the concordance between prenatal appearance and postnatal type of CLM in 80 fetuses. The CLM were classified according to prenatal ultrasound findings into congenital pulmonary airway malformation (CPAM; microcystic, macrocystic or mixed), bronchopulmonary sequestration, and hybrid lesion. The postnatal diagnosis was made using computed tomography (CT)-imaging and/or histology. The most striking finding was that microcystic CPAM on prenatal ultrasound appeared to be congenital lobar emphysema in 15 (43%) infants after birth.

We conclude that it is difficult to diagnose the specific type of CLM in a fetus. We propose to describe the CLM prenatally according to its ultrasound characteristics (i.e. hyperechoic, hypoechoic, or mixed, and with or without arterial blood supply from the aorta). The future parents should be informed that the type of CLM will be determined after postnatal CT-imaging.

Can we prenatally predict the need for postnatal respiratory support and/or surgical intervention?

Chapter 8 describes the predictive value of the CPAM volume ratio (CVR) for the need for respiratory support within 24 hours after birth, and for the need for surgical intervention within 2 years after birth in 80 fetuses with CLM. The CVR was determined at three time periods during gestation (18-24, 24-30, and 30-37 weeks). Overall, 14 (18%) infants required respiratory support, and 17 (21%) required surgery. The CVR from 24 weeks' onwards proved to be a reliable predictor of the need for surgery (sensitivity and specificity around 80%). We could not predict the need for respiratory support; the CVR-measurements on prenatal ultrasound in infants who required respiratory support had shown large differences, ranging from full regression to a CVR >1.6.

We conclude that the CVR from 24 weeks' gestation onwards is a reliable predictor of the need for surgery within 2 years after birth. We were unable to predict the need for respiratory support within 24 hours after birth; we therefore recommend to have all fetuses with a CLM delivered at a tertiary care hospital, regardless of lesion size and prenatal regression.

How do these children, either managed observationally or surgically, grow up in terms of physical growth, lung function, and exercise tolerance?

Chapter 9 describes physical growth, lung function, and exercise tolerance in 61 children with CLM at the age of 8 years. We evaluated these outcomes both in children who had required surgery, as well as in those who were managed by observation. Both groups had normal height and weight; the need for surgery did not affect physical growth. Most children in the observation group had normal lung function and exercise tolerance. About a quarter of children in this group did show reduced lung function and/or exercise tolerance, however, and clinicians and parents should be aware of this. In the surgery group, approximately half of the children had abnormal lung function, and mean exercise tolerance fell below -1 standard deviation.

We conclude that children born with CLM have normal physical growth. They are at risk for reduced lung function and exercise tolerance, especially those who require surgery. Continued follow-up until adulthood and beyond may be considered to evaluate the risk of malignancy.

General discussion

In **chapter 10**, we discuss the study results, put them into perspective, and make recommendations for clinical practice and future research. In general, our findings underline the necessity of a multidisciplinary, standardized approach in parental counseling, and long-term follow-up. We recommend to:

- Strive more towards a family-centered approach to care.
- Offer parents not only practical and emotional support, but also teach them how to stimulate their child's development.
- Involve parents in the decision-making process concerning their child's treatment policy.

The chapter is concluded with a summary on what to tell parents who are expecting a child with an AWD or a CLM.



12

Nederlandse samenvatting

Introductie

Ongeveer 3% van alle baby's in Europa wordt geboren met een anatomische afwijking. Sommige van deze afwijkingen kunnen al voor de geboorte worden gezien, tijdens de 20 weken echo. Voorbeelden van afwijkingen die meestal al voor de geboorte worden gezien, zijn een buikwanddefect (gastroschisis of omphalocele) en een aanlegstoornis van de long.

Wanneer er een afwijking wordt gezien op de echo, is het belangrijk om de aanstaande ouders voor te bereiden op wat ze kunnen verwachten. Wat betekenen bepaalde kenmerken op de echo? Wat zijn de overlevingskansen? Hoe ziet de periode van ziekenhuisopname eruit? En de periode daarna? Groeit het kind goed en zal hij of zij naar een gewone school kunnen?

Er is nog niet zoveel bekend over de langetermijnuitkomsten van kinderen met een buikwanddefect of een aanlegstoornis van de long. Het doel van de onderzoeken in dit proefschrift was daarom om de kennis over deze afwijkingen te vergroten. Met deze kennis kunnen we ouders beter voorbereiden en kan de langetermijnfollow-up worden afgestemd op wat deze kinderen nodig hebben.

We stelden onszelf de volgende algemene vragen:

- Kunnen we voor de geboorte, met behulp van kenmerken op de echo, al voorspellen hoe goed of slecht het na de geboorte met het kind zal gaan?
- Wat zijn de gevolgen van deze afwijkingen op de lange termijn?

Dit proefschrift is onderverdeeld in drie delen: gastroschisis, omphalocele en aanlegstoornis van de long.

Gastroschisis

Een kind met gastroschisis heeft een opening in de buikwand, naast de navel. Een deel van de darmen is door deze opening naar buiten gekomen. Soms komen ook andere organen naar buiten, zoals de maag of de blaas. De meeste baby's hebben een zogenoemde 'simpele' gastroschisis. Ongeveer 17% heeft een 'complexe' gastroschisis. Dat betekent dat de darmen een extra afwijking hebben. Er is bijvoorbeeld een darmafsluiting, of er zit een verdraaiing in de darm. Baby's met complexe gastroschisis zijn langer in het ziekenhuis opgenomen dan baby's met simpele gastroschisis. Dit komt omdat het langer duurt voordat hun darmen goed werken; ze hebben vaker voedingsproblemen en meer infecties. Het is daarom waardevol om voor de geboorte te kunnen voorspellen of er sprake is van een simpele of een complexe gastroschisis.

Kunnen we met 2D of 3D echografie tijdens de zwangerschap aanwijzingen vinden voor de aanwezigheid van complexe gastroschisis?

In **hoofdstuk 2** hebben we onderzocht of we met driedimensionale (3D) echografie tijdens de zwangerschap konden zien welke baby's complexe gastroschisis hadden. Complexe gastroschisis zou kunnen zorgen voor een uitgezette maag, maar met tweedimensionale (2D) echografie is dit lastig te meten. Daarnaast liet een eerdere studie met *magnetic resonance imaging* (MRI) zien dat de maag tegen de blaas aan lag bij alle baby's met simpele gastroschisis tijdens de zwangerschap, behalve bij degenen met een darmafsluiting. Dit kwam doordat zij uitgezette darmlissen hadden, die voorkwamen dat de maag de blaas raakte. We hebben daarom de grootte van de maag en de afstand tussen de maag en de blaas gemeten op verschillende momenten in de zwangerschap, met behulp van 3D echografie. We zagen dat de grootte van de maag tijdens de zwangerschap toenam, terwijl de afstand tussen de maag en de blaas steeds kleiner werd. Dit verloop was niet verschillend tussen simpele en complexe gastroschisis.

In **hoofdstuk 3** is met 2D echografie de mate van uitzetting van de maag en van de darmen bepaald bij 30 weken zwangerschap en bij de laatste echo voor de geboorte. Bij 30 weken zwangerschap waren de darmen buiten de buik vaker uitgezet bij complexe gastroschisis dan bij simpele gastroschisis, maar lang niet alle baby's met complexe gastroschisis hadden uitgezette darmen.

We concluderen dat we geen betrouwbare aanwijzingen tijdens de zwangerschap hebben gevonden voor complexe gastroschisis, niet met 2D en ook niet met 3D echografie.

Hoe is de groei en ontwikkeling van kinderen met simpele of complexe gastroschisis in de eerste twee levensjaren?

In **hoofdstuk 3** hebben we de groei en ontwikkeling beschreven van 61 kinderen met simpele of complexe gastroschisis, op de leeftijd van 1 en 2 jaar. Op de leeftijd van 2 jaar had 8% van de kinderen ondergewicht; er was een normale lengtegroei. Meer dan 80% van de kinderen met simpele gastroschisis had een normale mentale en motorische ontwikkeling. Van de kinderen met complexe gastroschisis had slechts de helft een normale ontwikkeling; het motorisch functioneren was het vaakst onder de norm.

We concluderen dat de meeste kinderen met gastroschisis goed groeien en zich normaal ontwikkelen. Kinderen met complexe gastroschisis hebben mogelijk een verhoogd risico op motorische achterstand. Zij moeten goed worden gevolgd en indien nodig op tijd worden verwezen voor kinderfysiotherapie.

Hoe beoordelen ouders het motorisch functioneren, het cognitief functioneren, de gezondheidsstatus, de kwaliteit van leven en het gedrag van hun kind op de schoolleeftijd?

Hoofdstuk 4 beschrijft het dagelijks functioneren van 31 kinderen met gastroschisis op de schoolleeftijd (4-17 jaar). Ouders hadden hiervoor vragenlijsten ingevuld. We vergeleken de mate van kwetsbaarheid zoals ervaren door ouders en het motorisch functioneren met Nederlandse referentiewaarden. De gegevens over cognitie, de gezondheidsstatus, kwaliteit van leven en gedrag werden vergeleken met die van gezonde kinderen van dezelfde leeftijd, hetzelfde geslacht en met hetzelfde opleidingsniveau van moeder (controlegroep). Driekwart van de ouders gaf aan dat hun kind een normale motorische ontwikkeling had. De scores op het gebied van gezondheidsstatus, kwaliteit van leven en gedrag waren vergelijkbaar met die van de gezonde kinderen. Meer dan 40% van de ouders van een kind met gastroschisis gaf aan dat hun kind cognitieve problemen had (vergeleken met 11% in de controlegroep). De kinderen die als baby langdurig infuusvoeding nodig hadden gehad en de kinderen die door hun ouders als kwetsbaarder werden gezien, leken vaker cognitieve problemen te hebben.

We concluderen dat ouders van een kind met gastroschisis over het algemeen positief zijn over het functioneren van hun kind op de schoolleeftijd. Dokters en ouders moeten op de hoogte worden gebracht van de mogelijk hogere kans op cognitieve problemen. We raden aan om de kinderen met gastroschisis die als baby langdurig infuusvoeding nodig hebben gehad op te volgen op de schoolleeftijd.

Omphalocele

In het begin van de zwangerschap ontwikkelen de darmen zich in de navelstreng. Normaal gesproken trekken de darmen zich weer terug in de buik, rond 11 weken zwangerschap. Als dit niet gebeurt is er sprake van een omphalocele. Bij een baby met een omphalocele komen de darmen – en soms ook andere buikorganen – door de navel heen naar buiten. Dit alles wordt bedekt door een dun vlies. Veel ongeboren baby's met een omphalocele hebben daarnaast ook andere afwijkingen, zoals een hartafwijking of een chromosoomafwijking. Dit leidt tot vele zwangerschapsafbrekingen en veel

sterfte voor de geboorte. Het perspectief voor de geboorte kan daarom verschillen van het perspectief na de geboorte. Naast de aanwezigheid van andere afwijkingen maakt het veel verschil of de omphalocele groot ('giant') of klein ('minor') is. Giant omphaloceles kunnen niet direct na de geboorte al operatief gesloten worden; vaak wordt dit pas gedaan rond de leeftijd van 1 jaar. Baby's geboren met een giant omphalocele hebben vaak minder goed ontwikkelde longen en vaker voedingsproblemen dan baby's met een minor omphalocele.

Hoe verschilt het perspectief voor de geboorte van het perspectief na de geboorte?

In **hoofdstuk 6** vergeleken we de overlevingskansen van ongeboren baby's (het perspectief voor de geboorte) met de overlevingskansen van levend geboren baby's (het perspectief na de geboorte). Zoals verwacht, zagen we dat het perspectief voor de geboorte veel slechter was dan dat na de geboorte. Van de 126 ongeboren baby's met omphalocele werden er slechts 50 (40%) levend geboren en overleefden er 35 (28%) tenminste tot de leeftijd van 2 jaar. Meer dan de helft van de ongeboren baby's had andere afwijkingen, die meestal niet met het leven verenigbaar waren. Veel van de bij de studie betrokken ouders besloten daarom de zwangerschap vroegtijdig te beëindigen en veel andere baby's overleden al voor de geboorte. Van alle 69 baby's die levend geboren werden, overleefden er 52 (75%) tenminste tot de leeftijd van 2 jaar.

We concluderen dat het perspectief voor de geboorte sterk verschilt van dat na de geboorte. De 2-jaarsoverleving van ongeboren baby's met een omphalocele is bijna drie keer zo laag als dat van levend geboren baby's. Het verdient aanbeveling dat de ouders door meerdere specialisten worden gecounseld: zowel door prenatale specialisten zoals gynaecologen en artsen prenatale geneeskunde, als door postnatale specialisten zoals kinderartsen en –chirurgen.

Kunnen we voor de geboorte voorspellen welk type operatie de baby na de geboorte nodig zal hebben?

Hoofdstuk 5 beschrijft de voorspellende waarde van de verhouding tussen de omtrek van de omphalocele en de buikomtrek (OC/AC-ratio) voor het type operatie en de overlevingskansen bij 63 ongeboren baby's met een omphalocele. De OC/AC-ratio en de positie van de lever werden bepaald op drie momenten tijdens de zwangerschap (11-16, 17-26 en 30-38 weken). Aangezien de OC/AC-ratio daalde gedurende de

zwangerschap, berekenden we verschillende afkapwaarden per tijdsperiode voor het voorspellen van het type operatie. Elke afkapwaarde bleek een goede voorspeller; de sensitiviteit en specificiteit waren rond de 90%. Bij alle 32 baby's bij wie de lever nog in de buik zat kon de omphalocele na de geboorte direct gesloten worden. In totaal kon de omphalocele bij 37 baby's direct na de geboorte gesloten worden; allen op één na overleefden.

We concluderen dat we, met behulp van de OC/AC-ratio en de positie van de lever, voor de geboorte goed kunnen voorspellen welke omphaloceles direct na de geboorte gesloten kunnen worden en wat de overlevingskansen zullen zijn.

Hoe is de groei en ontwikkeling van kinderen met een minor of giant omphalocele in de eerste twee levensjaren?

We bekeken de groei en ontwikkeling van 42 kinderen met een minor of giant omphalocele in **hoofdstuk 6**. Op de leeftijd van 2 jaar had 8% van de kinderen met een minor omphalocele een achterblijvende lengtegroei en 16% had ondergewicht. Van de 2-jarigen met een giant omphalocele had 30% een achterblijvende lengtegroei en 40% had ondergewicht. Zowel kinderen met een minor als die met een giant omphalocele hadden een normale mentale ontwikkeling. De motorische ontwikkeling was vertraagd bij 21% van de kinderen met een minor omphalocele en bij 82% van de kinderen met een giant omphalocele.

We concluderen dat kinderen met een omphalocele een verhoogd risico hebben op achterblijvende groei. De mentale ontwikkeling is normaal. Kinderen met een giant omphalocele hebben vaak een vertraagde motorische ontwikkeling, zij moeten goed gevolgd worden en op tijd worden verwezen voor kinderfysiotherapie.

Hoe beoordelen ouders de motorische functie, het functioneren op school, de gezondheidsstatus, de kwaliteit van leven en het gedrag van hun kind op de schoolleeftijd?

Hoofdstuk 7 beschrijft het dagelijks functioneren van 31 kinderen met een omphalocele op de schoolleeftijd (4-17 jaar). Ouders hadden hiervoor vragenlijsten ingevuld. We vergeleken de mate van kwetsbaarheid zoals ervaren door ouders en het motorisch functioneren met Nederlandse referentiewaarden. De gegevens over cognitie, de gezondheidsstatus, kwaliteit van leven en gedrag werden vergeleken met die van gezonde kinderen van dezelfde leeftijd, hetzelfde geslacht en met hetzelfde

opleidingsniveau van moeder (controlegroep). Meer dan 80% van de ouders van een kind met omphalocele gaf aan dat hun kind een normale motorische ontwikkeling had. Scores op het gebied van cognitie, gezondheidsstatus, kwaliteit van leven en gedrag waren vergelijkbaar met die van gezonde kinderen. Ruim een kwart van de ouders van een kind met omphalocele gaf aan dat hun kind cognitieve problemen had (vergeleken met 9% in de controlegroep). Kinderen met een giant omphalocele of meerdere aangeboren afwijkingen leken vaker cognitieve problemen te hebben.

We concluderen dat ouders van een kind met omphalocele over het algemeen positief zijn over het functioneren van hun kind op de schoolleeftijd. Kinderen met een geïsoleerde, minor omphalocele hebben geen langdurige follow-up nodig. Kinderen met een giant omphalocele of meerdere aangeboren afwijkingen hebben mogelijk een hogere kans op cognitieve problemen. We raden aan om deze groep op te volgen op de schoolleeftijd.

Aanlegstoornis van de long

Een aanlegstoornis van de long is een verzamelterm voor verschillende type aandoeningen; de meest bekende en meest voorkomende is een congenitale pulmonale luchtwegafwijking (CPAM). Andere aandoeningen zijn een longsekwester, congenitaal lobair emfyseem, bronchogene cyste en combinaties van deze afwijkingen. Sinds de invoering van de 20-weken echo en verbeterde kwaliteit van de echobeelden, worden steeds meer van deze aandoeningen al voor de geboorte ontdekt. Voor de geboorte is het lastig te zien om welk type aanlegstoornis het gaat, aangezien er nog geen lucht in de longen zit en omdat verschillende typen er hetzelfde uit kunnen zien op de echo. Na de geboorte ontwikkelen sommige kinderen klachten, zoals ademhalingsproblemen of luchtweginfecties; deze kinderen worden geopereerd. Andere kinderen blijven asymptomatisch; deze kinderen worden in het Erasmus MC-Sophia wel gevolgd, maar niet geopereerd – in tegenstelling tot sommige andere ziekenhuizen.

In hoeverre komt het beeld van een aanlegstoornis van de long voor de geboorte overeen met dat na de geboorte?

In **hoofdstuk 8** hebben we gekeken naar de overeenkomst tussen het beeld van een aanlegstoornis van de long voor de geboorte en dat erna. We onderzochten het type aanlegstoornis bij 80 ongeboren baby's. Met echoscopie tijdens de zwangerschap werd onderscheid gemaakt tussen CPAM (microcysteus, macrocysteus, of gemengd), longsequester, of een gecombineerde vorm. De diagnose na de geboorte werd gemaakt met een *computed tomography* (CT)-scan of met histologisch onderzoek. De meest

opvallende bevinding was dat een microcysteuze CPAM op de echo in 15 (43%) van de gevallen na de geboorte congenitaal lobair emfyseem bleek te zijn.

We concluderen dat het moeilijk is om voor de geboorte al te zien welk type aanlegstoornis van de long de baby heeft. We raden daarom aan om alle typen te beschrijven aan de hand van het echobeeld (hyperechogeen, hypoechogeen of gemixt; met of zonder arteriële bloedvoorziening vanuit de aorta). De ouders moet worden verteld dat het type aanlegstoornis van de long pas na de geboorte wordt vastgesteld met behulp van een CT-scan.

Kunnen we voor de geboorte voorspellen welke kinderen na de geboorte zuurstof en/of een operatie nodig zullen hebben?

Hoofdstuk 8 beschrijft de voorspellende waarde van de CPAM volume ratio (CVR) voor de behoefte aan ademhalingsondersteuning binnen 24 uur na de geboorte en de noodzaak tot een operatie binnen 2 jaar na de geboorte. We onderzochten 80 ongeboren baby's met een aanlegstoornis van de long. De CVR werd bepaald op drie momenten tijdens de zwangerschap (18-24, 24-30 en 30-37 weken). In totaal hadden 14 (18%) baby's extra zuurstof nodig en werden 17 (21%) baby's geopereerd. De CVR bleek een betrouwbare voorspeller voor de noodzaak tot een operatie (sensitiviteit en specificiteit rond 80%) vanaf 24 weken zwangerschap. We konden niet voorspellen welke baby's ademhalingsondersteuning nodig hebben na de geboorte; binnen de groep die dit nodig had zagen we grote verschillen in de CVR-metingen. Bij sommigen was de afwijking voor de geboorte zelfs helemaal verdwenen.

We concluderen dat de CVR vanaf 24 weken zwangerschap een betrouwbare voorspeller is voor de noodzaak tot een operatie. We kunnen niet voorspellen welke baby's na de geboorte ademhalingsondersteuning nodig zullen hebben; we raden daarom aan om alle ongeboren baby's met een CLM in een derdelijns ziekenhuis geboren te laten worden, onafhankelijk van de grootte van hun afwijking.

Hoe is de groei, de longfunctie en het uithoudingsvermogen van kinderen die al dan niet geopereerd zijn aan hun aanlegstoornis van de long?

Hoofdstuk 9 beschrijft de groei, de longfunctie en het uithoudingsvermogen van 61 kinderen geboren met een aanlegstoornis van de long, op 8-jarige leeftijd. We bekeken deze uitkomsten zowel voor de groep die een operatie nodig had gehad, als voor de groep die niet geopereerd was. Beide groepen hadden een normale lengtegroei en een

normaal gewicht. De meeste kinderen in de niet-geopereerde groep hadden een normale longfunctie en een normaal uithoudingsvermogen. Een kwart van deze groep had echter een verminderde longfunctie en/of verminderd uithoudingsvermogen. Het is daarom belangrijk om hier als dokter of ouder alert op te zijn. In de geopereerde groep had ongeveer de helft van de kinderen een verminderde longfunctie. Het gemiddelde uithoudingsvermogen in deze groep was minder goed dan dat van gezonde Nederlandse kinderen.

We concluderen dat kinderen met een aanlegstoornis van de long goed groeien. Ze hebben een verhoogd risico op een verminderde longfunctie en verminderd uithoudingsvermogen, met name als ze een operatie nodig hebben gehad. Langdurige follow-up tot op de volwassen leeftijd en daarna kan overwogen worden vanwege het mogelijke risico op kwaadaardige ontaarding.

Discussie

In **hoofdstuk 10** worden de belangrijkste bevindingen besproken en in perspectief geplaatst. Daarnaast geven we aanbevelingen voor de klinische praktijk en voor toekomstig onderzoek. Onze bevindingen onderstrepen het belang van een multidisciplinaire, gestandaardiseerde aanpak bij het counselen van toekomstige ouders en van langetermijnfollow-up. We raden aan om:

- Meer te streven naar gezinsgerichte zorg.
- Ouders niet alleen praktische en emotionele steun te bieden, maar hen ook te begeleiden in het stimuleren van de ontwikkeling van hun kind.
- Ouders meer te betrekken bij het beslisproces ten aanzien van het medisch beleid van hun kind.

Tot slot geven we een overzicht van wat te vertellen aan ouders in verwachting van een kind met een buikwanddefect of een aanlegstoornis van de long.

APPENDICES

LIST OF PUBLICATIONS

Annelieke Hijkoop*, Chiara CMM Lap*, Moska Aliasi, Eduard JH Mulder, William LM Kramer, Hens AA Brouwers, Robertine van Baren, Eva Pajkrt, Anton H van Kaam, Caterina M Bilardo, Lourens R Pistorius, Gerard HA Visser, René MH Wijnen, Dick Tibboel, Gwendolyn TR Manten, Titia E Cohen-Overbeek. Using three-dimensional ultrasound in predicting complex gastroschisis: a longitudinal, prospective, multicenter cohort study. *Prenat Diagn. 2019;* DOI 10.1002/pd.5568. * Both authors contributed equally.

Annelieke Hijkoop, André B Rietman, René MH Wijnen, Dick Tibboel, Titia E Cohen-Overbeek, Joost van Rosmalen, Hanneke IJsselstijn. Omphalocele at school age: what do parents report? A call for long-term follow-up of complex omphalocele patients. *Early Hum Dev.* 2019; 137:104830.

Nina CJ Peters, **Annelieke Hijkoop**, Rosan L Lechner, Alex J Eggink, Joost van Rosmalen, Dick Tibboel, René MH Wijnen, Hanneke IJsselstijn, Titia E Cohen-Overbeek. The validity of the viscero-abdominal disproportion ratio for type of surgical closure in all fetuses with an omphalocele. *Prenat Diagn. 2019*; 39(12):1070-1079.

Annelieke Hijkoop, André B Rietman, René MH Wijnen, Dick Tibboel, Titia E Cohen-Overbeek, Joost van Rosmalen, Hanneke IJsselstijn. Gastroschisis at school age: what do parents report? *Eur J Pediatr.* 2019; 178(9):1405-1412.

Annelieke Hijkoop, Marloes M van Schoonhoven, Joost van Rosmalen, Dick Tibboel, Monique HM van der Cammen-van Zijp, Mariëlle W Pijnenburg, Titia E Cohen-Overbeek, Johannes M Schnater, Hanneke IJsselstijn. Lung function, exercise tolerance, and physical growth of children with congenital lung malformations at 8 years of age. *Pediatr Pulmonol.* 2019; 54(8):1326-1334.

Annelieke Hijkoop, Nina CJ Peters, Rosan L Lechner, Yolande van Bever, Annabel PJM van Gils-Frijters, Dick Tibboel, René MH Wijnen, Titia E Cohen-Overbeek, Hanneke IJsselstijn. Omphalocele: from diagnosis to growth and development at 2 years of age. *Arch Dis Child Fetal Neonatal Ed.* 2019; 104(1):F18-F23.

Annelieke Hijkoop, Hanneke IJsselstijn, René MH Wijnen, Dick Tibboel, Joost van Rosmalen, Titia E Cohen-Overbeek. Prenatal markers and longitudinal follow-up in simple and complex gastroschisis. *Arch Dis Child Fetal Neonatal Ed.* 2018; 103(2):F126-F131.

Annelieke Hijkoop*, Nina CJ Peters*, Sergei Hermelijn, Marloes M van Schoonhoven, Alex J Eggink, Joost van Rosmalen, Suzan CM Cochius-den Otter, Dick Tibboel, Hanneke IJsselstijn, Johannes M Schnater, Titia E Cohen-Overbeek. Prediction of postnatal outcome of fetuses with a congenital lung malformation: a 2-year follow-up study. *Manuscript in preparation.* * Both authors contributed equally.

PHD PORTFOLIO

General information

Name	Annelieke Hijkoop
Department	Pediatric Surgery and Intensive Care
PhD period	November 2015 – October 2019
Promotor	Prof. dr. Dick Tibboel
Copromotors	Dr. Titia E. Cohen-Overbeek
	Dr. Hanneke IJsselstijn

	Year	**Workload** (ECTS)
General courses		
Photoshop and Illustrator CS6	2018	0.3
Biomedical English Writing and Communication	2017	3.0
Biostatistical methods I: Basic Principles	2016	5.7
Basiscursus Regelgeving Klinisch Onderzoek (BROK)	2016	1.5
Integrity in Scientific Research	2016	0.3
CPO course	2016	0.3
Systematic Literature Retrieval in PubMed and Other Databases & EndNote	2015	1.0
Specific courses and workshops		
ISUOG First Trimester Certificate, ISUOG World Congress, Singapore	2018	0.3
Erasmus MC PhD day, Rotterdam, The Netherlands	2017	0.3
VENA Workshops, Rotterdam, The Netherlands	2017	0.3
Prenatal Medicine for the Gynecologist: congenital anomalies and the perspective after birth (two-day course), Erasmus MC, Rotterdam, The Netherlands	2016	0.6
National conferences		
Pediatric surgery days, Maastricht – *oral presentation (n=1), winner 'best publication of the year'*	2019	1.3
Sophia Research Day (annually), Rotterdam – *oral presentations (n=2)*	2016-2019	2.0
3rd Young Investigators Symposium – hereditary and congenital anomalies, Nijmegen – *oral presentation (n=1)*	2017	1.3
2nd Young Investigators Symposium – hereditary and congenital anomalies, Veldhoven – *oral presentations (n=2)*	2016	2.3

PhD portfolio (*continued*)

	Year	**Workload** (ECTS)
International conferences		
28th World Congress on Ultrasound in Obstetrics and Gynecology, Singapore – *oral (n=3), oral poster (n=2), and poster (n=1) presentations*	2018	3.0
22nd International Conference on Prenatal Diagnosis and Therapy (ISPD), Antwerp, Belgium – *oral presentation (n=1)*	2018	2.0
18th Annual Congress of the European Pediatric Surgeons' Association (EUPSA), Limassol, Cyprus – *oral poster presentation (n=1)*	2017	1.0
10th World Congress Developmental Origins of Health and Disease (DOHaD), Rotterdam, The Netherlands	2017	0.3
17th Annual Congress of the European Pediatric Surgeons' Association (EUPSA), Milan, Italy – *oral presentations (n=2)*	2016	3.0
Other		
Board of the Sophia Researchers Network (SOV)	2018-2019	2.0
Coaching medical students 1st – 3rd year (n=7)	2016-2019	2.0
Organizing committee member (*Erasmus Tour, SOV weekends, New Year's Dinner*)	2016-2019	3.0
Research meetings department of Pediatric Surgery and Intensive Care	2015-2019	2.0
Ambassador Erasmus University Rotterdam	2015-2018	3.0

ECTS = European Credit Transfer and Accumulation System
1 EC represents 28 hours

ABOUT THE AUTHOR

Annelieke Hijkoop was born on January 4, 1993 in Gorinchem. She grew up in Meerkerk. During high school, she joined a 2-year science program at Utrecht University. She followed bilingual education, and completed her athenaeum degree cum laude in 2011 at Lyceum Oudehoven in Gorinchem.

That same year, she moved to Rotterdam to start her medical training. During medical school, she worked as an ambassador of Erasmus University Rotterdam, and as medical student at the Mother and Baby Unit of the department of Psychiatry.

Her enthusiasm for research on congenital anomalies started in 2013, during a research assignment on the long-term effects of neonatal pain under supervision of dr. Gerbrich van den Bosch. She continued doing research under supervision of dr. Hanneke IJsselstijn and dr. Titia Cohen-Overbeek, which resulted in her master's thesis on the prenatal monitoring protocol and postnatal outcome of gastroschisis in 2015. Subsequently, she was offered a PhD position at the department of Pediatric Surgery and Intensive care (promotor: prof. dr. Dick Tibboel), which she gratefully accepted, and which resulted in this thesis. During her PhD period, Annelieke was a board member of the Sophia Researchers Network. In September 2019, she started her clinical rotations.

Annelieke is married to Pascal, they live in Rotterdam.

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