Gastroschisis;
perinatal and postnatal aspects

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Gastroschisis; perinatal and postnatal aspects

Gastroschisis; perinatale en postnatale aspecten

(met een samenvatting in het Nederlands)

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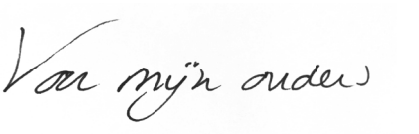
Voor mijn ouders

CONTENTS

LIST OF ABBREVIATIONS

AC	Abdominal circumference
AFI	Amniotic fluid index
AGA	Average birthweight for gestational age
AVLT	Rey Auditory Verbal Learning Test
BRIEF	Behavior Rating Inventory of Executive Function, Dutch version
BSID-III	Bayley Scales of Infant and Toddler Development -3rd Edition
CBCL	Child Behavior Checklist
CI	Confidence interval
CNVs	Copy number variants
CS	Caesarean section
CTG	Cardiotocography
DECIPHER	Database of Chromosomal Imbalance and Phenotype in Humans Using Ensemble Resources
DGV	Database of Genomic Variants
DNA	Deoxyribonucleic acid
GA	Gestational age
IQ	Intelligence quotient
IQR	Inter quartile range
IUFD	Intra-uterine fetal death
IUGR	Intra uterine growth retardation
LOS	Length of hospital stay
M-ABC	Movement Assessment Battery for Children
NEC	Necrotizing enterocolitis
Nepsy-2-NL	Developmental Neuropsychological Assessment Battery, Second Edition Dutch version
NICU	Neonatal intensive care unit
OMIM	Online Mendelian Inheritance in Man
OR	Odds ratio
PI	Pulsatility index
PIQ	Performance IQ
RR	Relative risk
SD	Standard deviation
SES	Socioeconomic status
SGA	Small for gestational age
TEA-Ch NL	Test of Everyday Attention for Children, Dutch version

TFEF	Time to full enteral feeding
TIQ	Total IQ
TPN	Total parenteral nutrition
TTP1	Tocopherol transfer protein 1
VIQ	Verbal IQ
VUS	Variance of uncertain signficance
WES	Whole exome sequencing
WISC-III-NL	Wechsler Intelligence Scale, Third Edition, Dutch Version

Chapter

1

General introduction

DEFINITION

Historical background

Gastroschisis, also known as laparoschisis, abdominoschisis or para-omphalocele, is a congenital defect of the abdominal wall that involves para-umbilical herniation of the abdominal organs, usually to the right of a normal inserted umbilical cord. The defect is generally small (2-5 cm). The intestines (always involving small bowel, often colon, stomach and bladder and occasionally gonads, gallbladder and liver) are not covered by a membrane, in contrast to omphalocele.

Congenital abdominal wall defects (probably omphalocele) were described as early as the first century AD.[1] The entity of gastroschisis is likely to have been described first by Conrad Lycosthenes (1518-1561) in 1557.[2,3] The term gastroschisis was used for the first time by Taruffi in 1894 but its description was of that of an omphalocele.[4] Until 1953 the term gastroschisis was used for both omphalocele and gastroschisis.[5] Moore and Stokes first described gastroschisis as a distinct clinical entity separated from omphalocele.[6]

Isolated and non isolated gastroschisis

In contrast to omphalocele, gastroschisis is not associated with aneuploidy and it is usually isolated.[7,8] The reported prevalence of additional anomalies vary widely between studies (5-50%).[9,10] Likely explanations for this discrepancy include miscoding of the type of abdominal wall defect (omphalocele), variation in data collection methods and their source, inclusion of syndromic forms (such as thoraco-abdomino schisis or limb-body wall complex) and classification of the associated malformations (structural (amyoplasia) versus transient and primary or secondary defects).[11,12] Secondary defects that may be caused by the gastroschisis itself are intestinal atresia, cryptorchidism and hydronephrosis.

Simple and complex gastroschisis

In 20 to 30% of cases of gastroschisis, atresia, volvulus, perforation or necrosis of the bowel is present at birth.[13-15] This effects the outcome of the child significantly.[14] Therefore, subdivision into simple and complex gastroschisis based on the appearance of these bowel complications at birth is recommended.[13]

AETIOLOGY

The aetiology of gastroschisis is unknown. Several theories have been proposed. The theory enjoying most support is the occurrence of a vascular disruption within the abdominal wall either by occlusion of the omphalo-mesenteric artery[16], or premature or delayed loss of the right umbilical vein needed to nourish the developing abdominal wall.[17] This would then lead to necrosis of the abdominal wall and subsequent gut herniation. Arguments against these theories include that the omphalo-mesenteric artery may not provide branches to the abdominal wall and that the intra-abdominal umbilical veins may not provide nutrition to the anterior wall.[18]

Other theories state that gastroschisis is a malformation (distorted embryogenesis) rather than a disruption. Feldkamp et al. have postulated that abnormal folding of the ventral body wall and thereby failure of the physiologic herniation of the bowel into the umbilical cord, leads to herniation of the bowel at the right side of the umbilicus because the left lateral fold advances ahead of the right in normal embryogenesis.[19] Stevenson also believes in a failure of the physiologic herniation of the gut into the umbilical cord. In his theory closure of the lateral abdominal walls occurs normally, but the vitelline duct and yolk sac remain outside both the main body stalk and abdominal wall. The vitelline structures are connected to the gut at a separate perforation through the abdominal wall, and hence prevent the normal herniation of the gut into the umbilical cord. The gut will now herniate through the separate perforation resulting in gastroschisis.[18]

The occurrence of atresia in about 20% of gastroschisis cases[15,20] may be caused by a vascular event comparable to the first vascular theory, secondary to compression and vascular obstruction of the bowel at the defect side[21] or by an early partial volvulus of the bowel caused by a bowel malrotation which is frequently seen in gastroschisis.[22]

PREVALANCE AND RISK FACTORS

The geographic prevalence of gastroschisis varies; the average incidence in Europe (from 2008-2012) is 2.40 per 10.000 births, ranging from 0.92 per 10.000 births in Tuscany (Italy) to 5.72 per 10.000 births in Northern England.[23] In the Netherlands the prevalence was 1.11 per 10.000 live births between 2002-2008 (Table 1) (data not published).

The prevalence of gastroschisis has increased during the last two decades in the whole Western World.[24-27] Within Europe a near fourfold increase was reported within two decades. This increase is still not understood and was found in all maternal age categories.[24]

Gastroschisis has a strong association with young maternal age (Table 2). The prevalence of gastroschisis for mothers aged <20 years is seven times higher than in 25- to 29-years-old women.[24]

Table 1. Gastroschisis prevalence in the Netherlands 2002-2009

Year	Cases	Number of births*	Prevalence**	95%-CI
2002	14	203,268	0.69	0.38 – 1.16
2003	19	201,421	0.94	0.57 – 1.47
2004	23	195,020	1.18	0.75 – 1.77
2005	19	188,893	1.01	0.61 – 1.57
2006	26	185,913	1.40	0.92 – 2.05
2007	21	182,117	1.15	0.71 – 1.76
2008	26	185,408	1.40	0.92 – 2.05
2009	20	185,563	1.08	0.66 – 1.66
2002-2009	**168**	**1,527,603**	**1.11**	**0.94 – 1.28**

* Number of births consists of all live births and stillbirths >24 weeks of gestation
** Prevalence expressed per 10.000 births

Table 2. Gastroschisis prevalence per age group in the Netherlands 2002-2009

Age group*	Cases	Number of births**	Prevalence***	95% CI
<20 y	26	23,086	11.26	7.32 – 15.99
20-24	56	154,202	3.63	2.74 – 4.72
25-29	47	435,707	1.08	0.97 - 1.43
30-34	26	594,681	0.44	0.29 – 0.62
≥ 35	7	319,927	0.22	0.09 – 0.45

* Maternal age at date of delivery
** Number of births consists of all live births and stillbirths >24 weeks of gestation
*** Prevalence expressed per 10.000 births

The association with low maternal age might be explained by lifestyle risk factors that could be related to vasoconstriction (as implied in the vascular aetiology theory of gastroschisis). These factors include smoking, aspirin or recreational drug use around conception and early pregnancy[28-34], but also low socioeconomic status, poor nutritional status, previous termination and genital tract infections.[35-39] Whether these risk factors are related to the young maternal age or independently influence the occurrence of gastroschisis remains unanswered.

The findings that gastroschisis is more common in Caucasians compared to African-Americans living in the same socio-economic area[40,41], that the recurrence risk (2.4%) is greater within families[42] and that the incidence of additional malformations is higher in case of gastroschisis all suggest that genetic factors also contribute to the aetiology of gastroschisis.[43] Thus far, not much attention is given to the potential genetic factors; few studies have investigated potential target genes related to vascular integrity and have been unsuccessful in identifying mutations.[44,45]

PRENATAL MANAGEMENT

Antenatal diagnosis

Before routine ultrasound was available, gastroschisis could only be diagnosed antenatally by raised maternal serum alpha-fetoprotein levels. Nowadays gastroschisis is diagnosed during routine second trimester screening in the majority of cases (>90%) and diagnosis as early as 11 weeks of gestation has been described.[46] In an axial plane of the abdomen at the right side of the umbilical cord, herniation of the bowel can easily be detected. Doppler colour can help to distinguish the umbilicus from the gut. In contrast to omphalocele there is no membrane that covers the bowels (Figure 1).

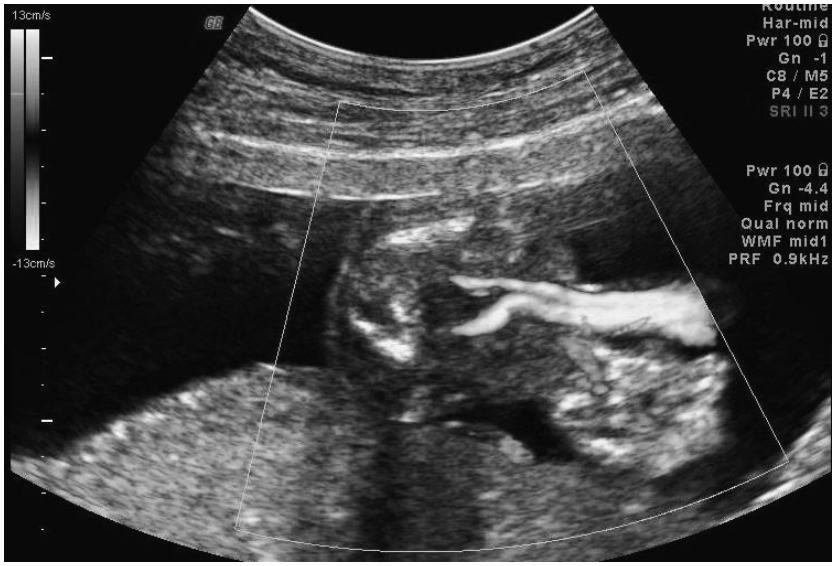

Figure 1. Axial plane of the abdomen with gastroschisis at 20 weeks of gestation

Although gastroschisis is often isolated, detailed structural ultrasound evaluation of the fetus is recommended to exclude additional defects in fetuses with gastroschisis. Gastroschisis is not associated with abnormalities detected by standard karyotyping[7,8] and prenatal genetic testing is therefore not routinely performed in gastroschisis.

Intra uterine growth restriction

There is no consensus on how and when antenatal monitoring of the fetus with gastroschisis should be performed. Intrauterine growth restriction (IUGR) in gastroschisis is common. Up to 61% are born small for gestational age (SGA, birth weight < 10th centile).[47-49] Performing fetal biometry in gastros-

chisis is challenging since the abdominal circumference is difficult to measure and the abdominal cavity of gastroschisis children is smaller. Several authors have suggested adjusted formulas for estimating fetal weight of children with gastroschisis.[50-52] These formulas are not yet widely established in clinical ultrasound evaluation of gastroschisis cases.

The cause of IUGR is not fully understood. The Doppler pulsatility index of the umbilical arteries are generally normal which makes a placental cause unlikely.[53] Children with gastroschisis have lower serum protein concentrations and higher amniotic fluid total protein than controls.[54] This suggests that there is a malabsorption either by mother (low BMI) or the fetus or a loss of protein from the fetus. The chronic inflammation of the bowel, caused by exposure of the exteriorized bowel to amniotic fluid or by compression of the bowel and venous engorgement at the side of the abdominal wall defect, may lead to albumin leakage and hypovolemia and both these conditions may affect fetal growth.

Intra uterine fetal death

Intra uterine death is 7-fold higher (4.48%) in gastroschisis cases compared tot the general population (0.62%).[55] Most deaths occur after 32 weeks of gestation and in the majority of cases the cause of death is not found. One can speculate whether hypoalbuminia or hypovolemia plays a role, but IUGR is not more common within this group as compared to gastroschisis survivors. Routine fetal heart rate monitoring using cardiotocography in the last trimester seems to prevent fetal death.[56] On the other hand, close monitoring of the fetal condition may also raise the percentage of unnecessary Caesarean sections since non-reassuring CTG patterns are more commonly found in gastroschisis cases. Fetal tachycardia and reduced accelerations are described in gastroschisis cases without postnatal signs of compromise (such as asphyxia, fever or complex gastroschisis).[57] Whether fetal pain, alteration in vagal tone caused by the mechanical effect of gut herniation or hypovolemia adversely affect the fetal heart rate, has not yet been elucidated.

CONDITION OF THE BOWEL

The antenatal exposure of exteriorized bowel to amniotic fluid, especially during the last trimester when amniotic fluid ureum, creatinine and meconium concentrations are higher, leads to chronic inflammation of the bowel.[58-60] This results in high levels of proinflammatory cytokines found in the amniotic fluid of fetuses with gastroschisis.[61] Inflammation of the bowel may also increase capillary leakage with tissue oedema[54] and hypovolemia, resulting in hypotension and hypoperfusion of the bowel, thus further increasing bowel injury. Bowel tension and compression on the exteriorized intestine may also alter the perfusion of the bowel.

The bowel condition at birth is an important prognostic factor for neonatal outcome.[62] If one could identify atresia, antenatal volvulus, bowel perforation and necrosis (complex gastroschisis) antenatally, subsequent obstetric delivery management may prevent further bowel damage. A wide range of potential ultrasound makers have been proposed to establish the bowel condition: bowel dilatation, either intra- or extra-abdominally (e.g. Figure 2), bowel wall thickness, gastric dilatation, the amount of amniotic fluid and blood flow patterns in the superior mesenteric artery. The study results are conflicting, which may be attributed to the fact that the studies were generally retrospective, often based on small sample sizes, using a large variety of measurement methods and threshold values to define an ultrasound finding as abnormal. Moreover, outcome definitions varied widely. A recent meta-analysis based on these studies showed that only intra-abdominal bowel dilation and polyhydramnios were associated with an increased risk of bowel atresia (OR 5.48 and 3.76). Based on the low quality of the studies they were not able to draw conclusions regarding the association between prenatal ultrasound markers, length of hospital stay and time to full enteral feeding.[63]

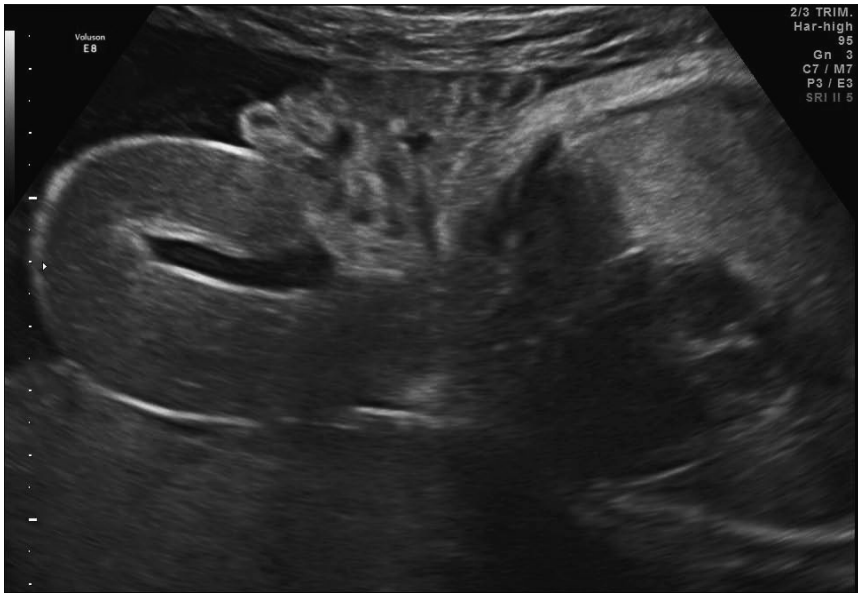

Figure 2. Gastroschisis and extra-abdominal bowel loop at 35 weeks of gestation

TIMING AND MODE OF DELIVERY

Delivery at a centre with a neonatal intensive care unit and paediatric surgery facilities is recommended.[64] To prevent severe bowel damage and sudden intra uterine fetal death, elective preterm delivery has been promoted.[65-71] Only one randomized controlled trial has been published comparing elective vaginal delivery at 36 weeks with spontaneous delivery. There were no differences in neonatal outcome. However, the difference in duration of gestation between both groups was only one week. This is due to the fact that most gastroschisis cases are born spontaneously around 36-37 weeks of gestation.[72] A recently published retrospective nationwide cohort study from the USA, based on 860 cases of gastroschisis, compared fetal and postnatal mortality with respect to the timing of delivery and showed that expectant management between 37 and 39 weeks significantly increased the risk of mortality. Delivery as early as 37 weeks minimized the pre- and postnatal mortality.[73]

The mode of delivery for gastroschisis cases, vaginally or by Caesarean section has long been a controversy. Although a vaginal delivery seems more traumatic for the fetal bowel, a systematic review based on 15 studies did not provide evidence to support a policy of routine Caesarean section for these infants.[74] This finding has been supported by more recent studies.[75,80]

After delivery the child will directly be placed in a plastic bag to prevent infection, dehydration and hypothermia.

NEONATAL MANAGMENT

Timing and type of closure

Gastroschisis can be closed using different techniques. Traditionally, primary closure of the abdomen direct after birth has been the preferred technique. This is performed under general anaesthesia. Failure of closure can be the result of difficulties in reducing the entire intestine into the abdominal cavity in combination with too high ventilation pressures. Initially, both fascia and skin were always closed, but later other techniques were proposed to reduce abdominal cavity pressure such as the flap technique, where only the abdominal skin was closed or the umbilicus was used to cover the wall defect (sutureless closure). Bianchi advocated an immediate bedside reduction under local anaesthesia.[76]

In a staged closure a silastic bag is used. It is placed over the exteriorized bowel and attached to the fascia or, in case of pre-formed spring-loaded silo, a ring is placed under the fascia. This bag is situated outside the abdomen with the intestines within. Slowly the intestines will be reduced completely by the gravity and by daily digital compression on the top of the transparant silastic

silo with direct inspection of the colour and the vascularity of the gut by the paediatric surgeon and controlling of the ventilation pressure by the neonatologist. Reherniation of the intestines is prevented by a transverse placed clamp on the top of the silo after the daily reduction. The gut is continuously decompressed by an open nasogastric tube. Feeding is only as total parenteral nutrition (TPN) by a central venous line cavity. Most often the child is ventilated during these reduction days. Elective closure of the abdominal wall is planned in the subsequent days.
The advantage of primary closure is the need of only one operation, which may prevent abdominal infection and might reduce the time to full enteral feeding. On the other hand, in staged closure lower ventilation pressures can be used, which may reduce ventilation time. The risk of an abdominal compartment syndrome is also lower. Atresia is often not diagnosed directly after birth, staged closure may give the opportunity to diagnose abdominal obstructions caused by atresia and resection of the atresia can be performed at the moment of secondary closure.[77] There is no consensus on which technique is superior with regard to neonatal outcome.[78]

POST-OPERATIVE MANAGEMENT

Introduction of feeding

Most of these children suffer from a disturbed intestinal mobility, impaired bowel absorption and sometimes obstruction of the bowel that will not allow enteral intake. Therefore a central intravenous catheter is placed for TPN. Minimal enteral feeding is usually started within the first days of life and gradually enteral feeding will be increased.

Survival and complications

Nowadays the neonatal survival rate of gastroschisis is more than 90%.[75,79-81] During hospitalisation central line, wound and respiratory infections, electrolyte disturbances and cholestasis are the most common complications. Especially in complex gastroschisis, repeated surgery is often required for central line replacement or bowel complications (such as atresia, abdominal adhesions, perforation or bowel compartment syndrome). In those cases this may lead to short bowel syndrome and prolonged TPN causing cholestasis and eventually liver damage. Gastroschisis is the most frequent cause of paediatric intestinal transplantation.[82]

LONG-TERM OUTCOME

The interventions and events in early life, in addition to the late preterm birth and dysmaturity in the majority of gastroschisis children, are likely to have long-term effects on growth and neurologic development. Most studies have focussed on the outcome of children with gastroschisis during hospitalisation. Only few studies are available on long-term outcome of these children. Growth delay is common but will be overcome within the first years of life.[83-85] Functional bowel complaints have been reported[48,83], although the quality of life reports of adolescents born with gastroschisis are comparable with those of the general population.[86] Studies on neurodevelopmental outcome of children with gastroschisis mostly regarded pre-scholars. They invariably reported cognitive outcomes in the normal range, although they seem to perform less well than their peers in studies using control groups.[48,87-90] Behavioural dysfunction seems to be more common in young children with gastroschisis.[91,92] Whether this can be contributed to the social economic status of children born with gastroschisis, their prematurity, IUGR or the gastroschisis and the events in early life has still to be established.[92]

AIMS OF THE THESIS

Given the many uncertainties regarding aetiology, diagnostic tools and prognosis of gastroschisis, we conducted a series of studies, to

- provide better information on short and long-term prognosis of a child with an isolated gastroschisis.
- investigate the value of genetic testing and morphological examination in gastroschisis
- investigate potential antenatal ultrasound markers that may better predict neonatal outcome and may influence obstetric management in timing of delivery

This information is important for caregivers, but will also help in antenatal counselling of parents.

PART I – OUTCOME OF GASTROSCHISIS

In **Chapter 2** we described the results of a Dutch/Brazilian retrospective study followed by a meta-analysis on the outcome of isolated simple and complex gastroschisis in order to give quantitative data on time to full enteral feeding and secondary, length of mechanical ventilation, length of hospitalisation and mortality.

In **Chapter 3** we assessed the functional and neurodevelopment of a cohort of school aged children born with gastroschisis and healthy controls matched for gestational age, birth weight and socio-economic status.
In addition we performed a study to identify potential genetic causes and risk factors of gastroschisis in a well-defined patient cohort by combining morphological examination and genetic analysis in cases and their parents (**Chapter 4**).

PART II – ANTENATAL ULTRASOUND MARKERS

To diagnosis dilated fetal bowel by ultrasound, knowledge of the sizes of the normal fetal bowel during gestation is needed. In **Chapter 5** we proposed a standardised method to identify and measure the fetal small bowel and colon and create normal reference curves based on prospective longitudinal measurements in 39 low-risk pregnancies. The usefulness of these reference curves was tested on a retrospective cohort of fetuses with suspected bowel dilatation.
In **Chapter 6** we described an exceptional case of a fetus with an isolated large gastroschisis including complete herniation of the liver. To outline the prognosis of such cases we performed a literature search.
In **Chapter 7** the results of the FLAMINGO-study (FetaL Abdominal Markers Identified by ultrasound to predict Neonatal Outcome) are presented. This was a national prospective study of isolated gastroschisis cases. According to a standardised antenatal and perinatal protocol these fetuses were assessed by ultrasound to identify potential prognostic ultrasound markers for outcome. Bowel diameter, Doppler of the mesenteric artery and fetal biometry were assessed to test their prognostic value regarding the diagnosis of simple and complex gastroschisis and overall short-term outcome (time to full enteral feeding, length of hospital stay and mortality).

REFERENCES

1. Jarcho J. Congenital umbilical hernia. [Aulus Cornelius Celsus, a roman physician and medical writer 25 B.C. to 50 A.D.]. 1937;65:593-600.
2. Lycosthenes C. *Prodigiorum ac ostentorum chronicon. basel : Per henricum petri, 1557*.
3. Klein M. Congenital abdominal wall defects. In: Ashcraft K, Holcomb G., Murphy J, Peds. *Pediatric Surgery.* 4th ed. Elsevier-Saunders; 2004.
4. Taruffi C. *Storia Della Teratologia.* Vol VII. Bologna, Italy: Regia Tipografia; 1894.
5. Johns FS. Congenital defect of the abdominal wall in the newborn: (gastroschisis). *Ann Surg*. 1946;123(5):886-896.
6. Moore TC, Stokes GE. Gastroschisis; report of two cases treated by a modification of the gross operation for omphalocele. *Surgery*. 1953;33(1):112-120.
7. Mastroiacovo P, Lisi A, Castilla EE, Martinez-Frias ML, Bermejo E, Marengo L, Kucik J, Siffel C, Halliday J, Gatt M, Anneren G, Bianchi F, Canessa MA, Danderfer R, de Walle H, Harris J, Li Z, Lowry RB, McDonell R, Merlob P, Metneki J, Mutchinick O, Robert-Gnansia E, Scarano G, Sipek A, Potzsch S, Szabova E, Yevtushok L. Gastroschisis and associated defects: An international study. *Am J Med Genet A*. 2007;143(7):660-671. 10.1002/ajmg.a.31607.
8. Hwang PJ, Kousseff BG. Omphalocele and gastroschisis: An 18-year review study. *Genet Med*. 2004;6(4):232-236.
9. Rankin J, Dillon E, Wright C. Congenital anterior abdominal wall defects in the north of England, 1986-1996: Occurrence and outcome. *Prenat Diagn*. 1999;19(7):662-668.
10. Stoll C, Alembik Y, Dott B, Roth MP. Omphalocele and gastroschisis and associated malformations. *Am J Med Genet A*. 2008;146A(10):1280-1285. 10.1002/ajmg.a.32297.
11. Corona-Rivera JR, Nieto-Garcia R, Lopez-Marure E, Cardenas-Ruiz Velasco JJ, Bobadilla-Morales L, Mellin-Sanchez EL, Aguirre-Guillen RL, Perez-Ramirez RO, Zapata-Aldana E, Sandoval-Talamantes AK, Solis-Ledezma S, Corona-Rivera A, Gomez-Ruiz LM. Associated congenital anomalies in infants with isolated gastroschisis: A single-institutional experience. *Am J Med Genet A*. 2015. 10.1002/ajmg.a.37433 [doi].
12. Hunter AG, Stevenson RE. Gastroschisis: Clinical presentation and associations. *Am J Med Genet C Semin Med Genet*. 2008;148C(3):219-230. 10.1002/ajmg.c.30178.
13. Molik KA, Gingalewski CA, West KW, Rescorla FJ, Scherer LR, Engum SA, Grosfeld JL. Gastroschisis: A plea for risk categorization. *J Pediatr Surg*. 2001;36(1):51-55. 10.1053/jpsu.2001.20004.
14. Bergholz R, Boettcher M, Reinshagen K, Wenke K. Complex gastroschisis is a different entity to simple gastroschisis affecting morbidity and mortality-a systematic review and meta-analysis. *J Pediatr Surg*. 2014;49(10):1527-1532. 10.1016/j.jpedsurg.2014.08.001 [doi].
15. Emil S, Canvasser N, Chen T, Friedrich E, Su W. Contemporary 2-year outcomes of complex gastroschisis. *J Pediatr Surg*. 2012;47(8):1521-1528. 10.1016/j.jpedsurg.2011.12.023; 10.1016/j.jpedsurg.2011.12.023.
16. Hoyme HE, Higginbottom MC, Jones KL. The vascular pathogenesis of gastroschisis: Intrauterine interruption of the omphalomesenteric artery. *J Pediatr*. 1981;98(2):228-231.
17. de Vries PA. The pathogenesis of gastroschisis and omphalocele. *J Pediatr Surg*. 1980;15(3):245-251.
18. Stevenson RE, Rogers RC, Chandler JC, Gauderer MW, Hunter AG. Escape of the yolk sac: A hypothesis to explain the embryogenesis of gastroschisis. *Clin Genet*. 2009;75(4):326-333. 10.1111/j.1399-0004.2008.01142.x.
19. Feldkamp ML, Carey JC, Sadler TW. Development of gastroschisis: Review of hypotheses, a novel hypothesis, and implications for research. *Am J Med Genet A*. 2007;143(7):639-652. 10.1002/ajmg.a.31578.

20. Goetzinger KR, Tuuli MG, Longman RE, Huster KM, Odibo AO, Cahill AG. Sonographic predictors of postnatal bowel atresia in fetal gastroschisis. *Ultrasound Obstet Gynecol*. 2013;4(43):420-425. 10.1002/uog.12568; 10.1002/uog.12568.
21. Brugger PC, Prayer D. Development of gastroschisis as seen by magnetic resonance imaging. *Ultrasound Obstet Gynecol*. 2011;37(4):463-470. 10.1002/uog.8894; 10.1002/uog.8894.
22. Houben C, Davenport M, Ade-Ajayi N, Flack N, Patel S. Closing gastroschisis: Diagnosis, management, and outcomes. *J Pediatr Surg*. 2009;44(2):343-347. 10.1016/j.jpedsurg.2008.10.084.
23. EUROCAT Website Database. EUROCAT Prevalence Data Tables, (A5-Gastroschisis (per 10,000 births) for the following registries: All Registries from 2008-2012. http://www.eurocat-network.eu/ACCESSPREVALENCE-DATA/prevalenceTables. Updated 2015.
24. Loane M, Dolk H, Bradbury I, EUROCAT Working Group. Increasing prevalence of gastroschisis in Europe 1980-2002: A phenomenon restricted to younger mothers? *Paediatr Perinat Epidemiol*. 2007;21(4):363-369. 10.1111/j.1365-3016.2007.00820.x.
25. Chabra S, Gleason CA, Seidel K, Williams MA. Rising prevalence of gastroschisis in Washington State. *J Toxicol Environ Health A*. 2011;74(5):336-345. 10.1080/15287394.2011.534424.
26. Hernandez MD, Elizondo G, Barron C, Martinez L. Rising incidence of gastroschisis in a medical center at northeast Mexico. *Birth Defects Res Part A Clin Mol Teratol*. 2009;85(5):440.
27. Mastroiacovo P, Lisi A, Castilla EE. The incidence of gastroschisis: Research urgently needs resources. *BMJ*. 2006;332(7538):423-424. 10.1136/bmj.332.7538.423-a.
28. Norgard B, Puho E, Czeizel AE, Skriver MV, Sorensen HT. Aspirin use during early pregnancy and the risk of congenital abnormalities: A population-based case-control study. *Am J Obstet Gynecol*. 2005;192(3):922-923. 10.1016/j.ajog.2004.10.598.
29. Kozer E, Nikfar S, Costei A, Boskovic R, Nulman I, Koren G. Aspirin consumption during the first trimester of pregnancy and congenital anomalies: A meta-analysis. *Am J Obstet Gynecol*. 2002;187(6):1623-1630.
30. M.werler M, Sheehan JE, Mitchell AA. Maternal medication use and risks of gastroschisis and small intestinal atresia. *Am J Epidemiol*. 2002;155(1):26-31.
31. Torfs CP, Katz EA, Bateson TF, Lam PK, Curry CJ. Maternal medications and environmental exposures as risk factors for gastroschisis. *Teratology*. 1996;54(2):84-92. 2-4.
32. Drongowski RA, Smith RK, Jr, Coran AG, Klein MD. Contribution of demographic and environmental factors to the etiology of gastroschisis: A hypothesis. *Fetal Diagn Ther*. 1991;6(1-2):14-27.
33. Draper ES, Rankin J, Tonks AM, Abrams KR, Field DJ, Clarke M, Kurinczuk JJ. Recreational drug use: A major risk factor for gastroschisis? *Am J Epidemiol*. 2008;167(4):485-491. 10.1093/aje/kwm335.
34. Werler MM, Mitchell AA, Moore CA, Honein MA, National Birth Defects Prevention Study. Is there epidemiologic evidence to support vascular disruption as a pathogenesis of gastroschisis? *Am J Med Genet A*. 2009;149A(7):1399-1406. 10.1002/ajmg.a.32897.
35. Paranjothy S, Broughton H, Evans A, Huddart S, Drayton M, Jefferson R, Rankin J, Draper E, Cameron A, Palmer SR. The role of maternal nutrition in the aetiology of gastroschisis: An incident case-control study. *Int J Epidemiol*. 2012;41(4):1141-1152. 10.1093/ije/dys092; 10.1093/ije/dys092.
36. Root ED, Meyer RE, Emch M. Socioeconomic context and gastroschisis: Exploring associations at various geographic scales. *Soc Sci Med*. 2011;72(4):625-633. 10.1016/j.socscimed.2010.11.025.
37. Rasmussen SA, Frias JL. Non-genetic risk factors for gastroschisis. *Am J Med Genet C Semin Med Genet*. 2008;148C(3):199-212. 10.1002/ajmg.c.30175.
38. Siega-Riz AM, Olshan AF, Werler MM, Moore C. Fat intake and the risk of gastroschisis. *Birth Defects Res A Clin Mol Teratol*. 2006;76(4):241-245. 10.1002/bdra.20249.
39. Feldkamp ML, Enioutina EY, Botto LD, Krikov S, Byrne JL, Geisler WM. Chlamydia trachomatis IgG3 seropositivity is associated with gastroschisis. *J Perinatol*. 2015;35(11):930-934. 10.1038/jp.2015.115 [doi].

40. Salihu HM, Pierre-Louis BJ, Druschel CM, Kirby RS. Omphalocele and gastroschisis in the state of New York, 1992-1999. *Birth Defects Res A Clin Mol Teratol.* 2003;67(9):630-636. 10.1002/bdra.10113.
41. Williams LJ, Kucik JE, Alverson CJ, Olney RS, Correa A. Epidemiology of gastroschisis in metropolitan Atlanta, 1968 through 2000. *Birth Defects Res A Clin Mol Teratol.* 2005;73(3):177-183. 10.1002/bdra.20114.
42. Kohl M, Wiesel A, Schier F. Familial recurrence of gastroschisis: Literature review and data from the population-based birth registry "mainz model". *J Pediatr Surg*. 2010;45(9):1907-1912. 10.1016/j.jpedsurg.2010.05.003.
43. Feldkamp ML, Botto LD, Byrne JL, Krikov S, Carey JC. Clinical presentation and survival in a population-based cohort of infants with gastroschisis in Utah, 1997-2011. *Am J Med Genet A*. 2016;170A(2):306-315. 10.1002/ajmg.a.37437 [doi].
44. Torfs CP, Christianson RE, Iovannisci DM, Shaw GM, Lammer EJ. Selected gene polymorphisms and their interaction with maternal smoking, as risk factors for gastroschisis. *Birth Defects Res A Clin Mol Teratol.* 2006;76(10):723-730. 10.1002/bdra.20310.
45. Cardonick E, Broth R, Kaufmann M, Seaton J, Henning D, Roberts N, Wapner R. Genetic predispositions for thromboembolism as a possible etiology for gastroschisis. *Am J Obstet Gynecol.* 2005;193(2):426-428. 10.1016/j.ajog.2004.12.010.
46. Cerekja A, Piazze J, Cozzi D. Early prenatal sonographic diagnosis of gastroschisis. *J Clin Ultrasound*. 2012;40(8):526-528. 10.1002/jcu.20901; 10.1002/jcu.20901.
47. Horton AL, Powell MS, Wolfe HM. Intrauterine growth patterns in fetal gastroschisis. *Am J Perinatol*. 2010;27(3):211-217. 10.1055/s-0029-1236440.
48. South AP, Marshall DD, Bose CL, Laughon MM. Growth and neurodevelopment at 16 to 24 months of age for infants born with gastroschisis. *J Perinatol*. 2008;28(10):702-706. 10.1038/jp.2008.71.
49. Payne NR, Simonton SC, Olsen S, Arnesen MA, Pfleghaar KM. Growth restriction in gastroschisis: Quantification of its severity and exploration of a placental cause. *BMC Pediatr.* 2011;11(1):90. 10.1186/1471-2431-11-90.
50. Adams SR, Durfee S, Pettigrew C, Katz D, Jennings R, Ecker J, House M, Benson CB, Wolfberg A. Accuracy of sonography to predict estimated weight in fetuses with gastroschisis. *J Ultrasound Med*. 2012;31(11):1753-1758.
51. Nicholas S, Tuuli MG, Dicke J, Macones GA, Stamilio D, Odibo AO. Estimation of fetal weight in fetuses with abdominal wall defects: Comparison of 2 recent sonographic formulas to the hadlock formula. *J Ultrasound Med*. 2010;29(7):1069-1074.
52. Chaudhury P, Haeri S, Horton A, Wolfe H, Goodnight W. Ultrasound prediction of birth weight and growth restriction in fetal gastroschisis. *Am J Obstet Gynecol*. 2009;201(6):S132.
53. Netta DA, Wilson RD, Visintainer P, Johnson MP, Hedrick HL, Flake AW, Adzick NS. Gastroschisis: Growth patterns and a proposed prenatal surveillance protocol. *Fetal Diagn Ther*. 2007;22(5):352-357. 10.1159/000103295.
54. Carroll SG, Kuo PY, Kyle PM, Soothill PW. Fetal protein loss in gastroschisis as an explanation of associated morbidity. *Am J Obstet Gynecol*. 2001;184(6):1297-1301. 10.1067/mob.2001.114031.
55. South AP, Stutey KM, Meinzen-Derr J. Meta-analysis of the prevalence of intrauterine fetal demise in gastroschisis. *Am J Obstet Gynecol*. 2013;2(209):114e1--13. 10.1016/j.ajog.2013.04.032; 10.1016/j.ajog.2013.04.032.
56. Burge DM, Ade-Ajayi N. Adverse outcome after prenatal diagnosis of gastroschisis: The role of fetal monitoring. *J Pediatr Surg*. 1997;32(3):441-444.
57. Dixon JC, Penman DM, Soothill PW. The influence of bowel atresia in gastroschisis on fetal growth, cardiotocograph abnormalities and amniotic fluid staining. *BJOG*. 2000;107(4):472-475.
58. Nichol PF, Hayman A, Pryde PG, Go LL, Lund DP. Meconium staining of amniotic fluid correlates with intestinal peel formation in gastroschisis. *Pediatr Surg Int*. 2004;20(3):211-214. 10.1007/s00383-003-1050-1.
59. Api A, Olguner M, Hakguder G, Ates O, Ozer E, Akgur FM. Intestinal damage in gastroschisis correlates with the concentration of intraamniotic meconium. *J Pediatr Surg*. 2001;36(12):1811-1815.

60. Albert A, Julia V, Morales L, Rovira J, Sancho A, Bombi JA. Role of the amniotic fluid in gastroschisis. an experimental study. *Cir Pediatr*. 1992;5(1):12-16.

61. Morrison JJ, Klein N, Chitty LS, Kocjan G, Walshe D, Goulding M, Geary MP, Pierro A, Rodeck CH. Intra-amniotic inflammation in human gastroschisis: Possible aetiology of postnatal bowel dysfunction. *Br J Obstet Gynaecol*. 1998;105(11):1200-1204.

62. Cowan KN, Puligandla PS, Laberge JM, Skarsgard ED, Bouchard S, Yanchar N, Kim P, Lee S, McMillan D, von Dadelszen P, Canadian Pediatric Surgery Network. The gastroschisis prognostic score: Reliable outcome prediction in gastroschisis. *J Pediatr Surg*. 2012;47(6):1111-1117. 10.1016/j.jpedsurg.2012.03.010; 10.1016/j.jpedsurg.2012.03.010.

63. D'Antonio F, Virgone C, Rizzo G, Khalil A, Baud D, Cohen-Overbeek TE, Kuleva M, Salomon LJ, Flacco ME, Manzoli L, Giuliani S. Prenatal risk factors and outcomes in gastroschisis: A meta-analysis. *Pediatrics*. 2015;136(1):e159-69. 10.1542/peds.2015-0017 [doi].

64. Nasr A, Langer JC, Canadian Paediatric Surgery Network. Influence of location of delivery on outcome in neonates with gastroschisis. *J Pediatr Surg*. 2012;47(11):2022-2025. 10.1016/j.jpedsurg.2012.07.037; 10.1016/j.jpedsurg.2012.07.037.

65. Wilson MS, Carroll MA, Braun SA, Walsh WF, Pietsch JB, Bennett KA. Is preterm delivery indicated in fetuses with gastroschisis and antenatally detected bowel dilation? *Fetal Diagn Ther*. 2012. 10.1159/000338925.

66. Braun SA, Carroll M, Bennett KA, Pietsch J, Walsh W, Wilson MS. The effect of preterm delivery on fetuses with gastroschisis. *Am J Obstet Gynecol*. 2011;204(1):S204.

67. Reigstad I, Reigstad H, Kiserud T, Berstad T. Preterm elective caesarean section and early enteral feeding in gastroschisis. *Acta Paediatr*. 2011;100(1):71-74. 10.1111/j.1651-2227.2010.01944.x; 10.1111/j.1651-2227.2010.01944.x.

68. Gelas T, Gorduza D, Devonec S, Gaucherand P, Downham E, Claris O, Dubois R. Scheduled preterm delivery for gastroschisis improves postoperative outcome. *Pediatr Surg Int*. 2008;24(9):1023-1029. 10.1007/s00383-008-2204-y.

69. Hadidi A, Subotic U, Goeppl M, Waag KL. Early elective cesarean delivery before 36 weeks vs late spontaneous delivery in infants with gastroschisis. *J Pediatr Surg*. 2008;43(7):1342-1346. 10.1016/j.jpedsurg.2007.12.050.

70. Serra A, Fitze G, Kamin G, Dinger J, Konig IR, Roesner D. Preliminary report on elective preterm delivery at 34 weeks and primary abdominal closure for the management of gastroschisis. *Eur J Pediatr Surg*. 2008;18(1):32-37. 10.1055/s-2007-965744.

71. Moir CR, Ramsey PS, Ogburn PL, Johnson RV, Ramin KD. A prospective trial of elective preterm delivery for fetal gastroschisis. *Am J Perinatol*. 2004;21(5):289-294. 10.1055/s-2004-829864.

72. Logghe HL, Mason GC, Thornton JG, Stringer MD. A randomized controlled trial of elective preterm delivery of fetuses with gastroschisis. *J Pediatr Surg*. 2005;40(11):1726-1731. 10.1016/j.jpedsurg.2005.07.047.

73. Sparks TN, Shaffer BL, Page J, Caughey AB. Gastroschisis: Mortality risks with each additional week of expectant management. *Am J Obstet Gynecol*. 2016. S0002-9378(16)30648-2 [pii].

74. Segel SY, Marder SJ, Parry S, Macones GA. Fetal abdominal wall defects and mode of delivery: A systematic review. *Obstet Gynecol*. 2001;98(5 Pt 1):867-873.

75. Abdel-Latif ME, Bolisetty S, Abeywardana S, Lui K, Australian and New Zealand Neonatal Network. Mode of delivery and neonatal survival of infants with gastroschisis in Australia and New Zealand. *J Pediatr Surg*. 2008;43(9):1685-1690. 10.1016/j.jpedsurg.2008.03.053.

76. Bianchi A, Dickson AP, Alizai NK. Elective delayed midgut reduction-no anesthesia for gastroschisis: Selection and conversion criteria. *J Pediatr Surg*. 2002;37(9):1334-1336.

77. Snyder CL, Miller KA, Sharp RJ, Murphy JP, Andrews WA, Holcomb GW,3rd, Gittes GK, Ashcraft KW. Management of intestinal atresia in patients with gastroschisis. *J Pediatr Surg*. 2001;36(10):1542-1545. 10.1053/jpsu.2001.27040.

78. Ross AR, Eaton S, Zani A, Ade-Ajayi N, Pierro A, Hall NJ. The role of preformed silos in the management of infants with gastroschisis: A systematic review and meta-analysis. *Pediatr Surg Int*. 2015;31(5):473-483. 10.1007/s00383-015-3691-2 [doi].

79. Fillingham A, Rankin J. Prevalence, prenatal diagnosis and survival of gastroschisis. *Prenat Diagn*. 2008;28(13):1232-1237. 10.1002/pd.2153.

80. Salihu HM, Emusu D, Aliyu ZY, Pierre-Louis BJ, Druschel CM, Kirby RS. Mode of delivery and neonatal survival of infants with isolated gastroschisis. *Obstet Gynecol*. 2004;104(4):678-683. 10.1097/01.AOG.0000139513.93115.81.

81. Sharp M, Bulsara M, Gollow I, Pemberton P. Gastroschisis: Early enteral feeds may improve outcome. *J Paediatr Child Health*. 2000;36(5):472-476.

82. Wada M, Kato T, Hayashi Y, Selvaggi G, Mittal N, Thompson J, Gonzalez M, Nishida S, Madariaga J, Tzakis A. Intestinal transplantation for short bowel syndrome secondary to gastroschisis. *J Pediatr Surg*. 2006;41(11):1841-1845. 10.1016/j.jpedsurg.2006.06.010.

83. Swartz KR, Harrison MW, Campbell JR, Campbell TJ. Long-term follow-up of patients with gastroschisis. *Am J Surg*. 1986;151(5):546-549.

84. Davies BW, Stringer MD. The survivors of gastroschisis. *Arch Dis Child*. 1997;77(2):158-160.

85. Henrich K, Huemmer HP, Reingruber B, Weber PG. Gastroschisis and omphalocele: Treatments and long-term outcomes. *Pediatr Surg Int*. 2008;24(2):167-173. 10.1007/s00383-007-2055-y.

86. Koivusalo A, Lindahl H, Rintala RJ. Morbidity and quality of life in adult patients with a congenital abdominal wall defect: A questionnaire survey. *J Pediatr Surg*. 2002;37(11):1594-1601.

87. Payne NR, Gilmore L, Svobodny S, Perdue NR, Hoekstra RE, Olsen S, Moore JR. A cross-sectional, case-control follow-up of infants with gastroschisis. *J Neonatal-Perinat Med*. 2010;3(3):207-215.

88. Gorra AS, Needelman H, Azarow KS, Roberts HJ, Jackson BJ, Cusick RA. Long-term neurodevelopmental outcomes in children born with gastroschisis: The tiebreaker. *J Pediatr Surg*. 2012;47(1):125-129. 10.1016/j.jpedsurg.2011.10.028.

89. Minutillo C, Rao SC, Pirie S, McMichael J, Dickinson JE. Growth and developmental outcomes of infants with gastroschisis at one year of age: A retrospective study. *J Pediatr Surg*. 2013;48(8):1688-1696. 10.1016/j.jpedsurg.2012.11.046; 10.1016/j.jpedsurg.2012.11.046.

90. van Manen M, Hendson L, Wiley M, Evans M, Taghaddos S, Dinu I. Early childhood outcomes of infants born with gastroschisis. *J Pediatr Surg*. 2013;48(8):1682-1687. 10.1016/j.jpedsurg.2013.01.021; 10.1016/j.jpedsurg.2013.01.021.

91. Ginn-Pease ME, King DR, Tarnowski KJ, Green L, Young G, Linscheid TR. Psychosocial adjustment and physical growth in children with imperforate anus or abdominal wall defects. *J Pediatr Surg*. 1991;26(9):1129-1135.

92. Harris EL, Hart SJ, Minutillo C, Ravikumara M, Warner TM, Williams Y, Nathan EA, Dickinson JE. The long-term neurodevelopmental and psychological outcomes of gastroschisis: A cohort study. *J Pediatr Surg*. 2016;51(4):549-553. 10.1016/j.jpedsurg.2015.08.062 [doi].

PART I

Outcome of Gastroschisis

Chapter

2

Outcome of isolated gastroschisis; an international study, systematic review and meta-analysis

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ABSTRACT

Objective: To determine outcome of children born with isolated gastroschisis (no extra-gastrointestinal congenital abnormalities).

Study design: International cohort study and meta-analysis. Primary outcome: Time to full enteral feeding (TFEF); secondary outcomes: Duration of mechanical ventilation, length of stay (LOS), mortality and differences in outcome between simple and complex gastroschisis (complex; born with bowel atresia, volvulus, perforation or necrosis).

To compare the cohort study results with literature three databases were searched. Studies were eligible for inclusion if cases were born in developed countries with isolated gastroschisis after 1990, number of cases >20 and TFEF was reported.

Results: The cohort study included 204 liveborn cases of isolated gastroschisis. The median TFEF, duration of ventilation and LOS was, 26 days (range 6-515), 2 days (range 0-90) and 33 days (range 11-515), respectively. Overall mortality was 10.8%. TFEF and LOS were significantly longer ($P<0.0001$) and mortality was fourfold higher in the complex group. Seventeen studies, amongst the current study, were included for further meta-analysis comprising a total of 1652 patients. Mean TFEF was 35.3 ± 4.4 days, length of ventilation was 5.5 ± 2.0 days, LOS was 46.4 ± 5.2 days and mortality risk was 0.06 (0.04-0.07 95%-CI).

Outcome of simple and complex gastroschisis was described in five studies. TFEF, ventilation time, LOS were significant longer and mortality rate was 3.64 (1.95 – 6.83 95%-CI) times higher in complex cases.

Conclusions: These results give a good indication of the expected TFEF, ventilation time, LOS and mortality risk in children born with isolated gastroschisis, although ranges remain wide. This study shows the importance of dividing gastroschisis into simple and complex for the prediction of outcome.

INTRODUCTION

Nowadays, gastroschisis is nearly always diagnosed prenatally during routine first and second trimester ultrasound examinations. However, even with early prenatal diagnosis, a recent meta-analysis has shown that intra-uterine fetal death is still 7-fold higher (4.48%) compared to the general population (0.62%).[1] Neonatal survival and quality of life of children born with gastroschisis are often expressed as excellent, however, numbers differ widely between studies. This quantitative wide range might be the result of different treatment strategies, or caused by the fact that most studies have included gastroschisis cases with additional extra-intestinal congenital abnormalities.[2] The incidence of associated anomalies in gastroschisis varies from 5 to over 20% between studies.[3,4] Reported associations include cardiac abnormalities and increased prevalence of central nervous system anomalies (amyoplasia), limb and kidney anomalies[5-7] and may influence the prognosis of the child with gastroschisis significantly.[8]

With this study we aimed to determine the outcome of children born with isolated gastroschisis in order to give the prognosis of solely the entity gastroschisis in a cohort of 204 cases and to systematically review the literature to compare our findings with studies describing isolated gastroschisis cases born in other Western countries. Our primary objective was to investigate the time to full enteral feedings (TFEF) in isolated cases of gastroschisis, since this reflects the condition of the child and its bowel, and secondarily to investigate length of mechanical ventilation, length of hospital stay (LOS) and mortality. In addition, we investigated the difference between simple and complex gastroschisis (additional atresia, volvulus, perforation or necrosis of the bowel at birth)[9] on outcome measurements. It was our goal to provide future parents and clinicians with more quantitative data regarding outcome of their child with isolated gastroschisis.

METHODS

Retrospective study

We conducted a cohort study of all live born gastroschisis cases, treated between January 2002 and January 2010 in six university hospitals in the Netherlands ('Netherlands') (Academic Medical Center Amsterdam, Maastricht University Medical Center+, Radboud University Medical Center Nijmegen, VU University Medical Center Amsterdam, University Medical Center Groningen, University Medical Center Utrecht) or born and treated at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo ('Brazil'), between August 2009 and January 2015.

All women suspected of being pregnant of a fetus with gastroschisis were referred to a university hospital for advanced ultrasound evaluation. If the diagnosis was confirmed, delivery was planned to

take place in one of the centres with a paediatric surgery department. If gastroschisis was diagnosed postnatally, the neonate was immediately transferred to one of these paediatric surgery centres. During the study period in the Netherlands there was no uniform policy regarding elective delivery and Caesarean delivery was only performed for obstetric reasons, such as fetal distress or failure to progress in labor. In Brazil an elective Caesarean delivery was planned in all women at 37 weeks of gestation. Signs of fetal distress, such as meconium stained amniotic fluid with premature rupture of membranes, or abnormal CTG were reasons to expedite the Caesarean delivery.

In all paediatric surgery centres a primary operative abdominal wall repair of gastroschisis was attempted in all cases based on the condition of the child, the exteriorized viscera volume and the judgment of the surgeon, neonatologist and anaesthetist. If the viscera could not be reduced primarily, a silo bag, either performed or created of a SILASTIC® sheet, was placed.[10] In case of silo placement, mechanical ventilation was continued if indicated and elective closure of the abdominal wall was planned in the subsequent days.

Hospital charts were reviewed for maternal, perinatal and neonatal characteristics. Isolated gastroschisis cases, according to the definition of Mastroiacovo et al.[5], were included. We categorised gastroschisis cases as simple or complex based on the gastrointestinal tract condition at birth. Atresia, antenatal volvulus, perforation or necrosis of the bowel was defined as complex gastroschisis.[9,11] Abdominal compartment syndrome, postnatal necrotizing enterocolitis (NEC) or volvulus were considered to be complications initiated by external factors and were therefore not labeled as complex. The primary outcome measurement was TFEF expressed in days i.e. the complete cessation of total parenteral nutrition (TPN). This primary endpoint was chosen since it reflects both the condition of the bowel as the general health of the child. Secondary outcome measurements were bowel complications, repeated operations after initial closure operation, non-gastrointestinal tract complications, length of mechanical ventilation, LOS and neonatal mortality. Due to the retrospective design not all data were available. If patients were transferred to regional hospitals efforts were made to extract the date of TFEF and date of discharge to home. If these data were not available the discharge date from the regional hospital or the tertiary centre was used.

The study protocol was reviewed and approved by the Medical Research Ethics Committee of University Medical Center Utrecht (no: 13-151/K).

Systematic review

In addition, we performed a systematic search (date: April 22th 2016), to compare our literature with the following study questions: What is the average TFEF in children born with gastroschisis? What is the average duration of ventilation, LOS and mortality rate in children born with gastroschisis? Is there a difference in these outcome parameters between simple and complex gastroschisis?

Literature search

We conducted an electronic literature search in three databases (Medline, Embase and the Cochrane library) to identify all articles addressing solely the keywords (gastroschisis) OR (laparoschisis). A period of 01-01-1990 to date was covered by the search, no other limits were used in the search. The statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[12] was followed as far as applicable. The nature of the studies was likely to make adherence to this protocol difficult, since we did not make a comparison between predefined groups but investigated outcome.

Study selection

Abstracts were reviewed and excluded based on; non-human subjects, non-original articles, studies from non-Western countries, cases born prior to 1990. The remaining studies were selected for full text review leading to further exclusion of articles that did not reported the TFEF or length of complete discontinuation of TPN, studies including non-isolated cases of gastroschisis, according to the definition of Mastroiacovo et al.[5], studies not describing variance (standard deviation (SD), Interquartile range (IQR), or range) in addition to the mean or median TFEF, studies with experimental treatments (e.g. amnio-exchange[13]), elective preterm delivery or change of treatment strategies during the study period. Case series with <20 cases, irrespective whether the anomalies were isolated, were also excluded to avoid publication bias. Mode of delivery and type of defect closure were no selection criteria. If more studies were published from the same or overlapping cohorts only the article with the most comprehensive information, reporting TFEF, was included.

All articles were considered for inclusion by three reviewers (CL, LP, GM) and disagreement was settled by consensus between four reviewers (CL, LP, GM, WK).

The data of our retrospective study was also included in the meta-analysis.

Data extraction

The following data were extracted and summarized in a descriptive table: study period, year of publication, mean gestational age at delivery, mean birth weight at delivery, percentage of Caesarean section (CS), percentage of complex gastroschisis cases and percentage of staged closure. Outcome measurements TFEF, ventilation duration, LOS expressed in days and postnatal mortality were described in outcome tables. We contacted the authors of articles describing TFEF for more information on categorization in simple or complex cases where appropriate.

Quality assessment:

Two reviewers (CL, WK) independently assessed the methodological quality of the studies using an adapted version of the quality criteria scoring list of Hayden; Quality in Prognostic Studies (QUIPS).[14] Two of the six original domains, measurement of prognostic factors and study attritions were be-

yond the scope of our review and were therefore removed. This left four important domains namely; study participation, outcome measurement, study confounding and statistical presentation. The risk of bias per domain was scored as low (2 points) moderate (1 point) or high (0 points). This resulted in a total ranking score per study from very poor quality (0 points) to excellent quality (8 points).

Statistical analysis

Retrospective study

We performed a comparative analysis between our gastroschisis study population and the general population. Differences in simple and complex cases were compared. The Mann-Whitney U test and t -test were used for continuous data and Chi-square test or Fisher's exact tests for categorical data were appropriate. P values of <0.05 were considered statistically significant.

Systematic review and meta-analysis

Continuous data were often presented in medians with (Inter Quartile) ranges due to suspicion of skewed data. However, for inclusion in a meta-analysis mean and SD are needed. Therefore, the authors were contacted. If they did not respond upon repeated requests we calculated the estimated means and corresponding SD assuming that the data had a log normal distribution. If the data were given in means or medians of multiple groups the estimated combined total mean and corresponding SD were calculated.

First, we compared the overall outcome of gastroschisis between studies. Odds were reported for the postnatal mortality data. The mean with SD was calculated for continuous data. Pooled estimates of odds and mean were computed using generic inverse variance weighting and a random-effects model. Interstudy heterogeneity was expressed as I^2. A forest plot was created to illustrate the TFEF, length of ventilation duration, LOS of each study, with 95%-confidence intervals (95%-CI). Secondly, the outcome of simple gastroschisis was compared with complex gastroschisis. Again a random effect model was used. Risk Ratio with 95%-CI was reported for mortality. The mean difference was calculated for TFEF, ventilation duration and LOS.

A P value <0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS v23.0, SPSS Inc., Chicago, IL, USA) and the Meta-analytic software Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Gastroschisis cohort of the Netherlands and Brazil

A total of 204 live born cases of isolated gastroschisis were identified. The characteristics of the cases treated in the Netherlands and in Brazil are presented and compared in Table 1. The gestational age and subsequent birth weight of cases treated in Brazil was significantly lower compared to cases treated in the Netherlands. However, the percentage of cases born with a birth weight <10 percentile was comparable between both groups (31.4% versus 38.2%, P=0.38). As expected, the CS rate was higher in Brazil compared to the Netherlands (94.1% versus 35.3% (P<0.0001)). The primary outcome, TFEF, as well as LOS and mortality did not differ between the two study populations (Table 1). However, the percentage of primary closure was higher in Brazil as was the incidence of sepsis. The length of mechanical ventilation was longer in the Netherlands.

In the complete gastroschisis cohort (the Netherlands and Brazil together) simple gastroschisis cases were compared to the complex gastroschisis cases (Table 2). The mean gestational age and mean birth weight of children born with complex gastroschisis was significant lower compared to simple cases. The incidence of small-for-gestational age (birth weight <p10) was comparable between both groups. The percentage of CS, Apgar Score <7 at 5 minutes and primary closure was comparable between both groups (Table 2).

The TFEF, median length of ventilation and LOS was, 26 days (range 6-515), 2 days (range 0-90) and 33 days (range 11-515), respectively, for both groups together. TFEF and LOS were significantly longer in the complex group (P<0.0001) (Table 2). Mortality occurred in 13 out of 174 patients (7.5%) of the simple group compared to 9 out of 30 (30.0%) patients of the complex group (P=0.001). Seventeen out of twenty-two (77.3%) deceased patients were born after 35 weeks of gestation (median 35.9 range 31.7-38.0 weeks). Nine (40.9%) patients had a birth weight <10^{th} percentile. Causes of death were sepsis with multi-organ failure (n=16), infectious respiratory insufficiency by progression of infection of the respiratory tract (n=2), respiratory failure due to severe edema (n=1), necrosis of the complete small intestine in silo (n=1) and operative hemorrhage with hypovolemic shock (n=1). One patient died at 133 days of life of multi-organ failure caused by anastomotic leaking and sepsis after repeated operations for bowel atresia, stenosis and adhesions. Complex cases had more repeated surgeries and were more likely to develop non-gastrointestinal tract complications.

Table 1. Comparison of isolated gastroschisis cases from 'Netherlands' and 'Brazil'

	Total Netherlands			Total Brazil			P
	N	n		N	n		
GA at birth (wk)	102	-	36.7 ±1.8	102	-	36.1 ±1.4	0.002
Caesarean section	102	36	(35.3 %)	102	96	(94.1 %)	<0.0001
Birth weight (g)	102	-	2508 ± 491	102	-	2322 ± 498	0.008
Birth weight <p10¥	102	32	(31.4 %)	102	39	(38.2 %)	0.38
Male gender	102	59	(57.8 %)	102	53	(52.0 %)	0.48
Apgar at 5 min <7	101	7	(6.9 %)	102	2	(2.0 %)	0.10
Primary closure	102	64	(62.7 %)	102	81	(79 %)	0.01
Complex gastroschisis	102	11	(10.8 %)	102	19	(18.6 %)	0.17
Bowel complication(s)							
Atresia	102	6	(5.9 %)	102	6	(5.9 %)	1.00
Antenatal volvulus	102	2	(2.0 %)	102	0	(0.0 %)	-
Necrosis	102	11	(10.9 %)	102	9	(9.0 %)	0.81
Perforation	102	9	(8.8 %)	102	8	(7.8 %)	1.00
Abd. Comp. Syndr.	102	3	(2.9 %)	102	1	(1.0 %)	0.62
Postnatal Volvulus	102	2	(2.0 %)	102	0	(0.0 %)	-
Obstructive adhesion	102	11	(10.9 %)	102	10	(9.8 %)	1.00
NEC	102	2	(2.0 %)	102	4	(3.9 %)	0.68
Non bowel complications							
(Line) Sepsis	102	47	(46.1 %)	102	63	(61.8 %)	0.03
Respiratory distress	102	14	(13.7 %)	102	11	(10.8 %)	0.67
TFEF (d)€	93	-	25 (6-484)	89	-	27 (12-515)*	0.754
Ventilation (d)€	88	-	3 (0-90)	89	-	1 (0-30)	<0.0001
Hospital stay (LOS)(d)€	93	-	32 (11-349)	89	-	33 (11-515)	0.498
Mortality	102	9	(8.8 %)	102	13	(12.7 %)	0.50

GA, gestational age; LOS, length of hospital stay; TFEF, time to full enteral feedings; Mean (SD) or Median (Range) / number (%), d (days)

¥, the Dutch reverence curves[46] were used for the cases of the Netherlands and the Brazilian reverence curves were used for the Brazilian cases[47]

*, one case still on total parenteral nutrition

€, data of surviving cases, for two cases the TFEF is unknown therefore the number of days to hospital discharge was used for two other cases the number of days to hospital discharge was unknown, therefore the number of days to transfer to a peripheral hospital was used.

Table 2. Comparison of simple and complex gastroschisis cases (Netherlands and Brazil)

	Simple gastroschisis (n =174)			Complex gastroschisis (n =30)			P
	N	n		N	n		
GA at birth (wk)	174	-	36.6 ± 0.4	30	-	35.4 ± 2.3	0.0001
Caesarean section	174	112	(64.3 %)	30	20	(66.7 %)	1.00
Birth weight (g)	174	-	2450 ± 484	30	-	2213 ± 565	0.02
Birth weight <p10	174	64	(36.8 %)	30	7	(23.3 %)	0.21
Male gender	174	99	(56.9 %)	30	13	(43.3 %)	0.23
Apgar at 5 min <7	173	7	(4.0 %)	30	2	(6.7 %)	0.62
Primary closure	173	124	(71.3 %)	30	21	(70 %)	0.83
Repeated surgery after	173	24	(13.8 %)	30	22	(73.3 %)	<0.0001
closure	173	10	(5.8 %)	30	15	(50.0 %)	<0.0001
No of surgeries 1	173	8	(4.6 %)	30	3	(10 %)	0.21
2	173	6	(3.5 %)	30	4	(13.3 %)	0.04
≥3							
(Line) Sepsis	174	58	(33.3 %)	30	21	(70.0 %)	0.0002
Respiratory distress	174	17	(9.8 %)	30	8	(26.7 %)	0.02
TFEF (d)€	161	-	25 (6-142)	21	-	71 (19-515)*	<0.0001
Ventilation (d)€	156	-	2.00 (0-90)	21	-	6.00 (0-45)	0.15
Hospital stay (LOS)(d)€	161	-	32.0 (11-187)	21	-	84 (21-515)	<0.0001
Mortality	174	13	(7.5 %)	30	9	(30.0 %)	0.001

GA, gestational age; NEC, necrotic enterocolitis; NICU, neonatal intensive care unit; LOS, length of hospital stay; TFEF, time to full enteral feedings; Mean (SD) or Median (Range) / number (%), d (days)

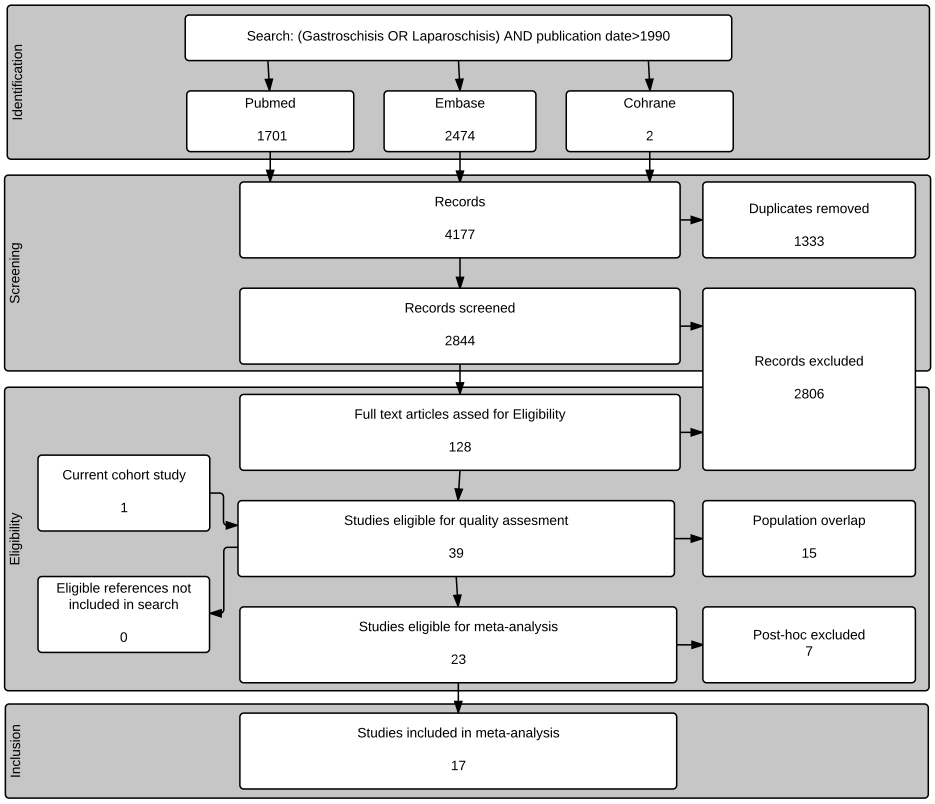
*, one case still on total parenteral nutrition

¥, the Dutch reverence curves[46] were used for the cases of the Netherlands and the Brazilian reverence curves were used for the Brazilian cases[47]

€, data of surviving cases; for two cases the TFEF is unknown therefore the number of days to hospital discharge was used. For two other cases the number of days to hospital discharge was unknown, therefore the number of days to transfer to a peripheral hospital was used.

Systematic review

Our search strategy yielded 4096 articles (Flowchart 1). There were 38 eligible studies. All but one had a retrospective design.[15] Fifteen studies used an overlapping population and were excluded. We excluded another 7 studies post-hoc since the mean TFEF and LOS included data of patients that died during the hospitalisation.[16-22] This left 16 studies for further analysis in addition to the current cohort study, comprising a total of 1652 patients that met the inclusion criteria. After contacting the authors to retrieve additional information on simple and complex cases, in nine studies, cases were differentiated into simple and complex according to the definition that we used in the current



Flowchart 1. Search strategy meta-analysis

study.[23-29] The outcomes of simple as compared to complex cases were only described (or additionally supplied by the author) in five studies, including the current one.[24,26,28,30]

Risk of bias among included studies

The methodical quality scores of the included studies are reported in Table 3. The majority of bias was the lack of reporting all potential confounders. Baseline characteristics of the study populations are given in Table 3. Primary CS was standard care in the Brazilian part of the current study and in three other studies, resulting in high CS rates.[26,28,31] Staged closure was the preferred treatment method in two studies.[27,32] resulting in a high incidence of staged closure in those studies. If we exclude these studies, the percentage of CSs and staged closure were 50.4% and 32.2%, respectively. Complex cases were found in 15.8% of cases.

Table 3. Included studies in the meta-analysis

Study	Period	Cases	Complex gs	GA at birth	Birth weight	CS	Staged closure	QUIPS score
		N	n (%)	Mean ± SD	mean± SD	n (%)	n (%)	
Aina-Mumuney et al. 2004[22]	1992-2002	34	10 (29.4)	35.9±2[&]	2501±487[&]	11 (32.4)	13 (38.2)	7
Ajayi et al. 2011[43]	2000-2008	74	NA	35.3±2.2[##]	2499±618[##]	30/72 (41.7)	35 (47.3)	8
Balgi et al. 2015[31]	jan 2000- jun 2013	52	NA	36.1±2.7**	2553±913**	34 (65.4)	44 (84.6)	8
Dimitriou et al. 2000[24]	1993-1998	32	5 (15.6)	37.1±2.1**	2260±574**	10 (31.3)	7 (21.9)	8
Emil et al. 2012[23]	jan 2001-mar 2007	83	19 (22.9)	36.2±0.5	2557±101	NA	NA	8
Frybova et el. 2015[29]	2004-2013	64	6 (9.3)	35.9±2	2270±464	30 (46.9)	13 (20.3)	8
Garcia et al. 2010[25]	jan 1997-aug 2009	89	8 (9.0)	36.5±1.4	2441±432	88 (98.9)	17 (19.1)	8
Goetzinger et al. 2013[28]	2001-2010	94	18 (19.1)	36.1±1.8	2437±594[&]	NA	NA	7
Huang et al. 2002[44]	1991-2001	57	NA	36.5±2[$]	NA	14 (24.6)	33 (57.9)	6
Huh et al. 2010[26]	2002-2008	43	8 (18.6)	35.4±2.2	2433±542	8 (18.6)	40 (93.0)	7
Jansen et al. 2012[45]	May 2005-May 2009	407	NA	36.2±2.0	2562±539	133 (32.7)	NA	7
Kuleva et al. 2012[27]	1999-2010	103	14 (13.6)	35.7±1.5[##]	2337±508[##]	100 (97.1)	28 (27.2)	8
Logghe et al. 2005, subgroup[¥14]	May 1995-Sep 1999	20	NA	36.7±1.5	2338±516	9 (45.0)	4 (20.0)	8
Murphy et al. 2007 [46]	1998-2004	53	NA	37.6±2.7[@]	2516±597[@]	26/51 (51.0)	9 (17.0)	6
Stuber et al. 2015[30]	1998-2011	23	NA	34.8 ±1.5	2391±357	23 (100)	3 (13.0)	8
Yang et al. 2014[47]	1990-2008	219	NA	36.6±1.4***	2532±539***	71 (32.4)	102 (46.6)	7
Current study (Netherlands and Brazil)	*2002-2010*	*204*	*30(14.7)*	*36.3±11.7*	*2508±491*	*36 (35.3)*	*38(37.3)*	*8*
	Aug 2009-Jan 2015							
Total		**1652**	**15.8 %**	**36.2±4.5**	**2478±538**	**63.8 %**	**37.2 %**	
I^2			**67 %**	**84 %**	**79 %**	**89 %**	**86 %**	

Gs, gastroschisis; GA, gestational age; NA; not available, QUIPS, adapted version of the quality criteria scoring list of Hayden; Quality in Prognostic Studies[14]; (very poor quality (0 points) to excellent quality (8 points)

$, estimated from 3 groups with given mean and SD

&, estimated from 2 groups with given mean and SD

@, estimated from 2 groups with given median and ranges

##, estimated from 2 groups with given median and IQR

**, estimated by log mean from given median and range

***, estimated by loge mean from given median and IQR

¥, sub group of randomized controlled trial; subgroup await the onset of spontaneous labor

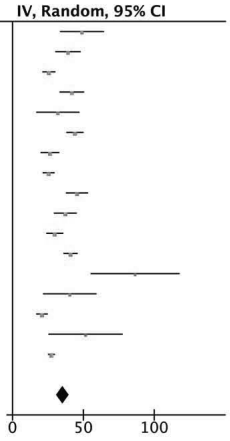
Outcome systematic review:

Length of ventilation, TFEF and LOS are shown in Figure 1ABC. The mean TFEF was 35.3 ± 4.4 days, length of ventilation was 5.5 ± 2.0 days and the mean LOS was 46.4 ± 5.2 days. The odds of postnatal mortality were 0.06 (0.04-0.08 95%-CI) corresponding with a risk 0.06 (0.04-0.07 95%-CI). The smallest study (n=20) of the meta-analysis reported a mortality of 0% in their case series.[15] Results of this study could therefore not be included in further meta-analysis statistics. The data of our study were all within the range of the reviewed studies (Fig.1). The TFEF, ventilation time and length of hospital

1A Time to full enteral feedings (days)

Study or Subgroup	Mean	SD	Total	Weight	Mean IV, Random, 95% CI
Aina-Mumuney et al. 2004 (1)	49	43	31	4.1%	49.00 [33.86, 64.14]
Ajayi et al. 2011 (2)	39.15	37.3	73	6.2%	39.15 [30.59, 47.71]
Balgi et al. 2015 (3)	25.65	15.4	52	7.5%	25.65 [21.46, 29.84]
Current study	41.85	56.8	182	6.3%	41.85 [33.60, 50.10]
Dimitriou et al. 2000 (3)	32	40	28	4.2%	32.00 [17.18, 46.82]
Emil et al. 2012 (4)	44.05	25.7	80	7.1%	44.05 [38.42, 49.68]
Frybova et al. 2015 (5)	26.4	24.6	61	6.9%	26.40 [20.23, 32.57]
Garcia et al. 2010 (5)	25.5	17.3	80	7.6%	25.50 [21.71, 29.29]
Goetzinger et al. 2013 (2)	45.46	36	91	6.6%	45.46 [38.06, 52.86]
Huang et al. 2002 (6)	37.3	29	55	6.5%	37.30 [29.64, 44.96]
Huh et al. 2010	29.8	18.3	41	7.1%	29.80 [24.20, 35.40]
Jansen et al. 2012	41	44.6	362	7.4%	41.00 [36.41, 45.59]
Kuleva et al. 2012	86.5	159	101	1.6%	86.50 [55.49, 117.51]
Logghe et al. subgroup 2005 (3)	40.4	42.2	20	3.3%	40.40 [21.91, 58.89]
Murphy et al. 2007 (4)	20.79	13.2	51	7.6%	20.79 [17.17, 24.41]
Stuber et al. 2015 (1)	51.57	60.3	21	2.1%	51.57 [25.78, 77.36]
Yang et al. 2014 (7)	27.48	15	200	7.9%	27.48 [25.40, 29.56]
Total (95% CI)			**1529**	**100.0%**	**35.33 [30.96, 39.69]**

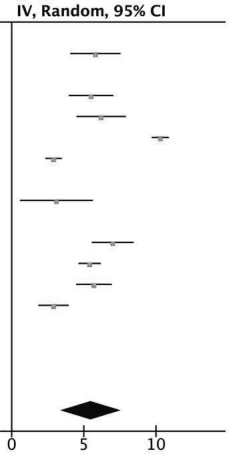
Heterogeneity: $Tau^2 = 61.47$; $Chi^2 = 142.61$, df = 16 ($P < 0.00001$); $I^2 = 89\%$
Test for overall effect: $Z = 15.86$ ($P < 0.00001$)



1B Duratin of ventilation (days)

Study or Subgroup	Experimental Mean	SD	Total	Weight	Mean IV, Random, 95% CI
Aina-Mumuney et al. 2004	0	0	0		Not estimable
Ajayi et al. 2011 (2)	5.8	7.4	73	9.8%	5.80 [4.10, 7.50]
Balgi et al. 2015	0	0	0		Not estimable
Current study	5.5	10.2	177	9.9%	5.50 [4.00, 7.00]
Dimitriou et al. 2000 (3)	6.2	4.5	28	9.8%	6.20 [4.53, 7.87]
Emil et al. 2012 (4)	10.3	2.5	80	10.4%	10.30 [9.75, 10.85]
Frybova et al. 2015 (5)	2.9	2.1	61	10.4%	2.90 [2.37, 3.43]
Garcia et al. 2010 (5)	0	0	0		Not estimable
Goetzinger et al. 2013 (2)	3.1	12.1	91	9.1%	3.10 [0.61, 5.59]
Huang et al. 2002	0	0	0		Not estimable
Huh et al. 2010	7	4.6	41	10.0%	7.00 [5.59, 8.41]
Jansen et al. 2012	5.4	7.1	362	10.3%	5.40 [4.67, 6.13]
Kuleva et al. 2012 (7)	5.7	6.1	101	10.1%	5.70 [4.51, 6.89]
Logghe et al. subgroup 2005 (3)	2.9	2.3	20	10.2%	2.90 [1.89, 3.91]
Murphy et al. 2007 (4)	0	0	0		Not estimable
Stuber et al. 2015 (1)	0	0	0		Not estimable
Yang et al. 2014	0	0	0		Not estimable
Total (95% CI)			**1034**	**100.0%**	**5.50 [3.43, 7.58]**

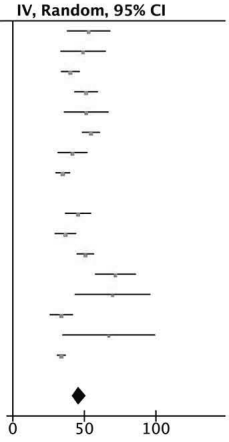
Heterogeneity: $Tau^2 = 10.71$; $Chi^2 = 415.85$, df = 9 ($P < 0.00001$); $I^2 = 98\%$
Test for overall effect: $Z = 5.20$ ($P < 0.00001$)



1C Length of stay (days)

Study or Subgroup	Mean	SD	Total	Weight	Mean IV, Random, 95% CI
Aina-Mumuney et al. 2004 (1)	53	42	31	5.1%	53.00 [38.22, 67.78]
Ajayi et al. 2011 (2)	49.1	67.4	73	4.9%	49.10 [33.64, 64.56]
Balgi et al. 2015 (3)	40.2	22.8	52	7.7%	40.20 [34.00, 46.40]
Current study	51.2	54.2	182	7.2%	51.20 [43.33, 59.07]
Dimitriou et al. 2000 (3)	51.3	41.2	28	4.9%	51.30 [36.04, 66.56]
Emil et al. 2012 (4)	54.6	27	80	7.8%	54.60 [48.68, 60.52]
Frybova et al. 2015 (5)	41.7	40	61	6.5%	41.70 [31.66, 51.74]
Garcia et al. 2010 (5)	34.9	22	84	8.1%	34.90 [30.20, 39.60]
Goetzinger et al. 2013 (2)	0	0	0		Not estimable
Huang et al. 2002 (6)	45.6	33	55	6.9%	45.60 [36.88, 54.32]
Huh et al. 2010	36.8	23.2	41	7.4%	36.80 [29.70, 43.90]
Jansen et al. 2012	50.7	55.3	362	7.8%	50.70 [45.00, 56.40]
Kuleva et al. 2012 (7)	71.7	71.1	101	5.3%	71.70 [57.83, 85.57]
Logghe et al. subgroup 2005 (3)	69.7	59.4	20	2.7%	69.70 [43.67, 95.73]
Murphy et al. 2007 (4)	33.9	28.3	51	7.2%	33.90 [26.13, 41.67]
Stuber et al. 2015 (1)	67	75	21	2.0%	67.00 [34.92, 99.08]
Yang et al. 2014 (8)	33.9	20	213	8.4%	33.90 [31.21, 36.59]
Total (95% CI)			**1455**	**100.0%**	**46.39 [41.20, 51.58]**

Heterogeneity: $Tau^2 = 81.31$; $Chi^2 = 107.82$, df = 15 ($P < 0.00001$); $I^2 = 86\%$
Test for overall effect: $Z = 17.52$ ($P < 0.00001$)



1D Mortality

Study or Subgroup	Events	Total	Weight	Odds Random, 95% CI
Aina-Mumuney et al. 2004	4	34	0.7%	0.13 [0.05, 0.38]
Ajayi et al. 2011	1	74	12.2%	0.01 [0.00, 0.10]
Balgi et al. 2015	1	53	6.3%	0.02 [0.00, 0.14]
Current study	22	204	4.6%	0.12 [0.08, 0.19]
Dimitriou et al. 2000	4	32	0.6%	0.14 [0.05, 0.41]
Emil et al. 2012	3	83	5.2%	0.04 [0.01, 0.12]
Frybova et al. 2015	3	64	3.1%	0.05 [0.02, 0.16]
Garcia et al. 2010	5	89	3.7%	0.06 [0.02, 0.15]
Goetzinger et al. 2013	3	94	6.7%	0.03 [0.01, 0.10]
Huang et al. 2002	2	57	3.7%	0.04 [0.01, 0.15]
Huh et al. 2010	2	43	2.1%	0.05 [0.01, 0.20]
Jansen et al. 2012	25	407	15.5%	0.07 [0.04, 0.10]
Kuleva et al. 2012	2	103	11.8%	0.02 [0.00, 0.08]
Logghe et al. subgroup 2005	0	20	2.0%	Not estimable
Murphy et al. 2007	2	53	3.2%	0.04 [0.01, 0.16]
Stuber et al. 2015	2	23	0.6%	0.10 [0.02, 0.41]
Yang et al. 2014	6	219	18.0%	0.03 [0.01, 0.06]
Total (95% CI)		**1652**	**100.0%**	**0.06 [0.04, 0.08]**
Total events	87			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 16 ($P = 1.00$); $I^2 = 0\%$
Test for overall effect: $Z = 0.00$ ($P = 1.00$)

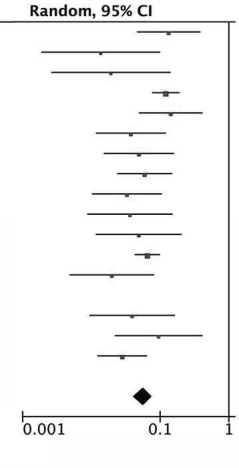


Figure 1ABCD. Meta-analysis outcome isolated gastroschisis

1A - Time to full enteral feedings (TFEF) expressed in days,
1B - Length of ventilation expressed in days,
1C - Length of hospital stay (LOS) expressed in days,
1D - Mortality
(1) Estimated from given mean and SD of 2 groups
(2) Estimated from given median and IQR of 2 groups
(3) Estimated from given median and range of 1 group
(4) Estimated from given median and range of 2 groups
(5) Given upon request by the author
(6) Estimated from given median and SD of 3 groups
(7) Estimated by given median and IQR of 8 groups
(8) Estimated by given median and IQR of 1 group

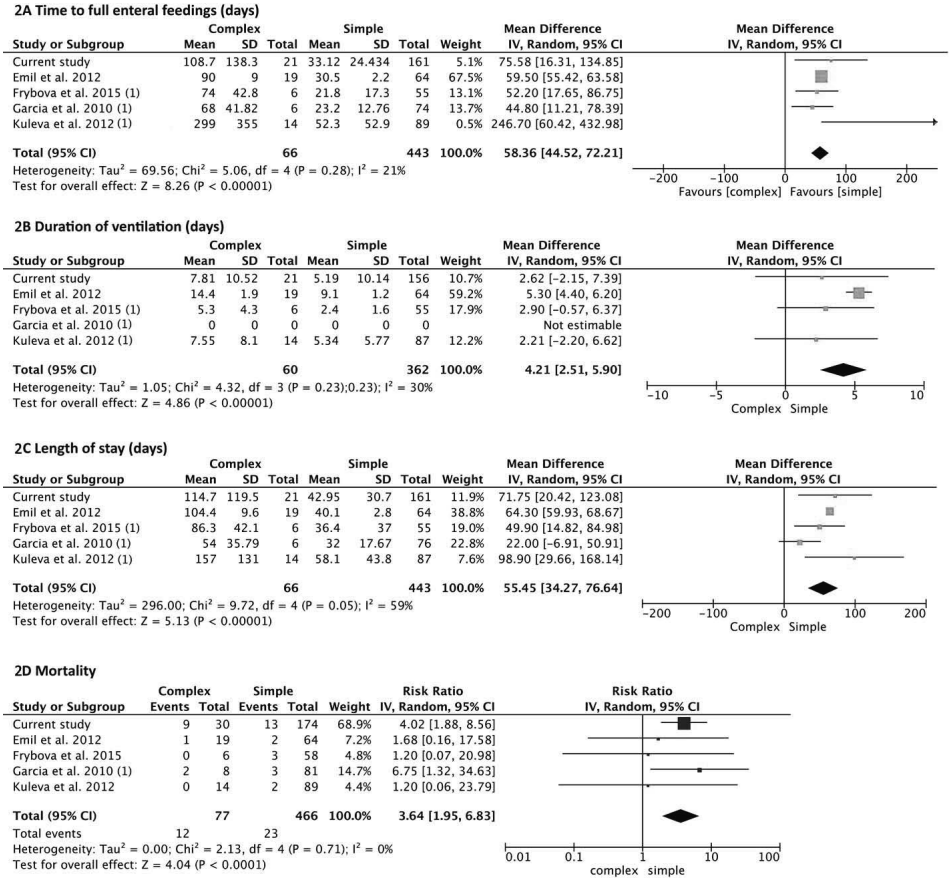


Figure 2 ABCD. Meta-analysis complex versus simple isolated gastroschisis

2A - Time to full enteral feedings (TFEF) expressed in days,

2B - Length of ventilation expressed in days,

2C - Length of hospital stay (LOS) expressed in days,

2D - mortality

(1) not described in the article, given upon request

stay and was significant longer for complex cases as compared to simple gastroschisis cases. Patients with complex gastroschisis had a 3.64 (1.95 – 6.83 95%-CI) times higher mortality rate (Fig. 2ABCD).

DISCUSSION

This study is the first meta-analysis on outcome of *isolated* gastroschisis cases, providing quantitative outcome measures which can be used for counselling future parents. The average TFEF, length of ventilation, LOS and mortality of the current study were in line with the studies from the systematic review and can be used for the counselling of parents. This study also confirms that children with a simple gastroschisis have a better outcome compared to children with a complex gastroschisis.

The international study was formed by the gastroschisis cases from cohorts of different countries with a difference in time and mode of delivery for gastroschisis. There was no difference in primary outcome (TFEF), although sepsis percentage was higher in Brazil and duration of mechanical ventilation was longer in the Netherlands. Interestingly to note that TFEF, LOS and mortality were comparable suggesting that time and route of delivery did not influence outcome. This is in line with findings of previous studies.[15,33,34] In the systematic review, mode and timing of delivery was not always described. We were therefore unable to draw conclusions on these differences in obstetric management.

In the systematic review there was a wide range of outcomes within studies in line with their heterogeneity, reflected in the high values of I^2. The pooled estimates by the random effect models should therefore be interpreted as the average effect over studies instead of a universally valid single effect. An explanation of this heterogeneity can be found in the distribution of outcome data of the relatively small sample sizes. However, our data showed that there were only a few outliers and that most cases were clustered together.

Most outcome data were given in median and (Inter Quartile) Range. Although scientifically correct, these data could not be used in the meta-analysis and estimated means and corresponding SD were calculated using the log-transformed data. The method of Hozo et al.[35] has also been used in meta-analyses to calculate mean and SD from median and range.[2] However, this method is based on the assumption that the given data are normally distributed which is most often not the case in data on duration. We therefore choose to calculate the Mean and SD using the log normal distribution. Especially in studies with a wide range, the chances due to outliers may have given a larger estimated mean and SD than the original data would give. Clinically, though, an overestimate of expected TFEF and LOS will give less disappointment to parents and professionals in personalized cases than an underestimate of these values.

To our surprise we found several studies that included TFEF and LOS of patients that died during the hospitalisation, the length of life was used as the TFEF and LOS for these cases.[19,20,36,37] This gives a distorted view of the outcome results and may be an additional cause of the variance in LOS and TFEF. Post-hoc we therefore excluded these studies from further analysis.

The occurrence of complex gastroschisis changes outcome drastically. In the current study complex gastroschisis cases had a longer TFEF, ventilation time, longer hospitalisation higher mortality compared to simple cases.

The other studies in which outcome of complex cases were described separately also showed increased TFEF and hospitalisation and pooled results including the current study showed a 3.6-fold increase of mortality. There is one other meta-analysis in which the outcome of simple and complex gastroschisis cases has been compared.[2] That meta-analysis included gastroschisis cases with additional congenital disorders such as cardiac abnormalities. Complex gastroschisis cases present more often with additional congenital disorders[38] and these additional disorders may influence the LOS, TFEF and risk of mortality drastically.[8] In our meta-analysis we have chosen to include only studies with isolated cases. In addition, Bergholz et al.[2] presented only the mean differences of TFEF and LOS between complex and simple cases, whereas the actual duration of both entities is important in counselling with respect to prognosis.

Early elective preterm delivery (before 37 weeks of gestation) has been suggested to protect the exteriorised bowel from severe damage due to exposure to amniotic fluid and compression. However, studies yield conflicting results.[39-44] Morbidity due to intrauterine bowel damage must outweigh morbidity caused by prematurity. Since only 15.8% of the gastroschisis patients are born with severe bowel damage (complex gastroschisis), elective preterm delivery of all gastroschisis cases could cause unnecessary morbidity due to prematurity. Complex gastroschisis may benefit from a different obstetric management with close fetal surveillance and even preterm delivery in order to protect the bowel from severe damage caused by venous compression, (partial) ischemia and chronic inflammation.[41,43] However, identifying complex gastroschisis cases prenatally remains a challenge. A recently published systematic review on the association between prenatal ultrasound signs and perinatal outcome in gastroschisis found three antenatal ultrasound findings (intra-abdominal bowel dilatation, polyhydamnios, gastric dilatation) that were associated with an increased risk of bowel atresia and neonatal death.[45] However, the results were based on retrospective small studies using different ultrasound measure cut-off values. The authors of the systematic review plead for prospective standardised studies.

Our study group has therefore started the prospective FLAMINGO-study (FetaL Abdominal Markers to Identify Neonatal Gastroschisis Outcome-study). This is an observational international multicentre study with a standardised perinatal protocol on fetal ultrasound, CTG surveillance and obstetric management in order to identify antenatal markers to predict neonatal outcome and to improve the counselling of future parents.

CONCLUSION

This international cohort study and systematic review focused on isolated gastroschisis outcome regarding, TFEF, ventilation duration, LOS and mortality. Although there was a wide range in outcome, these quantitative data may provide future parents and clinicians a better indication of the expected prognosis. This study also shows the importance of classification of cases into simple and complex cases for the prediction of outcome.

REFERENCES

1. South AP, Stutey KM, Meinzen-Derr J. Meta-analysis of the prevalence of intrauterine fetal demise in gastroschisis. *Am J Obstet Gynecol*. 2013;2(209):114e1--13. 10.1016/j.ajog.2013.04.032; 10.1016/j.ajog.2013.04.032.
2. Bergholz R, Boettcher M, Reinshagen K, Wenke K. Complex gastroschisis is a different entity to simple gastroschisis affecting morbidity and mortality-a systematic review and meta-analysis. *J Pediatr Surg*. 2014;49(10):1527-1532. 10.1016/j.jpedsurg.2014.08.001 [doi].
3. Rankin J, Dillon E, Wright C. Congenital anterior abdominal wall defects in the north of England, 1986-1996: Occurrence and outcome. *Prenat Diagn*. 1999;19(7):662-668.
4. Calzolari E, Bianchi F, Dolk H, Milan M. Omphalocele and gastroschisis in Europe: A survey of 3 million births 1980-1990. EUROCAT working group. *Am J Med Genet*. 1995;58(2):187-194. 10.1002/ajmg.1320580218.
5. Mastroiacovo P, Lisi A, Castilla EE, Martinez-Frias ML, Bermejo E, Marengo L, Kucik J, Siffel C, Halliday J, Gatt M, Anneren G, Bianchi F, Canessa MA, Danderfer R, de Walle H, Harris J, Li Z, Lowry RB, McDonell R, Merlob P, Metneki J, Mutchinick O, Robert-Gnansia E, Scarano G, Sipek A, Potzsch S, Szabova E, Yevtushok L. Gastroschisis and associated defects: An international study. *Am J Med Genet A*. 2007;143(7):660-671. 10.1002/ajmg.a.31607.
6. Stoll C, Alembik Y, Dott B, Roth MP. Omphalocele and gastroschisis and associated malformations. *Am J Med Genet A*. 2008;146A(10):1280-1285. 10.1002/ajmg.a.32297.
7. Garvin J, Sampath V, Karody VR. Gastroschisis complicated by septo-optic dysplasia: Two distinct anomalies with a common origin. *AJP Rep*. 2016;6(1):e15-7. 10.1055/s-0035-1563720 [doi].
8. Akhtar J, Skarsgard ED, Canadian Pediatric Surgery Network (CAPSNet). Associated malformations and the "hidden mortality" of gastroschisis. *J Pediatr Surg*. 2012;47(5):911-916. 10.1016/j.jpedsurg.2012.01.044.
9. Molik KA, Gingalewski CA, West KW, Rescorla FJ, Scherer LR, Engum SA, Grosfeld JL. Gastroschisis: A plea for risk categorization. *J Pediatr Surg*. 2001;36(1):51-55. 10.1053/jpsu.2001.20004.
10. Fischer JD, Chun K, Moores DC, Andrews HG. Gastroschisis: A simple technique for staged silo closure. *J Pediatr Surg*. 1995;30(8):1169-1171.
11. Abdullah F, Arnold MA, Nabaweesi R, Fischer AC, Colombani PM, Anderson KD, Lau H, Chang DC. Gastroschisis in the United States 1988-2003: Analysis and risk categorization of 4344 patients. *J Perinatol*. 2007;27(1):50-55. 10.1038/sj.jp.7211616.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ*. 2009;339:b2535. 10.1136/bmj.b2535.
13. Midrio P, Vannucchi MG, Pieri L, Alaggio R, Faussone-Pellegrini MS. Delayed development of interstitial cells of cajal in the ileum of a human case of gastroschisis. *J Cell Mol Med*. 2008;12(2):471-478. 10.1111/j.1582-4934.2008.00277.x.
14. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med*. 2006;144(6):427-437.
15. Logghe HL, Mason GC, Thornton JG, Stringer MD. A randomized controlled trial of elective preterm delivery of fetuses with gastroschisis. *J Pediatr Surg*. 2005;40(11):1726-1731. 10.1016/j.jpedsurg.2005.07.047.
16. Lobo JD, Kim AC, Davis RP, Segura BJ, Alpert H, Teitelbaum DH, Geiger JD, Mychaliska GB. No free ride? the hidden costs of delayed operative management using a spring-loaded silo for gastroschisis. *J Pediatr Surg*. 2010;45(7):1426-1432. 10.1016/j.jpedsurg.2010.02.047.
17. Driver CP, Bruce J, Bianchi A, Doig CM, Dickson AP, Bowen J. The contemporary outcome of gastroschisis. *J Pediatr Surg*. 2000;35(12):1719-1723. 10.1053/jpsu.2000.19221.

18. Villela Rodriguez J, Salinas Lopez MP, Navas R. Medical-surgical course of neonates with gastroschisis according to time, abdominal closure method and intestinal involvement: Six years of experience. *Cir Pediatr*. 2009;22(4):217-222.
19. Snyder CW, Biggio JR, Brinson P, Barnes LA, Bartle DT, Georgeson KE, Muensterer OJ. Effects of multidisciplinary prenatal care and delivery mode on gastroschisis outcomes. *J Pediatr Surg*. 2011;46(1):86-89. 10.1016/j.jpedsurg.2010.09.067.
20. Long AM, Court J, Morabito A, Gillham JC. Antenatal diagnosis of bowel dilatation in gastroschisis is predictive of poor postnatal outcome. *J Pediatr Surg*. 2011;46(6):1070-1075. 10.1016/j.jpedsurg.2011.03.033.
21. Harris J, Poirier J, Selip D, Pillai S, N Shah A, Jackson CC, Chiu B. Early closure of gastroschisis after silo placement correlates with earlier enteral feeding. *J Neonatal Surg*. 2015;4(3):28-Sep.
22. Johnston R, Haeri S. Oligohydramnios and growth restriction do not portend worse prognosis in gastroschisis pregnancies. *J Matern Fetal Neonatal Med*. 2016:1-4. 10.3109/14767058.2016.1154939 [doi].
23. Aina-Mumuney AJ, Fischer AC, Blakemore KJ, Crino JP, Costigan K, Swenson K, Chisholm CA. A dilated fetal stomach predicts a complicated postnatal course in cases of prenatally diagnosed gastroschisis. *Am J Obstet Gynecol*. 2004;190(5):1326-1330. 10.1016/j.ajog.2003.11.003.
24. Emil S, Canvasser N, Chen T, Friedrich E, Su W. Contemporary 2-year outcomes of complex gastroschisis. *J Pediatr Surg*. 2012;47(8):1521-1528. 10.1016/j.jpedsurg.2011.12.023; 10.1016/j.jpedsurg.2011.12.023.
25. Dimitriou G, Greenough A, Mantagos JS, Davenport M, Nicolaides KH. Morbidity in infants with antenatally-diagnosed anterior abdominal wall defects. *Pediatr Surg Int*. 2000;16(5-6):404-407.
26. Garcia L, Brizot M, Liao A, Silva MM, Tannuri AC, Zugaib M. Bowel dilation as a predictor of adverse outcome in isolated fetal gastroschisis. *Prenat Diagn*. 2010;30(10):964-969. 10.1002/pd.2596.
27. Huh NG, Hirose S, Goldstein RB. Prenatal intraabdominal bowel dilation is associated with postnatal gastrointestinal complications in fetuses with gastroschisis. *Am J Obstet Gynecol*. 2010;202(4):396.e1-396.e6. 10.1016/j.ajog.2009.10.888.
28. Kuleva M, Salomon LJ, Benoist G, Ville Y, Dumez Y. The value of daily fetal heart rate home monitoring in addition to serial ultrasound examinations in pregnancies complicated by fetal gastroschisis. *Prenat Diagn*. 2012;32(8):789-796. 10.1002/pd.3903; 10.1002/pd.3903.
29. Goetzinger KR, Tuuli MG, Longman RE, Huster KM, Odibo AO, Cahill AG. Sonographic predictors of postnatal bowel atresia in fetal gastroschisis. *Ultrasound Obstet Gynecol*. 2013;4(43):420-425. 10.1002/uog.12568; 10.1002/uog.12568.
30. Frybova B, Vlk R, Kokesova A, Rygl M. Isolated prenatal ultrasound findings predict the postnatal course in gastroschisis. *Pediatr Surg Int*. 2015;31(4):381-387. 10.1007/s00383-015-3675-2 [doi].
31. Stuber TN, Frieauff E, Weiss C, Zollner U, Wockel A, Meyer T, Rehn M. Prenatal sonographic ultrasound predictors for the outcome in fetal gastroschisis: A retrospective analysis. *Arch Gynecol Obstet*. 2016;293(5):1001-1006. 10.1007/s00404-015-3936-2 [doi].
32. Balgi S, Singhal S, Mueller G, Batton B. Feeding intolerance and poor growth in infants with gastroschisis: Longitudinal experience with consecutive patients over thirteen years. *J Neonatal Surg*. 2015;4(4):42-Dec.
33. Segel SY, Marder SJ, Parry S, Macones GA. Fetal abdominal wall defects and mode of delivery: A systematic review. *Obstet Gynecol*. 2001;98(5 Pt 1):867-873.
34. Abdel-Latif ME, Bolisetty S, Abeywardana S, Lui K, Australian and New Zealand Neonatal Network. Mode of delivery and neonatal survival of infants with gastroschisis in australia and new zealand. *J Pediatr Surg*. 2008;43(9):1685-1690. 10.1016/j.jpedsurg.2008.03.053.
35. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13. 10.1186/1471-2288-5-13.
36. Mears AL, Sadiq JM, Impey L, Lakhoo K. Antenatal bowel dilatation in gastroschisis: A bad sign? *Pediatr Surg Int*. 2010;26(6):581-588. 10.1007/s00383-010-2600-y.

37. Sydorak RM, Nijagal A, Sbragia L, Hirose S, Tsao K, Phibbs RH, Schmitt SK, Lee H, Farmer DL, Harrison MR, Albanese CT. Gastroschisis: Small hole, big cost. *J Pediatr Surg*. 2002;37(12):1669-1672. 10.1053/jpsu.2002.36689.

38. Arnold MA, Chang DC, Nabaweesi R, Colombani PM, Bathurst MA, Mon KS, Hosmane S, Abdullah F. Risk stratification of 4344 patients with gastroschisis into simple and complex categories. *J Pediatr Surg*. 2007;42(9):1520-1525. 10.1016/j.jpedsurg.2007.04.032.

39. Wilson MS, Carroll MA, Braun SA, Walsh WF, Pietsch JB, Bennett KA. Is preterm delivery indicated in fetuses with gastroschisis and antenatally detected bowel dilation? *Fetal Diagn Ther*. 2012. 10.1159/000338925.

40. Reigstad I, Reigstad H, Kiserud T, Berstad T. Preterm elective caesarean section and early enteral feeding in gastroschisis. *Acta Paediatr*. 2011;100(1):71-74. 10.1111/j.1651-2227.2010.01944.x; 10.1111/j.1651-2227.2010.01944.x.

41. Gelas T, Gorduza D, Devonec S, Gaucherand P, Downham E, Claris O, Dubois R. Scheduled preterm delivery for gastroschisis improves postoperative outcome. *Pediatr Surg Int*. 2008;24(9):1023-1029. 10.1007/s00383-008-2204-y.

42. Serra A, Fitze G, Kamin G, Dinger J, Konig IR, Roesner D. Preliminary report on elective preterm delivery at 34 weeks and primary abdominal closure for the management of gastroschisis. *Eur J Pediatr Surg*. 2008;18(1):32-37. 10.1055/s-2007-965744.

43. Moir CR, Ramsey PS, Ogburn PL, Johnson RV, Ramin KD. A prospective trial of elective preterm delivery for fetal gastroschisis. *Am J Perinatol*. 2004;21(5):289-294. 10.1055/s-2004-829864.

44. Ergun O, Barksdale E, Ergun FS, Prosen T, Qureshi FG, Reblock KR, Ford H, Hackam DJ. The timing of delivery of infants with gastroschisis influences outcome. *J Pediatr Surg*. 2005;40(2):424-428. 10.1016/j.jpedsurg.2004.10.013.

45. D'Antonio F, Virgone C, Rizzo G, Khalil A, Baud D, Cohen-Overbeek TE, Kuleva M, Salomon LJ, Flacco ME, Manzoli L, Giuliani S. Prenatal risk factors and outcomes in gastroschisis: A meta-analysis. *Pediatrics*. 2015;136(1):e159-69. 10.1542/peds.2015-0017 [doi].

46. Visser GH, Eilers PH, Elferink-Stinkens PM, Merkus HM, Wit JM. New dutch reference curves for birthweight by gestational age. *Early Hum Dev*. 2009;85(12):737-744. 10.1016/j.earlhumdev.2009.09.008; 10.1016/j.earlhumdev.2009.09.008.

47. Pedreira CE, Pinto FA, Pereira SP, Costa ES. Birth weight patterns by gestational age in Brazil. *An Acad Bras Cienc*. 2011;83(2):619-625. S0001-37652011005000008 [pii].

48. Ajayi FA, Carroll PD, Shellhaas C, Foy P, Corbitt R, Osawe O, Caniano DA, O'Shaughnessy R. Ultrasound prediction of growth abnormalities in fetuses with gastroschisis. *J Matern Fetal Neonatal Med*. 2011;24(3):489-492. 10.3109/14767058.2010.500428.

49. Huang J, Kurkchubasche AG, Carr SR, Wesselhoeft CW,Jr, Tracy TF,Jr, Luks FL. Benefits of term delivery in infants with antenatally diagnosed gastroschisis. *Obstet Gynecol*. 2002;100(4):695-699.

50. Jansen LA, Safavi A, Lin Y, MacNab YC, Skarsgard ED, Canadian Pediatric Surgery Network (CAPSNet). Preclosure fluid resuscitation influences outcome in gastroschisis. *Am J Perinatol*. 2012;29(4):307-312. 10.1055/s-0031-1295639.

51. Murphy FL, Mazlan TA, Tarheen F, Corbally MT, Puri P. Gastroschisis and exomphalos in Ireland 1998-2004. does antenatal diagnosis impact on outcome? *Pediatr Surg Int*. 2007;23(11):1059-1063. 10.1007/s00383-007-2001-z.

52. Yang EY, Davies LM, Buchanan P, Kling C, Banyard DA, Ramones T. Spontaneous onset of labor, not route of delivery, is associated with prolonged length of stay in babies with gastroschisis. *J Pediatr Surg*. 2014;49(12):1776-1781. 10.1016/j.jpedsurg.2014.09.021 [doi].

Chapter

3

Functional outcome at school age of children born with gastroschisis

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ABSTRACT

Objective: We aimed to determine motor, cognitive and behavioural outcomes of school aged children born with gastroschisis compared to matched controls.

Study design: We compared outcomes of 16 children born with gastroschisis treated at the University Medical Center Groningen, the Netherlands, between 1999-2006 with 32 controls matched for gender, gestational age, birth weight, and corrected for small for gestational age (SGA) and parental socioeconomic status (SES). Intelligence, auditory-verbal memory, attention, response inhibition, visual perception, motor skills, visuomotor integration, problem behaviour and executive functioning were evaluated.

Results: Median verbal intelligence quotient and global executive functioning scores of children born with gastroschisis were poorer than of controls (95 (inter quartile range (IQR) 88-100) vs. 104 (IQR 98-113), P=0.001, and 29 (IQR 6.8-63.8) vs. 5.0 (IQR 2.8-19.8), P=0.03, respectively). Children with gastroschisis were more often classified as borderline or abnormal than controls regarding response inhibition (odds ratio (OR) 20.4; 95%-confidence interval (95%-CI) 2.4-171.5), selective visual attention (OR 40.4; 95%-CI 5.9-275.4), sustained auditory attention (OR 88.1; 95%-CI 5.8-1342.8), and fine motor skills (50% vs. 0%). Grade retention was more prevalent in gastroschisis children (OR 6.07; 95%-CI 1.42-25.9). These associations persisted after adjustment for SGA and SES. The auditory-verbal memory, visuomotor integration and behavioural problems did not significantly differ from the controls.

Conclusions: Gastroschisis is associated with poorer verbal intelligence, and with an increased risk for poor performance on several aspects of attention, response inhibition and fine motor skills at school age. The follow-up of children born with gastroschisis deserves attention regarding these specific domains, to improve their functional outcomes.

INTRODUCTION

Gastroschisis is a congenital disorder with evisceration of the bowels trough an abdominal wall defect. It is often an isolated finding, with good survival (>90%).[1,2] Gastroschisis needs surgical intervention within 24 hours of life to protect the extra-abdominal intestine. Intensive care is necessary for several days to weeks and total parenteral nutrition (TPN) for weeks to months. Repeated surgical procedures are often required. Such events in early life may affect neurodevelopment.[3] The majority of gastroschisis children is born preterm (60%)[4] and up to 61% is born small for gestational age (SGA).[5-7] Both conditions increase the vulnerability for impaired neurodevelopment.[8-11]

Studies on neurodevelopmental outcome in gastroschisis are sparse. The current study aimed to determine motor, cognitive and behavioural outcome at school age of children with gastroschisis. Comparing children with gastroschisis with a control group matched for gender, gestational age, and birth weight enabled us to explore whether the gastroschisis in early life impacted the children's development beyond other risk factors often seen in children with gastroschisis. We hypothesized that gastroschisis hampers all aspects of development.

METHODS

Participants

We selected all infants with gastroschisis, treated at the University Medical Center Groningen (UMCG) between 1999 and 2006. Children with additional major nonintestinal abnormalities were excluded. For every gastroschisis case we included two controls, matched, in order of importance, on gestational age (GA), gender, and birth weight.

We derived the children of the control group from two cohorts that covered similar populations and centres as we derived our patients from. The first was derived from the LOLLIPOP cohort, a large community-based prospective follow-up study on growth, development and general health in moderately preterm (GA 32-35 weeks) born children and a full-term control group, without major congenital malformations, infections or syndromes, born in 2002-2003 in the Northern provinces of the Netherlands.[10] The second cohort consisted of children included in a prospective follow-up study with very preterm (<32 weeks of gestation) SGA children as the clinical group and with very preterm average for GA (AGA) children as the control group, admitted at the NICU of the UMCG.[9]

Small for gestational age was defined as birth weight below the 10th percentile of the Dutch growth charts.[12] Neonatal data, type of gastroschisis (simple or complex, defined as atresia, volvulus, perforation or necrosis of the bowel)[13], number of operations, length of total parenteral nutrition (TPN),

length of hospital stay and socioeconomic status (SES) of both parents were extracted from hospital charts and a parental questionnaire, respectively. Surgical treatment consisted of primary closure or construction of a silo.
The UMCG Medical Ethical Review Board approved the study.

Measures and procedures

After parental informed consent, children of the gastroschisis group and their parents underwent a 3-hour assessment of cognitive, behavioural and motor development by a trained investigator (SB) at the outpatient clinic. The cognitive, behavioural and motor development of the control group originating from the two cohorts were evaluated by trained investigators at the outpatient clinic or at well-child clinics.[9,10]

Cognitive outcomes

To test verbal, performance and total intelligence, we used a short version of the Wechsler Intelligence Scale, Third Edition, Dutch Version (WISC-III-NL).[14] Total IQ (TIQ) was estimated based on two verbal IQ (VIQ) (i.e. Vocabulary, Similarities) and two performance IQ (PIQ) subtests (i.e. Picture arrangement, Block design), all scored according to age-scaled norms.[15]
We assessed selective visual attention, sustained auditory attention, and response inhibition with the subtests Map Mission, Score!, and Opposite world of the Test of Everyday Attention for Children, Dutch version (TEA-Ch NL)[16], respectively. Selective attention refers to a child's ability to select target information from an array of distractors. Response inhibition refers to the ability to inhibit an automatic response and to replace it by another response.
We used the Dutch version of the Rey Auditory Verbal Learning Test (AVLT) to assess auditory-verbal memory.[17] This test consists of five learning trials with immediate recall of words tested after each presentation assessing auditory-verbal learning, a delayed recall trial assessing long-term memory, and a delayed recognition trial. Visuomotor integration was assessed with the Design Copying subtest of the Developmental Neuropsychological Assessment Battery, Second Edition, Dutch version (Nepsy-2-NL).[18]
Grade repetition and special or regular education were derived from information provided by parents in the Dutch version of the Child Behavior Checklist (CBCL).[19]

Motor outcome

To appraise motor skills required in daily life, we used the Dutch version of the Movement Assessment Battery for Children (M-ABC).[20]

Behavioural outcome

Parents were asked to complete two questionnaires concerning behaviour. To assess behavioural and emotional problems the Dutch version of the CBCL[19] was used. Executive functioning in daily life was assessed using the Behaviour Rating Inventory of Executive Function, Dutch version (BRIEF).[21] Executive functioning is involved in well-organized, purposeful, goal-directed and problem-solving behaviour.

Statistical Analysis

We used ANOVA and Mann-Whitney U test, where appropriate. IQs were classified into 'normal' (IQ>85), 'borderline' (IQ 70-85) and 'abnormal' (IQ<70). We used percentiles from standardisation samples of cognitive tests and M-ABC as described in the manual to classify raw scores into 'normal' (>p15), 'borderline' (p5-p15) and 'abnormal' (<p5). For the CBCL and the BRIEF, we used a similar classification following their manuals. Differences in categorical data were tested using Chi-square tests. Logistic regression analyses were used to calculate odds ratios (OR) for adverse outcomes when comparing children with gastroschisis to controls. Patient demographics that differed in the gastroschisis group compared to the control group (P<0.10) were entered as potential confounders in a backward logistic regression model.

A P-value <0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS v20.0, SPSS Inc., Chicago, IL, USA.

RESULTS

Neonatal outcome

Nineteen neonates with gastroschisis were treated at our centre during the study period. Two patients died early due to respiratory insufficiency, and total necrosis of the small intestine caused by antenatal volvulus, respectively. We were able to contact the parents of 16 out of the 17 survivors. All agreed to participate.

Table 1 depicts demographic and perinatal characteristics of 16 children born with gastroschisis and 32 children in the control group, matched for GA, gender and birth weight in order of importance. SGA at birth was more common in gastroschisis cases (n=7, 44% versus n=5, 16%, respectively) and was therefore considered a potential confounder. We found no significant differences between SES of parents and Apgar scores <7 at 5 minutes.

Table 1. Patient demographics and perinatal characteristics for the gastroschisis group and control group

	Gastroschisis group (n=16)	Control group (n=32)	P ‡
Males (n)	9	18	1.00
GA (weeks)	37.1 (3.0; 29-42) *	37.1 (3.3; 27-41) *	0.99
GA<32 weeks (n)	1	2	1.00
Birth weight (grams)	2409 (559; 806-3130) *	2694 (611; 1040-3520) *	0.12
Apgar at 5 min< 7	1/12	2/29	0.66
SGA			
Normal (n)	9 (56%)	27 (84%)	0.004 ¶
P<10 (n)	7 (44%)	5 (16%)	
SES‖			0.98
Low (n)	0	2 (6 %)	
Middle (n)	9 (56%)	15 (47%)	
High (n)	7 (44%)	15 (47%)	
Type of Gastroschisis			
Simple (n)	13 (81%)		
Complex (n)	3 (19%)		
Number of operations §	2 (1-17) †		
Length of hospital stay (d)	24 (12-357) †		

GA; gestational age, SGA; small for gestational age, SES; socioeconomic status
*, Presented as mean (SD; range) for normally distributed variables
†, Presented as median (range) for non-normally distributed variables
‡, P-values derived from ANOVA, Fisher's exact test or Mann-Whitney U test; t-test
§, Number of operations in first year of life
‖, Highest completed education of father and mother (low, ≤ 6 years of elementary school; medium, high school or specially trained professional; high, vocational college, university degree)
¶, P< 0.01

Gastroschisis defects were closed primarily in 9/16 (56%). Repeated operations were necessary in 56%. Three children (19%) had additional gastrointestinal tract disorders at birth. Median length of TPN and hospitalisation were 16 (range 9-401) and 24 days (range 12-357), respectively.

Cognitive outcome

Three children (19%) in the gastroschisis group received special education versus none of controls (P = 0.07). Of the children with gastroschisis, 7/12 (58%) repeated a grade versus 6/32 (19%) controls (P = 0.02). Table 2 depicts cognitive results. One child's intelligence was assessed at school shortly before our evaluation, thus we used the school's test results. Another child was tested with the AVLT

shortly before our evaluation, but results could not be obtained. Other missing data are related to lack of cooperation from the child. The gastroschisis group scored significantly lower on verbal and total intelligence, response inhibition, selective visual attention and sustained auditory attention. Mean PIQ, mean scores on verbal learning, verbal long-term memory, and visuomotor integration did not differ significantly.

Table 2. Cognitive, motor and behavioural outcomes for the gastroschisis group and control group

	Gastroschisis group			Control group			P‡
	(n)			(n)			
Age at assessment (years) (median (range))	16	8.5	(5-13)	32	6	(6-11)	0.04
Total intelligence	16	92.3	(13.3; 55-109) *	32	102.3	(10.4; 85-119) *	0.016
Verbal intelligence	16	95	(88-100) †	32	104	(98-113) †	0.001
Performance intelligence	16	92.6	(15.7; 55-115) *	32	99.8	(12.7; 78-128) *	0.20
Response inhibition **	13	32.3	(27.9; 1-93) *	32	58.7	(33.3; 9-100) *	0.011
Selective visual attention **	14	6.7	(2.9-14.2) †	32	37	(25-72) †	<0.001
Sustained auditory attention **	14	6.7	(5.9-43.4) †	30	50	(16-75) †	0.006
Verbal learning **	15	37.7	(34.0; 1-99) *	32	58.3	(33.5; 1-100) *	0.076
Verbal long-term memory **	15	41.1	(32.3; 1-95) *	31	50.8	(33.5; 0-100) *	0.55
Visuomotor integration **	16	18.5	(11-51) †	32	26	(1-51) †	0.19
Movement-ABC total **	16	18.6	(20.1; 1-67) *	30	56.5	(27.4; 3-92) *	<0.001
Fine motor skills¶		4.0	(1.5-8.25) †		0.25	(0.00-1.50) †	<0.001
Ball skills¶		3.75	(2.25-4.88) †		1.00	(0.00-3.00) †	0.02
Balance¶		2.3	(0.00-4.875) †		0.00	(0.00-1.50) †	0.01
Total behavioural problems **	16	49.6	(11.9; 30-67) *	31	49.9	(10.4; 29-71) *	0.80
Global executive functioning in daily life **	16	29.0	(6.8-63.8) †	30	5.0	(2.8-19.8) †	0.03

*, Data presented as mean (SD; range) for normally distributed variables
†, Data presented as median (25^{th} -75^{th} interquartile range) for non-normally distributed variables
‡, P-values derived from the ANOVA corrected for SES and SGA or Mann-Whitney U test
¶, Raw scores
**, Percentile
Higher scores represent better performance on the tests, except for the scores of Fine motor skills, Ball skills, Balance, Total behavioural problems, and Global executive functioning where higher scores indicate poorer performance.

In Table 3, the classification of children into the categories normal, borderline and abnormal and ORs for poorer outcome after adjusting for SGA and SES is shown. ORs confirmed the analyses of the mean scores. Analyses without correction for SGA and SES revealed similar results with slightly different ORs, but without changes in level of significance (data not shown).

Table 3. Clinical classification of cognitive, behavioural and motor outcomes for the gastroschisis group and control group, and odds ratios for differences in borderline and abnormal outcomes after adjusting for small for gestational age and parental socioeconomic status

	Gastroschisis group			Control group				
	Normal n (%)	Borderline n (%)	Abnormal n (%)	Normal n (%)	Borderline n (%)	Abnormal n (%)	OR * (95%-CI)	OR † (95%-CI)
Total intelligence	14 (87.5)	1 (6.3)	1 (6.3)	32 (100)			‖	‖
Verbal intelligence	14 (87.5)	1 (6.3)	1 (6.3)	32 (100)			‖	‖
Performance intelligence	12 (75)	3 (18.8)	1 (6.3)	28 (87.5)	4 (12.5)		2.7 (0.5-14.0)	‖
Response inhibition	8 (57.1)	3 (21.4)	3 (21.4)	30 (93.8)	2 (6.3)		20.4 § (2.4-171.5)	‖
Selective visual attention	3 (21.4)	7 (50)	4 (28.6)	29 (90.6)	3 (9.4)		40.4 § (5.9-275.4)	‖
Sustained auditory attention	5 (35.7)	6 (42.9)	3 (21.4)	27 (90)	1 (3.3)	2 (6.7)	88.1 § (5.8-1342.8)	4.8 (0.6-36.5)
Verbal learning	10 (66.7)	1 (6.7)	4 (26.7)	28 (87.5)	1 (3.1)	3 (9.4)	4.6 (0.9-23.3)	5.4 (0.9-32.5)
Verbal long-term memory	11 (73.3)	1 (6.7)	3 (20)	24 (77.4)	6 (19.4)	1 (3.2)	1.3 (0.3-5.7)	9.9 (0.8-118.1)
Verbal recognition memory	12 (80)	1 (6.7)	2 (13.3)	21 (70)	4 (13.3)	5 (16.7)	0.7 (0.1-3.5)	1.0 (0.2-6.5)
Visuomotor integration	8 (50)	6 (37.5)	2 (12.5)	23 (71.9)	9 (28.1)		2.3 (0.6-8.5)	‖
Movement-ABC total	7 (43.8)	3 (18.8)	6 (37.5)	26 (86.7)	3 (10)	1 (3.3)	16.3 § (2.6-100.1)	25.0 § (2.2-281.3)
Fine motor skills	8 (50)	3 (18.8)	5 (31.3)	30 (100)			‖	‖
Ball skills	7 (43.8)	5 (31.3)	4 (25)	20 (66.7)	5 (16.7)	5 (16.7)	3.4 (0.9-13.5)	2.6 (0.5-13.1)
Coordination	12 (75)	1 (6.3)	3 (18.8)	27 (90)	1 (3.3)	2 (6.7)	3.6 (0.6-22.0)	3.0 (0.4-23.7)
Total behavioural problems	12 (75)	1 (6.3)	3 (18.8)	25 (80.6)	3 (9.7)	3 (9.7)	2.2 (0.4-10.8)	3.0 (0.5-20.0)
Global executive functioning	14 (87.5)	1 (6.3)	1 (6.3)	29 (96.7)		1 (3.3)	4.3 (0.3-57.5)	3.0 (0.2-53.5)

Data are given as number (%). Normal was defined as >P15, borderline as P5-P15, and abnormal <P5. For intelligence, normal was defined as intelligence quotient (IQ)>85, borderline as IQ=70-85, and abnormal as IQ<70. Data are given as odds ratio (OR) (95%-confidence interval, 95%-CI) derived from logistic regression analyses adjusted for small for gestational age (SGA) and parental socioecnoic status (SES).

*, Odds ratio's for borderline and abnormal outcomes

†, Odds ratio's for abnormal outcomes

§, P< 0.01

‖, Could not be determined due to absence of abnormal controls

Motor outcome

As shown in Table 2, the gastroschisis group performed significantly poorer on all M-ABC scores. ORs for abnormal/borderline Total M-ABC scores adjusted for SGA and SES confirmed the analysis of the mean scores. ORs without correction for SGA and SES were slightly different, but without changes in significance level (data not shown). More specifically, the gastroschisis group performed poorer on fine motor skills. On fine motor skills 19% scored borderline and 31% scored abnormal compared to 100% normal scores for controls. However, ORs of the M-ABC ball skills and balance scores were not significantly different between the gastroschisis and control group.

Behavioural outcome

The prevalence of total behavioural problems did not differ significantly. Although parents of gastroschisis children reported significantly more severe problems in executive functioning, analysis of ORs did not show a significant difference between the gastroschisis and control group.

DISCUSSION

In a group of school aged children born with gastroschisis, TIQ, VIQ, several aspects of attention, response inhibition, executive functioning, and fine motor skills were poorer compared to a control group matched for GA, gender, and birth weight. Adjusting for SGA and parental SES did not change these results. Fifty-eight per cent of children with gastroschisis repeated a grade and 19% required special education compared to 19% and 0% of the control group, respectively. Auditory-verbal memory, visuomotor functioning, and behavioural outcome were not different from controls.

The few studies on neurodevelopmental outcome of children with gastroschisis mostly investigated pre-scholars. The studies of pre-scholars invariably reported the cognitive outcomes to be in the normal range.[6,22-25] Deficits we found might become apparent after the child enters school, when higher cognitive demands are required. Only two other studies assessed the outcome of school-aged gastroschisis survivors but none of these studies had a control group.[26,27] Harris et al.[26] assessed intellectual ability[28,29] and neurological status, such as hearing, vision and behavioural status,[30] of 39 children born with gastroschisis (median age 10 years with range 5-17 years) and compared the results with normative means, thus without correction for comorbidity, such as prematurity and low birth weight. Giudici et al.[27] performed a follow-up study, including screening for neurodevelopmental problems using the Neurology-Psychomotor Developmental Index (NPDI)[31], at 3 years interval, of 17 gastroschisis survivors from birth until the age of six years. They found that, as children became older, the proportion of deficits increased, which is consistent with our hypothesis

of poorer outcome in school age than in pre-school age children with gastroschisis. They did not specify which domains of the NPDI were affected.

In contrast with Harris et al., we found a lower average TIQ in the gastroschisis group than the control group, which seemed rather related to a lower average VIQ. However, our lower IQ-scores represented subtle differences, since the clinical classification of IQ-scores did not differ between the gastroschisis and the control groups, which is consistent with Harris et al. Similar to Harris et al., gastroschisis children had an increased risk for impaired attention, i.e. selective visual attention and sustained auditory attention, and executive functioning in school age gastroschisis cases was poorer compared with matched controls.

Previous studies assessing pre-school age gastroschisis cases reported no impaired motor functioning[6,22-24] whereas we found such differences. These seem to be related to lower fine motor scores and thus most likely to impaired fine motor skills. Fine motor skills were not specifically assessed in the earlier studies. Therefore, impairment in these fine motor skills may have been missed, which may explain the difference in motor outcomes between previous studies and our study.

Fine motor skills, attention, response inhibition and executive functioning were all poorer in the gastroschisis group. These skills and abilities are strongly related to school performance.[32-34] Subtle problems in intellectual abilities, such as lower VIQ, in combination with impairments in the above skills and abilities may hamper school performance even further. This hypothesis is consistent with the findings of Giudici et al.[27]; six of the 17 gastroschisis survivors (35%) attended special education. This hypothesis is further in line with our findings; 19% of the gastroschisis group attended special education compared with none of controls. In addition, we found that 58% of the children older than 5 years born with gastroschisis repeated a grade, which is higher than the Dutch population average (17%).[35] The group of children repeating a grade scored not differently from controls on intelligence and auditory-verbal memory, but showed impaired attention, response inhibition and fine motor skills (data not shown). Their impairments may be less prominent between their younger classmates and therefore special education services have not been implemented. However, our results suggest close follow-up of these children is prudent to assure keeping up with their fellow students.

Not all domains investigated were affected. The prevalence of visuomotor functioning, auditory-verbal memory and behavioural problems in the gastroschisis group was not different from the control group. This may be interpreted as that these domains are less affected in this group of children, but it should preferably be confirmed in another study.

The impact of gastroschisis on the development of the group investigated by us may be caused by several pathways, due to the multiple factors to which the infants with gastroschisis were subjected during fetal and early life. First, the antenatal exposure of exteriorized bowel to amniotic fluid may cause chronic bowel inflammation. This leads to high levels of proinflammatory cytokines in amniotic fluid.[36] Systemic inflammation is associated with cerebral white matter abnormalities.[37] Since this inflammation starts already antenatally, but continues after birth, during a period of rapid brain

organization, the impact of inflammation on brain development may be very large. Next, the inflammation of bowel may also increase capillary leak with tissue oedema[38], and hypovolemia, leading to hypotension and hypoperfusion of the brain, which persist after birth, thus further increasing the risk for impaired brain development.

A second explanation may be fetal stress as result of pain caused by compression and tension on the exteriorized intestine. Fetal heart rate abnormalities, such as tachycardia and decreased variability are often seen in gastroschisis, which may implicate pain.[39] Extremely preterm children experiencing pain are at higher risk of impaired cognitive outcome at school age.[40]

A third explanation for our findings may concern the surgical procedures required during the first days after birth. Major surgery and anaesthesia during the postnatal period, a period of rapid cerebral growth, are associated with developmental delay.[41] Consistently, literature has shown that children with surgically treated congenital intestinal obstructions are also at risk for adverse neurodevelopmental outcomes, especially poor motor functioning and an impaired selective attention at school age.[3]

Finally, intra-uterine growth restriction, often seen in children with gastroschisis, is also a risk factor for impaired neurodevelopment.[42] In the present study, however, adjustment for SGA did not change any of our significant differences between the groups, and thus SGA is unlikely to underlie our findings.

Prematurity does not seem to have a large impact on the neurodevelopmental outcome in gastroschisis survivors, either. Most children with gastroschisis are born moderately preterm, which may have a negative impact on cognitive and motor functioning of children at school age.[10] This has been hypothesized to play a greater role in the outcome of gastroschisis than the condition itself.[6,23,25] However, after matching for GA, we found that poorer scores persisted on several aspects of neurodevelopment.

Our study has several limitations, most importantly the small single centre population. By using standardised tests, we were able to make the results more generally applicable. Due to the small number of cases we were unable to investigate the effect of additional gastrointestinal tract disorders at birth (complex gastroschisis), the effect of the number of operations, and the effect of different surgical strategies. Studies comparing type of closing surgeries have demonstrated conflicting results of short-term outcome.[43,44] To assess whether different surgical strategies influence long-term outcome large follow-up studies are necessary. Another limitation is the difference in testing age between cases and controls. We used, however, age-validated tests and age-normed scores, which allowed us to compare the results of different age groups.

A strength of our study was the assessment of children at school age, since motor and cognitive test results at school age are known to be more robust and predictive for functioning in adulthood than when measured at pre-school age.[20] Another strength was our comparison of cases with controls, matched for GA, gender, birth weight, and corrected for SGA and SES. The adverse effect on

verbal intelligence, attention, response inhibition, executive functioning and fine motor outcome at school age as found in the present study seem therefore ascribed to gastroschisis, its treatment and consequences.

CONCLUSION

School aged children born with gastroschisis scored significantly lower on several aspects of attention, response inhibition, executive functioning, verbal intelligence, and fine motor skills than matched controls. Functional outcome at school age of gastroschisis children is poorer than expected from studies at pre-school age. Given our results, we recommend monitoring the neurodevelopment of these children at early school age to improve their school performance via early school intervention. This may lead to improvement of functional outcomes in these children.

REFERENCES

1. Aljahdali A, Mohajerani N, Skarsgard ED, Canadian Pediatric Surgery Network (CAPSNet). Effect of timing of enteral feeding on outcome in gastroschisis. *J Pediatr Surg*. 2013;48(5):971-976. 10.1016/j.jpedsurg.2013.02.014; 10.1016/j.jpedsurg.2013.02.014.
2. Kuleva M, Khen-Dunlop N, Dumez Y, Ville Y, Salomon LJ. Is complex gastroschisis predictable by prenatal ultrasound? *BJOG Int J Obstet Gynaecol*. 2012;119(1):102-109.
3. Elsinga RM, Roze E, Van Braeckel KN, Hulscher JB, Bos AF. Motor and cognitive outcome at school age of children with surgically treated intestinal obstructions in the neonatal period. *Early Hum Dev*. 2013;89(3):181-185. 10.1016/j.earlhumdev.2012.09.014; 10.1016/j.earlhumdev.2012.09.014.
4. Barseghyan K, Aghajanian P, Miller DA. The prevalence of preterm births in pregnancies complicated with fetal gastroschisis. *Arch Gynecol Obstet*. 2012;286(4):889-892. 10.1007/s00404-012-2394-3.
5. Horton AL, Powell MS, Wolfe HM. Intrauterine growth patterns in fetal gastroschisis. *Am J Perinatol*. 2010;27(3):211-217. 10.1055/s-0029-1236440.
6. South AP, Marshall DD, Bose CL, Laughon MM. Growth and neurodevelopment at 16 to 24 months of age for infants born with gastroschisis. *J Perinatol*. 2008;28(10):702-706. 10.1038/jp.2008.71.
7. Payne NR, Simonton SC, Olsen S, Arnesen MA, Pfleghaar KM. Growth restriction in gastroschisis: Quantification of its severity and exploration of a placental cause. *BMC Pediatr*. 2011;11(1):90. 10.1186/1471-2431-11-90.
8. Kerstjens JM, de Winter AF, Bocca-Tjeertes IF, ten Vergert EM, Reijneveld SA, Bos AF. Developmental delay in moderately preterm-born children at school entry. *J Pediatr*. 2011;159(1):92-98. 10.1016/j.jpeds.2010.12.041; 10.1016/j.jpeds.2010.12.041.
9. Tanis JC, van der Ree MH, Roze E, Huis In 't Veld AE, van den Berg PP, Van Braeckel KN, Bos AF. Functional outcome of very preterm-born and small for gestational age children at school age. *Pediatr Res*. 2012. 10.1038/pr.2012.130; 10.1038/pr.2012.130.
10. Cserjesi R, Van Braeckel KN, Butcher PR, Kerstjens JM, Reijneveld SA, Bouma A, Geuze RH, Bos AF. Functioning of 7-year-old children born at 32 to 35 weeks' gestational age. *Pediatrics*. 2012;130(4):e838-46. 10.1542/peds.2011-2079; 10.1542/peds.2011-2079.
11. Arcangeli T, Thilaganathan B, Hooper R, Khan KS, Bhide A. Neurodevelopmental delay in small babies at term: A systematic review. *Ultrasound Obstet Gynecol*. 2012;40(3):267-275. 10.1002/uog.11112; 10.1002/uog.11112.
12. Kloosterman GJ. Intrauterine growth: The significance of prenatal care. *Int J Gynaecol Obstet*. 1970;8:895-912.
13. Molik KA, Gingalewski CA, West KW, Rescorla FJ, Scherer LR, Engum SA, Grosfeld JL. Gastroschisis: A plea for risk categorization. *J Pediatr Surg*. 2001;36(1):51-55. 10.1053/jpsu.2001.20004.
14. Kort W, Compaan E, Bleichrodt N, et al. *WISC-III NL Handleiding*. NIP ed. Amsterdam: Dienstencentrum; 2002.
15. Gregoire J. Comparison of three short forms of the wechsler intelligence scale for children – third edition (WISC-III) *European Review of Applied Psychology*. 2000(50):437-441.
16. Manly T, Robertson IH, Anderson V, Nimmosmith I. *TEA-Ch, Test of Everyday Attention for Children*. Handleiding ed. The Netherlands: Harcourt Assessment; 2004.
17. van den Burg W, Kingma A. Performance of 225 dutch school children on rey's auditory verbal learning test (AVLT): Parallel test-retest reliabilities with an interval of 3 months and normative data. *Arch Clin Neuropsychol*. 1999;14(6):545-559.
18. Korkman M, Kirk U, Kemp S. *NEPSY: A Developmental Neuropsychological Assessment*. San Antonio: Psychological Corporation; 1998.

19. Achenbach T, Edelbrock C. *Manual for the Child Behavior Checklist: 4-8 and 1991.* Burlington University of Vermont, Department of Psychiatry; 1991.

20. Smits-Engelsman B. *Movement Assessment Battery for Children.* Handbook ed. Lisse, The Netherlands: Swets & Zeitlinger Test Publishers; 1998.

21. Smidts D, Huizinga M. *BRIEF Executive Functies Gedragsvragenlijst.* Handleiding ed. Amsterdam, The Netherlands: Hogrefe Uitgevers B.V.; 2009.

22. Payne NR, Gilmore L, Svobodny S, Perdue NR, Hoekstra RE, Olsen S, Moore JR. A cross-sectional, case-control follow-up of infants with gastroschisis. *J Neonatal-Perinat Med*. 2010;3(3):207-215.

23. Gorra AS, Needelman H, Azarow KS, Roberts HJ, Jackson BJ, Cusick RA. Long-term neurodevelopmental outcomes in children born with gastroschisis: The tiebreaker. *J Pediatr Surg*. 2012;47(1):125-129. 10.1016/j.jpedsurg.2011.10.028.

24. Minutillo C, Rao SC, Pirie S, McMichael J, Dickinson JE. Growth and developmental outcomes of infants with gastroschisis at one year of age: A retrospective study. *J Pediatr Surg*. 2013;48(8):1688-1696. 10.1016/j.jpedsurg.2012.11.046; 10.1016/j.jpedsurg.2012.11.046.

25. van Manen M, Hendson L, Wiley M, Evans M, Taghaddos S, Dinu I. Early childhood outcomes of infants born with gastroschisis. *J Pediatr Surg*. 2013;48(8):1682-1687. 10.1016/j.jpedsurg.2013.01.021; 10.1016/j.jpedsurg.2013.01.021.

26. Harris EL, Hart SJ, Minutillo C, Ravikumara M, Warner TM, Williams Y, Nathan EA, Dickinson JE. The long-term neurodevelopmental and psychological outcomes of gastroschisis: A cohort study. *J Pediatr Surg*. 2016;51(4):549-553. 10.1016/j.jpedsurg.2015.08.062 [doi].

27. Giudici L, Bokser VS, Maricic MA, Golombek SG, Ferrario CC. Babies born with gastroschisis and followed up to the age of six years faced long-term morbidity and impairments. *Acta Paediatr*. 2016;105(6):e275-80. 10.1111/apa.13374 [doi].

28. Wechsler D, ed. *Wechsler Intelligence Scale for Children.* Fourth Edition Australin Standerdised Edition (WISC-IV Australian) ed. Pearson; 2005.

29. Wechsler D, ed. *Wechsler Preschool & Primary Scale of Intelleigence- Australian Standardised Edition (WPPSI-III Australian).* Third Edition ed. Pearson; 2004.

30. YouthinMind: Strengths and difficulties questionnaire..

31. Lejarraga H, Menendez AM, Menzano E, Guerra L, Biancato S, Pianelli P, Fattore MJ, De Raco P, Schejter V, Contreras MM, Glomba C, Bellusci C, Lusnig A, Rautenstrauch C, Paris V, Galeana A, Feinsilber V, Garay ML, Alves L, Del Pino M, Andrews M, Pagano A, Larigoitia D. PRUNAPE: Screening for psychomotor development problems at primary care level. *Arch Argent Pediatr*. 2008;106(2):119-125. 10.1590/S0325-00752008000200005 [doi].

32. Marlow N, Hennessy EM, Bracewell MA, Wolke D, EPICure Study Group. Motor and executive function at 6 years of age after extremely preterm birth. *Pediatrics*. 2007;120(4):793-804. 10.1542/peds.2007-0440.

33. Breslau J, Miller E, Breslau N, Bohnert K, Lucia V, Schweitzer J. The impact of early behavior disturbances on academic achievement in high school. *Pediatrics*. 2009;123(6):1472-1476. 10.1542/peds.2008-1406; 10.1542/peds.2008-1406.

34. Piek JP, Dyck MJ, Nieman A, Anderson M, Hay D, Smith LM, McCoy M, Hallmayer J. The relationship between motor coordination, executive functioning and attention in school aged children. *Arch Clin Neuropsychol*. 2004;19(8):1063-1076. 10.1016/j.acn.2003.12.007.

35. Dutch ministry of education, culture and science http://www.onderwijsinspectie.nl/actueel/nieuwsberichten/nederlandse-scholieren-blijven-vaker-zitten.html. Accessed 6/24, 2013.

36. Morrison JJ, Klein N, Chitty LS, Kocjan G, Walshe D, Goulding M, Geary MP, Pierro A, Rodeck CH. Intra-amniotic inflammation in human gastroschisis: Possible aetiology of postnatal bowel dysfunction. *Br J Obstet Gynaecol*. 1998;105(11):1200-1204.

37. Shah DK, Doyle LW, Anderson PJ, Bear M, Daley AJ, Hunt RW, Inder TE. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. *J Pediatr*. 2008;153(2):170-5, 175.e1. 10.1016/j.jpeds.2008.02.033; 10.1016/j.jpeds.2008.02.033.

38. Carroll SG, Kuo PY, Kyle PM, Soothill PW. Fetal protein loss in gastroschisis as an explanation of associated morbidity. *Am J Obstet Gynecol*. 2001;184(6):1297-1301. 10.1067/mob.2001.114031.

39. Dixon JC, Penman DM, Soothill PW. The influence of bowel atresia in gastroschisis on fetal growth, cardiotocograph abnormalities and amniotic fluid staining. *BJOG*. 2000;107(4):472-475.

40. Doesburg S, Chau C, Cheung TPL, Moiseev A, Ribary U, Herdman A, Miller S, Cepeda I, Synnes A, Grunau R. Neonatal pain-related stress, functional cortical activity and visual-perceptual abilities in school-age children born at extremely low gestational age. *Pain*. 2013. 10.1016/j.pain.2013.04.009.

41. Walker K, Badawi N, Holland AJA, Halliday R. Developmental outcomes following major surgery: What does the literature say? *J Paediatr Child Health*. 2011;47(11):766-770.

42. Peng Y, Huang B, Biro F, Feng L, Guo Z, Slap G. Outcome of low birthweight in china: A 16-year longitudinal study. *Acta Paediatr*. 2005;94(7):843-849. 10.1080/08035250510027589.

43. Driver CP, Bowen J, Doig CM, Bianchi A, Dickson AP, Bruce J. The influence of delay in closure of the abdominal wall on outcome in gastroschisis. *Pediatr Surg Int*. 2001;17(1):32-34.

44. Davies MW, Kimble RM, Cartwright DW. Gastroschisis: Ward reduction compared with traditional reduction under general anesthesia. *J Pediatr Surg*. 2005;40(3):523-527. 10.1016/j.jpedsurg.2004.11.030.

Chapter

4

The value of genetic testing and morphological examination in children with gastroschisis

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ABSTRACT

Objectives: To assess the value of genetic testing and morphological examination in a cohort of patients with gastroschisis.

Methods: A single centre cohort study was performed, including cases with gastroschisis born between 1982-2002, and their parents. Structural clinical examination directed to morphologic anomalies was performed and compared to a validated control group. Array was used to identify copy number variants (CNVs). CNVs were compared to previously reported patients with gastroschisis and healthy controls derived from the local and publicly available databases. In cases with intellectual disability whole exome sequencing (WES) was performed.

Results: Twenty-one cases were included (median age 11, range 4-27 years). Cases had a significant increase of ≥ 2 minor abnormalities compared to controls (89.5% versus 55.7%, P=0.004). The occurrence of ≥ 1 major anomaly was not significant increased compared to controls. Seven inherited and one *de novo* CNVs were detected in five cases. No overlap with the CNVs region was found between cases of this study or gastroschisis cases described in literature or databases. Two cases had intellectual disability. WES detected a pathogenic *de novo* mutation in the *MECP2* gene in one case and a single nucleotide variant, variant of uncertain significance, in the *KCNQ2* gene in the second case.

Conclusions: In a cohort of 21 gastroschisis cases, we detected significantly more minor morphological anomalies, one *de novo* CNV and one, possibly two, monogenetic disorders. Paediatric follow-up, syndrome diagnosis and genetic analysis are indicated in children with gastroschisis, especially when additional anomalies and/or intellectual disability are present.

INTRODUCTION

Gastroschisis is a congenital abdominal wall defect, with evisceration of the bowel, without a covering, through a defect adjacent to an otherwise normal umbilicus. The prevalence of gastroschisis is rising in the Western world[1-4] and currently in the Netherlands around 1.1:10.000 newborns are affected. In most children gastroschisis is isolated. The incidence of associated anomalies varies from 5 to 50% between studies, due to different inclusion and classification criteria.[5,6] Reported associations include septo-optic dysplasia, an increased prevalence of central nervous system anomalies, and limb and kidney anomalies.[6-8] Young maternal age, associated with environmental factors like smoking and low economic status, is a well-recognized risk factor for gastroschisis.[9-12] The finding that gastroschisis is more common in Caucasians compared to African-Americans living in the same socio-economic area[13,14] and that the recurrence risk (2.4%) is increased within families[15], suggests that the aetiology of gastroschisis is multifactorial and that genetic factors contribute. The pathogenesis of gastroschisis is poorly understood. The most commonly accepted theory is that failure of abdominal closure results from a thrombotic event within the abdominal wall during embryogenesis.[12,16] Thus far, studies in gastroschisis cases have been unsuccessful in identifying mutations in target genes related to vascular integrity or a genetic predisposition to thromboembolism.[17,18]
Gastroschisis is not associated with abnormalities at standard chromosome analysis.[7,19] Molecular karyotyping now allows for the detection of deletions and duplications at the submicroscopic level, so called single copy number variants (CNVs). Although in many congenital disorders the application of array has led the identification of new monogenetic causes and target genes[20,21], this has not been systematically studied in gastroschisis cases. Studying minor and major morphologic findings in children with congenital anomalies allows for the detection of patterns of anomalies and may provide clues for causative genes.[22-25] Available morphological studies in gastroschisis patients are scarce, retrospective and lack structural clinical examination.[7,26]
The main objectives of this study were to investigate the value of morphological examination and genetic analysis in gastroschisis patients and to identify potential genetic causes.

MATERIALS AND METHODS

Participants

We selected all liveborn infants with gastroschisis treated at the University Medical Center Utrecht (UMCU) between January 1982 and December 2008, using the obstetric, neonatal and paediatric surgery database. The UMCU Medical Ethical Review Board has approved the study

(NL34256.041.10/11-009/K). An invitation letter explaining the goal and the procedures of the present study was sent to the participants.

Measures and procedures

Participants and their parents, after consenting to participate, were invited to the UMCU outpatient clinic for a 1.5-hour assessment. Maternal, antenatal and neonatal follow-up data were extracted from the hospital charts. During the assessment additional information on the obstetric, medical and familial history was obtained. In particular, previously identified exposures and risk factors associated with gastroschisis were reviewed and compared to the obstetric Dutch population.[27,28] Current growth and development and educational level were evaluated. All patients were subjected to a physical examination of the body surface by a paediatric geneticist (KL) directed to morphologic abnormalities. Additionally height, weight, head circumference, inner canthal distance, outer canthal distance, hand length and palm length were measured.[29-32] Photographs of the patients and parents, if present, were taken. Any dysmorphologic features were photographed in detail and, if in doubt, discussed with a second investigator (PT). To classify morphologic abnormalities and differentiate between major abnormalities and minor anomalies (prevalence ≥4%), we used the normal values generated by Merks et al.[33] Common variants (prevalence >4%) were excluded. The incidence of minor anomalies and abnormalities were compared with the normal population.[34]

Array platforms and analysis

DNA samples obtained from whole blood were used for copy number profiling using 180K (amadid#27730) Human Genome CGH Microarray slides from Agilent Technologies (Santa Clara, California, USA) or the Infinium Human Omni Express Exome Bead Chip (Illumina, San Diego, Calif., USA) following manufacturer's protocols. Data analysis was performed with Nexus 7.5 software (BioDiscovery, Los Angeles, CA, USA). A CNV was stated as neutral (non-pathogenic), and not reported, when it was either present in > three studies in the Database of Genomic Variants (http://dgv.tcag.ca/dgv/app/home), > three times in our control database containing CNV data of approximately 2000 parents (with the exception of known incomplete penetrance regions), or >1% in an in-house database containing the CNVs of all previously analysed patients. Of all the patients carrying a non-neutral CNV parental blood was requested for follow up. All CNV calls are provided in hg19 genomic coordinates.

To gain more insight in the potential pathogenic contribution of the CNVs identified, we analysed the genes in the CNVs in patients with gastroschisis. Size, location and gene-content of deletions and/or duplications in gastroschisis patients and their parents were compared to patients with gastroschisis previous described in literature, patients with other anomalies and healthy controls derived from the local database of the medical genetics and publicly available databases ((DGV), Database of Chromosomal Imbalance and Phenotype in Humans Using Ensemble Resources (DECIPHER)(ref: http://

decipher.sanger.ac.uk), Online Mendelian Inheritance in Man (OMIM) database, NCBI Gene Database, MEDLINE, Embase, Genecards.org), consulted August *2016*). Variants were classified as benign if they were reported three times or more in the DGV, as rare variants if they were reported less than three times in the DGV and as a variant of unknown significance (VUS) if they were not reported in the DGV, nor in the local database.[35]

Statistical methods

Normally distributed data was expressed in mean and SD, not normally distributed data was expressed in median and range. Physical measurements were expressed in Z-scores and compared with the acknowledged curves using a one-sample t-test. Fisher's exact test or Mann-Whitney U tests were performed when appropriate. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS v23.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Participants

Forty neonates with gastroschisis were treated during the study period. One child born with a stenosis of the transverse colon, necessitating repeated surgeries, died at the age of 40 days due to sepsis and respiratory insufficiency. He had a normal male karyotype. His parents were consanguineous (first cousins). Another child had severe pulmonary hypertension and died at 3.5 months, due to acute respiratory insufficiency caused by Bordetella pertussis pneumonia and candida sepsis. Two patients emigrated and six patients did not respond to our letters. Of the thirty remaining patients, twenty-one (70%) consented to inclusion. Two patients completed the questionnaire and returned DNA samples, but were unable to visit the hospital due to logistic problems.

Maternal baseline characteristics are summarized in Table 1. The maternal age was lower compared to the Dutch obstetric population, and women were more likely to smoke during pregnancy.[27,28]

Table 1. Maternal characteristics of children born with gastroschisis

	N*	n	Median (range) / %
Maternal age at birth (y) #		20	26 (16-36)
Toxic chemical contact Chloric gas and Mercury	20	1	5
Maternal smoking$	20	8	40
Maternal alcohol use	20	3	15
Maternal drugs use (sporadic; XTC, GHB)	20	2	10
Maternal medication	20	3	15
First pregnancy	21	15	71
Education mother¥	20		
Low		0	0
Medium		14	70
High		6	30
Highest education father¥	20		
Low		2	10
Medium		12	60
High		6	30

#, The mean maternal age of Dutch women at first pregnancy was 28.2 year ± 4.7 during the same study period. (CBS Medline 2012)[27]
$, 9% of Dutch women smoked during pregnancy between 2001-2008[28]
¥, highest completed education (low, ≤ 6 years of elementary school; medium, high school or specially trained professional; high, vocational college, university degree)
*, The mother of case 1 was deceased therefore maternal data could not be retrieved

Neonatal characteristics were available for 20 of the 21 cases and are summarized in Table 2. Median gestational age at birth was 36 3/7 (range: 32 2/7 - 41 3/7) with a median birth weight of 2360 (1750-3700) gram. Four children had gastrointestinal complications. One child was born with a jejunal stenosis requiring surgical resection. Another child developed an abdominal compartment syndrome after primary closure. Two children had ileal perforation after secondary closure, whereafter partial ileal resection was performed. Additionally, three boys had unilateral cryptorchidism necessitating orchidopexy. One patient had a glandular hypospadias.

Table 2. Neonatal characteristics

	N	n	Median (range), %
Male	21	11	52.4
GA at delivery (wks)	20		36 3/7 (32 2/7 - 41 3/7)
Birth weight (g)	20		2360 (1750-3700)
Birth weight <p10	20	4	20
Primary closure	20	9	45
LOS (d)		20	35.5 (16-159)

GA, gestational age; LOS, Length of hospital stay; y, year; g, gram; d, day

Table 3. Physical measurements

	n	median	range	Z-score mean(SD; range)	Reference curve deviation from SD 0 (mean, 95%-CI)	p
Length	19	153	(105-191)	0.06 (1.03; -1.90-1.48)	0.23 (-0.25-0.72)	0.326
Weight	17	49.5	(16.7-95.0)	0.36 (1.49; -1.59-3.79)	0.57 (-0.24-1.38)	0.152
OFC	19	53.7	(49.5-59)	0.26 (1.16; -1.50-2.70)	0.26 (-0.30-0.83)	0.339
Arm span	17	154	(98-192)	0.29 (0.68; 0.00-2.00)	0.29 (-0.06-0.65)	0.096
Hand length	18	16.8	(12.0-20.5)	0.56 (1.20; -1.50-2.50)	0.56 (-0.03-1.16)	0.063
Palm length	18	9.5	(7.0-11.5)	0.39 (1.60; -2.50-2.00)	0.39 (-0.40-1.19)	0.310

OFC, occipital frontal cicumference; ICD, inner canthal distance; OCD, outer canthal distance; SD; standard deviation, n; number of cases

Four cases had mild neurodevelopmental abnormalities: Case 7 was diagnosed with Asperger syndrome. Case nr 4 had dyslexia and attended an individualized high school. Case 12 and case 16 needed physiotherapy for delayed gross and fine motor skills.

Three children displayed severe neurological disorders; case 8, born at 33 weeks of gestation, had a hemorrhage infarction in the left parietal lobe in the neonatal period, which led to right sided hemiplegia and epilepsy. He has no intellectual disability. Case 13, born at 36 weeks of gestation, with difficulties in feeding in the first year of life, has a borderline IQ (73) and motor impairment (apraxia) with pyramidal and extrapyramidal signs. At the age of thirteen she was re-evaluated because of progressive apraxia. Case 14 is now eleven years old and has epilepsy, autism and severe intellectual and motor disability. He was born at 38 weeks of gestation with Apgar scores of 8 and 9 (1 and 5 minutes) needed repeated abdominal surgeries and prolonged mechanical ventilation after primary closure, due to abdominal compartment syndrome and bowel adhesions. At the age of two years brain MRI, EEG, metabolic and ophthalmological investigations were normal. No syndromic diagnosis could be made.

Thirty-three per cent (7/21) of participants reported abdominal symptoms, obstipation (n=1), irritable bowel syndrome (n=3), severe reflux necessitating Percutaneous Endoscopic Gastrostomy-feeding (n=1), localized scar pain (n=2).

Family history

The parental education levels are described in Table 1. Parents were separated in 45% of cases. There was no family history of gastroschisis. One case had a sister with bilateral Wilms' tumor and a positive family history for Wilms' tumor. One patient had a fourth-degree relative with an omphalocele and situs inversus. Another case had a fifth degree relative with anal atresia. There were three cases with sibling stillbirths: a triplet with two intra uterine fetal deaths (IUFD) and one liveborn, an unexplained IUFD at seven months of gestation and one IUFD at six months of gestation with severe growth restriction and placental infarction.

Anthropometry and morphological examination

The median age at inclusion was 11 years (range 4-27 years). Two participants had a non-Caucasian father and a Caucasian mother. All other participants were of Caucasian descent. Physical and morphological examination could be performed in 19 children. Z-scores are shown in Table 2. Physical measurements in gastroschisis cases were not significantly abnormal.

The percentage of cases with one or more major abnormalities (excluding gastroschisis) was 15.8%, not significantly different (P=0.78) compared to the 21.8% in the normal population.[34] The percentage of cases with one or more minor anomalies was 94.7% versus 82.5% (P=0.23). The percentage of cases with two or more minor abnormalities was significantly increased in our cohort: 89.5% compared to 55.7% in the normal population (P=0.004).

Array results

Array was performed in 20 out of 21 cases. One participant completed the questionnaire and underwent physical examination, but had no blood drawn. In total eight CNVs were detected in five cases, accounting for a prevalence of 25% (5/20). The location and size of the CNVs, the corresponding protein-coding genes and the associated genetic disorders and the classification are summarized in Table 4. Array in the parents showed that all CNVs were inherited but one: a *de novo* 790-kb duplication of 8p23.3p23.2, comprising five protein-coding genes (case 7).

Table 4. Case characteristics

Case	Age at examination	Gender	Associated Gastroschisis	Neurocognitive deficits	Minor anomaly	Major anomaly	Array
1	27	F			7	0	Normal
2	25	F			2	0	Normal
3	23	F			3	0	Normal
4	23	M		Severe dyslexia	7	1, glandular hypospadias	NA
5	22	F			1	0	Normal
6	19	F			3	1, café au lait	Table 5
7	16	M		Asperger syndrome	6	0	Table 5
8	15	M		Hemiplegia and seizures	NA	NA	Normal
9	11	M			5	0	Normal
10	11	F			7	0	Normal
11	11	F			4	0	Normal
12	10	M			5	0	Normal
13	6	F		Mild intellectual (TIQ 62) and motor disability	5	0	Normal *
14	11	M		Severe intellectual and motor disability, autism, seizures	NA	NA	Table 5 ¥
15	6	M	Unilateral cryptorchism		2	1, bifid uvula	Normal
16	7	M	Unilateral cryptorchism		4	0	Normal
17	6	M	Unilateral cryptorchism		2	0	Table 5
18	5	F			3	0	Normal
19	4	M			0	0	Table 5
20	4	M			10	0	Normal
21	4	F			6	0	Normal

F; female, M; male, NA; not available, TIQ; total intelligent quotient, Table 5; see Table 5,
;additional Whole exome sequenscing (WES): 1164_1207 del p(pro389) mutation in the *MECP2* gene explaining the neurocognitive deficits,
(¥; additional WES: c.556G>A p.(Gly186Ser) (variant of unknown significance) was detected in the *KCNQ2* gene. *De novo* mutations in this gene cause an epileptic encephalopathy with poor developmental outcome. Inheritance is currently being determined by parental analysis.

Table 5. Array results

Case	Genetic test	Genetic finding Hg19	Gain/loss	Inherited	Size (kb)	Gene(s)	Description	OMIM morbid	Disorder(s) and inheritance	Classification
6	array-CGH	12q24.31 2: 125.087.355 - 125.375.986	Gain	Paternal	289	SCARB1 12:125.261.402-125.367.214	Scavenger receptor class B, member 1 [Source:HGNC Symbol;Acc:1664]	610762	High density lipoprotein cholesterol level quantitative trait locus?	Rare familial variant
		13q12.13 3: 26.043.098 - 26.134.801	Loss	Paternal	13	ATP8A2 13:25.946.209-26.599.989	ATPase, aminophospholipid transporter, class I, type 8A, member 2 [Source:HGNC Symbol;Acc:13533]	615268	Cerebellar ataxia, mental retardation, and disequilibrium syndrome AR	Rare familial variant
7	SNP-array	8p23.3p23.2 8: 1.547.527 - 2.337.112	Gain	*de novo*	790	MYOM 28:1.993.155-2.113.475	Myomesin 2 [Source:HGNC Symbol;Acc:7614]			VUS (variant of unknown significance)
						ARHGEF10 8:1.772.142-1.906.807	Rho guanine nucleotide exchange factor (GEF) 10 [Source:HGNC Symbol;Acc:14103]	608236	Slowed nerve conduction velocity AD	
						KBTBD11 8:1.922.044-1.955.102	Kelch repeat and BTB (POZ) domain containing 11 [Source:HGNC Symbol;Acc:29104]			
						CLN8 8:1.703.944-1.734.738	Ceroid-lipofuscinosis, neuronal 8 (epilepsy, progressive with mental retardation) [Source:HGNC Symbol;Acc:2079]	610003/600143	Ceroid lipofuscinosis, neuronal, 8; CLN8 Northern epilepsy variant AR/AR	

						DLGAP2 8:1.449.532- 1.656.642	Discs, large (Drosophila) homolog-associated protein 2 [Source:HGNC Symbol;Acc:2906]			
		5q35.1 5: 170.362.481 - 170.550.300	Loss	Paternal	190	RANBP17 5:170.288.874- 170.727.019	RAN binding protein 17 [Source:HGNC Symbol;Acc:14428]			Rare familial variant
14	SNP-array	Xp22.33 X: 1.531.648 - 1.674.744	Loss	Maternal	143	ASMTL X:1522032- 1572655	Acetylserotonin O-methyltransferase-like [Source:HGNC Symbol;Acc:751]			Rare familial variant
						P2RY8 X:1581465- 1656000	Purinergic receptor P2Y, G-protein coupled, 8 [Source:HGNC Symbol;Acc:15524]			
17	array-CGH	1p21.2 1: 100.583.680 - 100.653.766	Gain	Paternal	70	TRMT13 1:100.598.706- 100.616.053	tRNA methyltransferase 13 homolog (S. cerevisiae) [Source:HGNC Symbol;Acc:25502]			Rare familial variant
						LRRC39 1:100.614.409- 100.643.771	Leucine rich repeat containing 39 [Source:HGNC Symbol;Acc:28228]			
						DBT 1:100.652.475- 100.715.390	Dihydrolipoamide branched chain transacylase E2 [Source:HGNC Symbol;Acc:2698]	248600	Maple syrupe urine disease AR	
						SASS6 1:100.549.119- 100.598.511	Spindle assembly 6 homolog (C. elegans) [Source:HGNC Symbol;Acc:25403]			
19	array-CGH	4q35.2 4: 188.866.342 - 189.609.300	Loss	Maternal	740	TRIML2 4:189.012.427- 189.030.757	Tripartite motif family-like 2 [Source:HGNC Symbol;Acc:26378]			Rare familial variant
						ZFP42 4:188.916.925- 188.926.204	ZFP42 zinc finger protein [Source:HGNC Symbol;Acc:30949]			

					TRIML1 4:189.060.573-189.068.897	Tripartite motif family-like 1 [Source:HGNC Symbol;Acc:26698]	
	10q26.3 10: 134.582.745 - 134.998.388	Gain	Paternal	415	INPP5A 10:134.351.324-134.596.979	Inositol polyphosphate-5-phosphatase, 40kDa [Source:HGNC Symbol;Acc:6076]	Rare familial variant
					NKX6-2 10:134.598.297-134.599.556	NK6 homeobox 2 [Source:HGNC Symbol;Acc:19321]	
					KNDC1 10:134.973.951-135.039.916	Kinase non-catalytic C-lobe domain (KIND) containing 1 [Source:HGNC Symbol;Acc:29374]	
					TTC40 10:134.621.896-134.756.327	Tetratricopeptide repeat domain 40 [Source:HGNC Symbol;Acc:25247]	
					GPR123 10:134.884.433-134.945.179	G protein-coupled receptor 123 [Source:HGNC Symbol;Acc:13838]	

AR; autosomal recessive, AD; autosomal dominant, ?; inheritance unknown

Whole exome sequencing (WES)

Two patients (case 13 and 14) had intellectual disability. Because no specific syndrome diagnosis could be made, WES was performed. In case 13 a *de novo* 1164_1207del p. (Pro389*) mutation in the *MECP2* gene (methyl-CpG-binding protein 2) was detected. She was therefore diagnosed with a forme thruste of Rett syndrome, preserved speech variant.[36] In case 14 a single nucleotide variant (SNV) c.556G>A p.(Gly186Ser) (VUS) was detected in the *KCNQ2* gene. Inheritance is currently being determined by parental analysis. *De novo* mutations in this gene cause an epileptic encephalopathy with poor developmental outcome.[37] This is compatible with the phenotype in this case, who developed seizures the first year and has severe intellectual disability, without dysmorphic features or structural brain anomalies on MRI.

DISCUSSION

In this study we performed clinical morphological examination and array-analysis in a cohort of 21 gastroschisis cases and their parents in order to assess the value of genetic testing in these patients and to identify potential genetic causes or risk factors for gastroschisis. Additionally, WES was performed in two cases with intellectual disability. We found a significantly increased percentage of two or more minor morphological anomalies per patient as compared to healthy controls. The incidence of major morphological abnormalities was not increased, which is likely due to the fact that we only studied surviving patients. Previous studies reviewing morphological anomalies in gastroschisis patients were all retrospective and did not include systematic physical examination and scoring of minor morphological findings.[7,38,39] Normal values for the validation of classifications of phenotypic abnormalities, allowing for a proper evaluation of patterns of phenotypic abnormalities in patient groups with specific disorders, have only been available since 2008.[34,40] Minor anomalies have been shown to be more prevalent in patients with neurodevelopmental disorders[41-43], but also in patients with major congenital anomalies like congenital thyroid dysgenesis.[40] They are of particular interest, because they can serve as indicators of aberrant fetal development, not only referring to specific monogenetic syndromes, but also resulting from interaction between genetic and environmental disturbances.[34]

The minor anomalies at clinical morphological examination did not lead to a syndrome diagnosis in our gastroschisis cases. However, our finding that the percentage of minor anomalies is increased in patients with gastroschisis, cannot be explained by a localized event like vascular disruption or clot formation, a frequently hypothesized cause of gastroschisis.[12,44,45]

There is no established association between gastroschisis and cytogenetically visible chromosomal abnormalities.[39,46] Sporadic reports on trisomy 13 or 18 in newborns with gastroschisis are likely due

to omphalocele misclassification.[7,39] In our study also no major chromosomal abnormalities were found. This could be biased, because we included children who were presently alive, while children with a major chromosomal anomaly have a shortened lifespan.

It has been shown that in children with ID or congenital anomalies array-analysis has an increased diagnostic yield (15-20%) compared to standard karyotyping (3%).[47] Of the eight CNVs that were detected in five of our cases, all but one were inherited from a healthy parent. The *de novo* 790 kb duplication of 8p23.3p23.2 in case 7 was classified as VUS, because there is no overlap in the DGV and only two cases with 75% overlap are reported in our in house database, of which one is familiar and one also *de novo*. Both cases with overlapping duplications do not display gastroschisis. Duplication of either of the five genes in this duplication 8p is not known to cause monogenetic syndromes. Although the inherited nature of the CNVs in the other cases makes it unlikely that they are causal, it does not per definition exclude pathogenicity. CNVs are well recognized as susceptibility factors for various disorders and can have incomplete penetrance.[48-51] In many disorders, isolated structural anomalies as well as multifactorial disorders[21,52,53], array-analysis has allowed identification of CNVs containing candidate genes with a dosage dependent effect. The new monogenetic causes and target genes thus identified, yield valuable information on the pathogenesis of the disease.[20,49] Within the inherited CNVs in our patients, no genes could be identified that are currently known to be involved in causing gastroschisis. In the deleted / duplicated regions in our cases and the few gastroschisis cases in publically available databases, we could not identify a pattern pointing towards involvement of a specific genetic pathway (Appendix). Because we are the first to perform array in a cohort of children with gastroschisis, interpretation of our findings is hindered by the lack of knowledge on the contribution of genetics to the aetiology of gastroschisis in general and more specific by the limited data available on array-findings in children with gastroschisis. Future systematic application of array in all children with a congenital anomalies, including gastroschisis, is expected to yield sufficient data to enable the detection of rare pathogenic / risk conferring CNVs that are present significantly more often in patients with gastroschisis. This will allow determination of the prevalence of specific CNVs in cases versus healthy controls, as well as the detection of rare *de novo* causal gains or losses. In isolated structural defects like cardiac anomalies, craniofacial and renal disorders this has been shown to be successful only after several hundreds to thousands of patients were analysed.

In patients with normal array findings, WES has an additional diagnostic yield of at least 27%.[54] Sequencing the genomes of parent-offspring trios has revealed *de novo* single nucleotide variants (SNVs) in single genes as the major cause of rare sporadic malformation syndromes.[55] For reproductively lethal disease, which gastroschisis in essence is, the frequency with which the disease occurs, is proportional to the chance of pathogenic *de novo* mutations affecting the causative gene. Most monogenic disorders are therefore rare, because of the low probability of a mutational event in that specific gene. Polygenic disorders however, that can be caused by (one or more) mutations in multi-

ple genes, are more common.[55] Evidence to suggest that the genetic risk factors for gastroschisis are polygenic comes from studies in an inbred mouse strain with a high incidence (11%) of gastroschisis after X-ray exposure to the 1-cell stage zygote. Back-crossing yielded a frequency of gastroschisis too low for a single-recessive locus and statistical analysis was compatible with an additive threshold model, in which two or three genetic loci increased the susceptibility to an environmental factor (in this study: X-ray).[56,57] In line with this, Manley et al. showed that proper ventral body wall formation requires signaling of both *Hoxb2* and *Hoxb4* and that the involvement of other genes in generating the phenotype cannot be excluded.[58]

In our cohort, one, possibly two, monogenic disorders were identified by WES in cases with gastroschisis and intellectual disability. This is surprising in a cohort of only 21 patients and suggests that monogenetic disorders in cases with gastroschisis are underreported, especially since our inclusion criteria did not bias in favour of additional anomalies. Evidence that monogenic diagnosis can help unraveling genetic susceptibility pathways comes from another mostly sporadic disorder: Hirschsprung's disease. In 30% of cases however, congenital anomalies are present. Associated syndromes are diverse and the genetics highly complex, with the majority of rare genetic causes relating to susceptibility pathways. For many of the syndromic forms, it is still under discussion whether the genetic aberration is causative for the Hirschsprung's disease, or acts as a modifier in one of the susceptibility pathways.

Reports on monogenic disorders in patients with gastroschisis are rare and hard to find because the gastroschisis is almost exclusively labeled to be coincidental. Quelin reports on molecularly proven Smith-Lemli-Opitz syndrome in a fetus with gastroschisis.[59] Dy et al. detected compound heterozygous *TPP1* mutations in an eight year-old girl with gastroschisis and progressive ataxia, diagnosing her with late infantile neuronal ceroid lipofuscinosis (CLN2).[60] Because genetics diagnosis are often made later in life, and widespread application of WES to patients diagnostics has only become available around five years ago, underreporting of monogenetic diagnosis in population-based cohort studies of gastroschisis patients is likely. The consistent finding that major unrelated malformations are present in one in six (15%) children with gastroschisis[7,26,61,62] however, now justifies systematic genetic analysis in this subgroup.

CONCLUSIONS AND RECOMMENDATIONS

A (mono)genetic disorder should be actively sought for by genetic analysis, by a combination of array analysis and whole exome sequencing or, in the near future, whole genome sequencing. Associated anomalies / ID in children with gastroschisis should not be attributed to events in pre- and postnatal life associated with the gastroschisis or be regarded as coincidental. Syndrome evaluation

and genetic analysis are indicated when additional abnormalities / ID are present. We therefore recommend structural morphologic examination of all children with gastroschisis and paediatric follow-up of growth and development.

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REFERENCES

1. Loane M, Dolk H, Bradbury I, EUROCAT Working Group. Increasing prevalence of gastroschisis in Europe 1980-2002: A phenomenon restricted to younger mothers? *Paediatr Perinat Epidemiol*. 2007;21(4):363-369. 10.1111/j.1365-3016.2007.00820.x.
2. Chabra S, Gleason CA, Seidel K, Williams MA. Rising prevalence of gastroschisis in Washington State. *J Toxicol Environ Health A*. 2011;74(5):336-345. 10.1080/15287394.2011.534424.
3. Hernandez MD, Elizondo G, Barron C, Martinez L. Rising incidence of gastroschisis in a medical center at northeast mexico. *Birth Defects Res Part A Clin Mol Teratol*. 2009;85(5):440.
4. Mastroiacovo P, Lisi A, Castilla EE. The incidence of gastroschisis: Research urgently needs resources. *BMJ*. 2006;332(7538):423-424. 10.1136/bmj.332.7538.423-a.
5. Rankin J, Dillon E, Wright C. Congenital anterior abdominal wall defects in the north of England, 1986-1996: Occurrence and outcome. *Prenat Diagn*. 1999;19(7):662-668.
6. Stoll C, Alembik Y, Dott B, Roth MP. Omphalocele and gastroschisis and associated malformations. *Am J Med Genet A*. 2008;146A(10):1280-1285. 10.1002/ajmg.a.32297.
7. Mastroiacovo P, Lisi A, Castilla EE, Martinez-Frias ML, Bermejo E, Marengo L, Kucik J, Siffel C, Halliday J, Gatt M, Anneren G, Bianchi F, Canessa MA, Danderfer R, de Walle H, Harris J, Li Z, Lowry RB, McDonell R, Merlob P, Metneki J, Mutchinick O, Robert-Gnansia E, Scarano G, Sipek A, Potzsch S, Szabova E, Yevtushok L. Gastroschisis and associated defects: An international study. *Am J Med Genet A*. 2007;143(7):660-671. 10.1002/ajmg.a.31607.
8. Garvin J, Sampath V, Karody VR. Gastroschisis complicated by septo-optic dysplasia: Two distinct anomalies with a common origin. *AJP Rep*. 2016;6(1):e15-7. 10.1055/s-0035-1563720 [doi].
9. Drongowski RA, Smith RK,Jr, Coran AG, Klein MD. Contribution of demographic and environmental factors to the etiology of gastroschisis: A hypothesis. *Fetal Diagn Ther*. 1991;6(1-2):14-27.
10. Torfs CP, Velie EM, Oechsli FW, Bateson TF, Curry CJ. A population-based study of gastroschisis: Demographic, pregnancy, and lifestyle risk factors. *Teratology*. 1994;50(1):44-53. 10.1002/tera.1420500107.
11. Haddow JE, Palomaki GE, Holman MS. Young maternal age and smoking during pregnancy as risk factors for gastroschisis. *Teratology*. 1993;47(3):225-228. 10.1002/tera.1420470306.
12. Lubinsky M. Hypothesis: Estrogen related thrombosis explains the pathogenesis and epidemiology of gastroschisis. *Am J Med Genet A*. 2012;158A(4):808-811. 10.1002/ajmg.a.35203; 10.1002/ajmg.a.35203.
13. Salihu HM, Pierre-Louis BJ, Druschel CM, Kirby RS. Omphalocele and gastroschisis in the state of New York, 1992-1999. *Birth Defects Res A Clin Mol Teratol*. 2003;67(9):630-636. 10.1002/bdra.10113.
14. Williams LJ, Kucik JE, Alverson CJ, Olney RS, Correa A. Epidemiology of gastroschisis in metropolitan Atlanta, 1968 through 2000. *Birth Defects Res A Clin Mol Teratol*. 2005;73(3):177-183. 10.1002/bdra.20114.
15. Kohl M, Wiesel A, Schier F. Familial recurrence of gastroschisis: Literature review and data from the population-based birth registry "mainz model". *J Pediatr Surg*. 2010;45(9):1907-1912. 10.1016/j.jpedsurg.2010.05.003.
16. Hoyme HE, Higginbottom MC, Jones KL. The vascular pathogenesis of gastroschisis: Intrauterine interruption of the omphalomesenteric artery. *J Pediatr*. 1981;98(2):228-231.
17. Torfs CP, Christianson RE, Iovannisci DM, Shaw GM, Lammer EJ. Selected gene polymorphisms and their interaction with maternal smoking, as risk factors for gastroschisis. *Birth Defects Res A Clin Mol Teratol*. 2006;76(10):723-730. 10.1002/bdra.20310.
18. Cardonick E, Broth R, Kaufmann M, Seaton J, Henning D, Roberts N, Wapner R. Genetic predispositions for thromboembolism as a possible etiology for gastroschisis. *Am J Obstet Gynecol*. 2005;193(2):426-428. 10.1016/j.ajog.2004.12.010.

19. Hwang PJ, Kousseff BG. Omphalocele and gastroschisis: An 18-year review study. *Genet Med*. 2004;6(4):232-236.

20. Southard AE, Edelmann LJ, Gelb BD. Role of copy number variants in structural birth defects. *Pediatrics*. 2012;129(4):755-763. 10.1542/peds.2011-2337 [doi].

21. Chen X, Shen Y, Gao Y, Zhao H, Sheng X, Zou J, Lip V, Xie H, Guo J, Shao H, Bao Y, Shen J, Niu B, Gusella JF, Wu BL, Zhang T. Detection of copy number variants reveals association of cilia genes with neural tube defects. *PLoS One*. 2013;8(1):e54492. 10.1371/journal.pone.0054492 [doi].

22. Merks JH, Ozgen HM, Koster J, Zwinderman AH, Caron HN, Hennekam RC. Prevalence and patterns of morphological abnormalities in patients with childhood cancer. *JAMA*. 2008;299(1):61-69. 10.1001/jama.2007.66; 10.1001/jama.2007.66.

23. Ozgen H, Hellemann GS, Stellato RK, Lahuis B, van Daalen E, Staal WG, Rozendal M, Hennekam RC, Beemer FA, van Engeland H. Morphological features in children with autism spectrum disorders: A matched case-control study. *J Autism Dev Disord*. 2011;41(1):23-31. 10.1007/s10803-010-1018-7; 10.1007/s10803-010-1018-7.

24. Gorlin R, Cohen M, Hennekam R. *Syndromes of the Head and Neck*. 4th ed. Oxford England: Oxford University Press; 2001.

25. Marden PM, Smith DW, Mcdonald MJ. Congenital anomalies in the newborn infant, including minor variations. a study of 4,412 babies by surface examination for anomalies and buccal smear for sex chromatin. *J Pediatr*. 1964;64:357-371.

26. Feldkamp ML, Botto LD, Byrne JL, Krikov S, Carey JC. Clinical presentation and survival in a population-based cohort of infants with gastroschisis in utah, 1997-2011. *Am J Med Genet A*. 2016;170A(2):306-315. 10.1002/ajmg.a.37437 [doi].

27. CBS. Statistics Netherlands, The Hague/Heerlen.. http://www.cbs.nl. Updated 2012. Accessed 11/08, 2012.

28. Lanting CI, Buitendijk SE, Crone MR, Segaar D, Bennebroek Gravenhorst J, van Wouwe JP. Clustering of socioeconomic, behavioural, and neonatal risk factors for infant health in pregnant smokers. *PLoS One*. 2009;4(12):e8363. 10.1371/journal.pone.0008363.

29. Fredriks, A M van Buuren, S Burgmeijer, R J Meulmeester, J F Beuker, R J Brugman, E Roede, M J Verloove Vanhorick, S P Wit,J M. Continuing positive secular growth change in the Netherlands 1955-1997. *Pediatr Res*. 2000;47(3):316-323.

30. Watson EH, Lowrey GH. *In Growth and Development of Children*. Chicago, USA: Year book medical publishers Chicago; 1962.

31. Laestadius ND, Aase JM, Smith DW. Normal inner canthal and outer orbital dimensions. *J Pediatr*. 1969;74(3):465-468.

32. Feingold M, Bossert WH. Normal values for selected physical parameters: An aid to syndrome delineation. *Birth Defects Orig Artic Ser*. 1974;10(13):1-16.

33. Merks JH, van Karnebeek CD, Caron HN, Hennekam RC. Phenotypic abnormalities: Terminology and classification. *Am J Med Genet A*. 2003;123A(3):211-230. 10.1002/ajmg.a.20249.

34. Merks JH, Ozgen HM, Cluitmans TL, van der Burg-van Rijn JM, Cobben JM, van Leeuwen FE, Hennekam RC. Normal values for morphological abnormalities in school children. *Am J Med Genet A*. 2006;140(19):2091-2109. 10.1002/ajmg.a.31355 [doi].

35. Coe BP, Witherspoon K, Rosenfeld JA, van Bon BW, Vulto-van Silfhout AT, Bosco P, Friend KL, Baker C, Buono S, Vissers LE, Schuurs-Hoeijmakers JH, Hoischen A, Pfundt R, Krumm N, Carvill GL, Li D, Amaral D, Brown N, Lockhart PJ, Scheffer IE, Alberti A, Shaw M, Pettinato R, Tervo R, de Leeuw N, Reijnders MR, Torchia BS, Peeters H, O'Roak BJ, Fichera M, Hehir-Kwa JY, Shendure J, Mefford HC, Haan E, Gecz J, de Vries BB, Romano C, Eichler EE. Refining analyses of copy number variation identifies specific genes associated with developmental delay. *Nat Genet*. 2014;46(10):1063-1071. 10.1038/ng.3092 [doi].

36. De Bona C, Zappella M, Hayek G, Meloni I, Vitelli F, Bruttini M, Cusano R, Loffredo P, Longo I, Renieri A. Preserved speech variant is allelic of classic rett syndrome. *Eur J Hum Genet.* 2000;8(5):325-330. 10.1038/sj.ejhg.5200473 [doi].

37. Kato M, Yamagata T, Kubota M, Arai H, Yamashita S, Nakagawa T, Fujii T, Sugai K, Imai K, Uster T, Chitayat D, Weiss S, Kashii H, Kusano R, Matsumoto A, Nakamura K, Oyazato Y, Maeno M, Nishiyama K, Kodera H, Nakashima M, Tsurusaki Y, Miyake N, Saito K, Hayasaka K, Matsumoto N, Saitsu H. Clinical spectrum of early onset epileptic encephalopathies caused by KCNQ2 mutation. *Epilepsia.* 2013;54(7):1282-1287. 10.1111/epi.12200 [doi].

38. Corona-Rivera JR, Nieto-Garcia R, Lopez-Marure E, Cardenas-Ruiz Velasco JJ, Bobadilla-Morales L, Mellin-Sanchez EL, Aguirre-Guillen RL, Perez-Ramirez RO, Zapata-Aldana E, Sandoval-Talamantes AK, Solis-Ledezma S, Corona-Rivera A, Gomez-Ruiz LM. Associated congenital anomalies in infants with isolated gastroschisis: A single-institutional experience. *Am J Med Genet A*. 2016;170A(2)316-321. 10.1002/ajmg.a.37433 [doi].

39. Hunter AG, Stevenson RE. Gastroschisis: Clinical presentation and associations. *Am J Med Genet C Semin Med Genet.* 2008;148C(3):219-230. 10.1002/ajmg.c.30178.

40. Kempers MJ, Ozgen HM, Vulsma T, Merks JH, Zwinderman KH, de Vijlder JJ, Hennekam RC. Morphological abnormalities in children with thyroidal congenital hypothyroidism. *Am J Med Genet A.* 2009;149A(5):943-951. 10.1002/ajmg.a.32777 [doi].

41. Alexander RC, Mukherjee S, Richter J, Kaufmann CA. Minor physical anomalies in schizophrenia. *J Nerv Ment Dis*. 1994;182(11):639-644.

42. Ozgen HM, Hop JW, Hox JJ, Beemer FA, van Engeland H. Minor physical anomalies in autism: A meta-analysis. *Mol Psychiatry*. 2010;15(3):300-307. 10.1038/mp.2008.75 [doi].

43. McGrath JJ, van Os J, Hoyos C, Jones PB, Harvey I, Murray RM. Minor physical anomalies in psychoses: Associations with clinical and putative aetiological variables. *Schizophr Res.* 1995;18(1):9-20. 092099649500016X [pii].

44. Hoyme HE, Jones MC, Jones KL. Gastroschisis: Abdominal wall disruption secondary to early gestational interruption of the omphalomesenteric artery. *Semin Perinatol.* 1983;7(4):294-298.

45. Lubinsky MS. Association of prenatal vascular disruptions with decreased maternal age. *Am J Med Genet.* 1997;69(3):237-239.

46. Nicolaides KH, Snijders RJ, Cheng HH, Gosden C. Fetal gastro-intestinal and abdominal wall defects: Associated malformations and chromosomal abnormalities. *Fetal Diagn Ther.* 1992;7(2):102-115.

47. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA, Feuk L, Friedman JM, Hamosh A, Jackson L, Kaminsky EB, Kok K, Krantz ID, Kuhn RM, Lee C, Ostell JM, Rosenberg C, Scherer SW, Spinner NB, Stavropoulos DJ, Tepperberg JH, Thorland EC, Vermeesch JR, Waggoner DJ, Watson MS, Martin CL, Ledbetter DH. Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet*. 2010;86(5):749-764. 10.1016/j.ajhg.2010.04.006 [doi].

48. Hanemaaijer NM, Sikkema-Raddatz B, van der Vries G, Dijkhuizen T, Hordijk R, van Essen AJ, Veenstra-Knol HE, Kerstjens-Frederikse WS, Herkert JC, Gerkes EH, Leegte LK, Kok K, Sinke RJ, van Ravenswaaij-Arts CM. Practical guidelines for interpreting copy number gains detected by high-resolution array in routine diagnostics. *Eur J Hum Genet*. 2012;20(2):161-165. 10.1038/ejhg.2011.174 [doi].

49. Bianco AM, Girardelli M, Tommasini A. Genetics of inflammatory bowel disease from multifactorial to monogenic forms. *World J Gastroenterol.* 2015;21(43):12296-12310. 10.3748/wjg.v21.i43.12296 [doi].

50. Jarick I, Volckmar AL, Putter C, Pechlivanis S, Nguyen TT, Dauvermann MR, Beck S, Albayrak O, Scherag S, Gilsbach S, Cichon S, Hoffmann P, Degenhardt F, Nothen MM, Schreiber S, Wichmann HE, Jockel KH, Heinrich J, Tiesler CM, Faraone SV, Walitza S, Sinzig J, Freitag C, Meyer J, Herpertz-Dahlmann B, Lehmkuhl G, Renner TJ, Warnke A, Romanos M, Lesch KP, Reif A, Schimmelmann BG, Hebebrand J, Scherag A, Hinney A. Genome-

wide analysis of rare copy number variations reveals PARK2 as a candidate gene for attention-deficit/ hyperactivity disorder. *Mol Psychiatry*. 2014;19(1):115-121. 10.1038/mp.2012.161 [doi].

51. Girirajan S, Rosenfeld JA, Cooper GM, Antonacci F, Siswara P, Itsara A, Vives L, Walsh T, McCarthy SE, Baker C, Mefford HC, Kidd JM, Browning SR, Browning BL, Dickel DE, Levy DL, Ballif BC, Platky K, Farber DM, Gowans GC, Wetherbee JJ, Asamoah A, Weaver DD, Mark PR, Dickerson J, Garg BP, Ellingwood SA, Smith R, Banks VC, Smith W, McDonald MT, Hoo JJ, French BN, Hudson C, Johnson JP, Ozmore JR, Moeschler JB, Surti U, Escobar LF, El-Khechen D, Gorski JL, Kussmann J, Salbert B, Lacassie Y, Biser A, McDonald-McGinn DM, Zackai EH, Deardorff MA, Shaikh TH, Haan E, Friend KL, Fichera M, Romano C, Gecz J, DeLisi LE, Sebat J, King MC, Shaffer LG, Eichler EE. A recurrent 16p12.1 microdeletion supports a two-hit model for severe developmental delay. *Nat Genet*. 2010;42(3):203-209. 10.1038/ng.534 [doi].
52. Mullen SA, Carvill GL, Bellows S, Bayly MA, Trucks H, Lal D, Sander T, Berkovic SF, Dibbens LM, Scheffer IE, Mefford HC. Copy number variants are frequent in genetic generalized epilepsy with intellectual disability. *Neurology*. 2013;81(17):1507-1514. 10.1212/WNL.0b013e3182a95829 [doi].
53. Green RF, Moore C. Incorporating genetic analyses into birth defects cluster investigations: Strategies for identifying candidate genes. *Birth Defects Res A Clin Mol Teratol*. 2006;76(11):798-810. 10.1002/bdra.20280.
54. Gilissen C, Hehir-Kwa JY, Thung DT, van de Vorst M, van Bon BW, Willemsen MH, Kwint M, Janssen IM, Hoischen A, Schenck A, Leach R, Klein R, Tearle R, Bo T, Pfundt R, Yntema HG, de Vries BB, Kleefstra T, Brunner HG, Vissers LE, Veltman JA. Genome sequencing identifies major causes of severe intellectual disability. *Nature*. 2014;511(7509):344-347. 10.1038/nature13394 [doi].
55. Veltman JA, Brunner HG. De novo mutations in human genetic disease. *Nat Rev Genet*. 2012;13(8):565-575. 10.1038/nrg3241 [doi].
56. Hillebrandt S, Streffer C, Montagutelli X, Balling R. A locus for radiation-induced gastroschisis on mouse chromosome 7. *Mamm Genome*. 1998;9(12):995-997.
57. Hillebrandt S, Streffer C, Muller WU. Genetic analysis of the cause of gastroschisis in the HLG mouse strain. *Mutat Res*. 1996;372(1):43-51. 10.1016/S0027-5107(96)00109-1.
58. Manley NR, Barrow JR, Zhang T, Capecchi MR. Hoxb2 and hoxb4 act together to specify ventral body wall formation. *Dev Biol*. 2001;237(1):130-144. 10.1006/dbio.2001.0365 [doi].
59. Quelin C, Loget P, Verloes A, Bazin A, Bessieres B, Laquerriere A, Patrier S, Grigorescu R, Encha-Razavi F, Delahaye S, Jouannic JM, Carbonne B, D'Herve D, Aubry MC, Mace G, Harvey T, Ville Y, Viot G, Joye N, Odent S, Attie-Bitach T, Wolf C, Chevy F, Benlian P, Gonzales M. Phenotypic spectrum of fetal smith-lemli-opitz syndrome. *Eur J Med Genet*. 2012;55(2):81-90. 10.1016/j.ejmg.2011.12.002; 10.1016/j.ejmg.2011.12.002.
60. Dy ME, Sims KB, Friedman J. TPP1 deficiency: Rare cause of isolated childhood-onset progressive ataxia. *Neurology*. 2015;85(14):1259-1261. 10.1212/WNL.0000000000001876 [doi].
61. Stoll C, Alembik Y, Dott B, Roth MP. Risk factors in congenital abdominal wall defects (omphalocele and gastroschisi): A study in a series of 265,858 consecutive births. *Ann Genet*. 2001;44(4):201-208.
62. Molik KA, Gingalewski CA, West KW, Rescorla FJ, Scherer LR, Engum SA, Grosfeld JL. Gastroschisis: A plea for risk categorization. *J Pediatr Surg*. 2001;36(1):51-55. 10.1053/jpsu.2001.20004.

APPENDIX 1A

Decipher search

Decipher ID	Phenotype	Age at initial presentation	Gender	CNV Location	Inherited	Genes	Morbid
282125	Bladder exstrophy	3	M	8:82061218-84510562	Unknown	CHMP4C	-
	Gastroschisis					FABP12	-
	Global developmental delay					FABP4	-
	Growth delay					FABP5	-
	Hypdronephrosis					FABP9	-
	Hypospadia					IMPA1	-
	Motor delay					PMP2	-
						SLC10A5	-
						SNX16	-
						ZFAND1	-
				15: 85790660-86431300	Unknown	AKAP13	-
						KLHL25	
285774	Agenesis of corpus	<1	M	15:55547690-55945030	Paternal	C150rf65	-
	callosum, Cardiomyopathy,				constitutive in	CCPG1	-
	Cataract, Cerebellar vermis				father	DYX1C1	susceptibility dyslexia, ciliary
	hypoplasia, Concentric					PIGB	dyskinesia, primary, 25, with or
	hypertrophic cardiomyopathy,					PRTG	without situs inversus
	Encephalopathy, Gastroschisis,					PYGO1	-
	Global developmental delay,					RAB27A	-
	Hyperreflexia, Microcephaly,						-
	Optic nerve hypoplasia						griscelli syndrome with
							hemophagocytic syndrome
							partial albinism and
							immunodeficiency syndrome
							paid syndrome
287967	Gastroschisis		Unknown	11:38910017-39041736	Unknown	-	

				21:36679995-36780711	Unknown	RUNX1	Platelet disorder, with associated AML
289276	Gastroschisis, Cholestatic liver disease	Unknown	Unknown	1:229151474-229318534	Paternal, constitutive in father	-	
294472	Gastroschisis	<1	F	2:2783017-3863117	Maternal, constitutive in mother	ADI1 ALLC COLEC11 DCDC2C RNASEH1 RPS7 TRAPPC12 TSSC1	- - ptosis of eyelids with diastasis recti and hip dysplasia oculo-skeletal-abdominal syndrome osa syndrome carnevale syndrome, formerly - Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal recessive 2 Diamond-Blackfan anemia (DBA) is an inherited red blood cell aplasia - -

319617	Gastroschisis	Prenatal	M	22:23833937-35065576	Paternal, constitutive in father	ADORA2A	-
						C22orf15	-
						C22orf43	-
						CABIN1	-
						CHCHD10	Frontotemporal dementia and/or
						DDT	amyotrophic lateral sclerosis 2
						DDTL	-
						DERL3	-
						FAM211B	-
						GGT1	-
						GGT5	-
						GSTT1	-
						GSTT2	-
						GSTT2B	-
						GUCD1	Agammaglobulinemia 2
						IGLL1	Rheumatoid arthritis, systemic
						MIF	juvenile
						MMP11	-
						RGL4	-
						SLC2A11	-
						SMARCB1	Schwannomatosis, Rhabdoid
						SNRPD3	predisposition syndrome 1
						SPECC1L	-
						SUSD2	Opitz GBBB syndrome, type II facial
						UPB1	cleft, oblique 1
						VPREB3	-
						ZNF70	Beta-ureidopropionase deficiency
							-
							-

F; female, M; male, NA; not available
Search query: (gastroschisis) Search date: 28-7-2016.

APPENDIX 1B

MEDLINE and Embase search

Author	study	Phenotype	Genetic testing results	Genes identified
Brockmann K	Overlap of Moebius and oromandibular limb hypogenesis syndrome with gastroschisis and pulmonary hypoplasia. *Am J Med Genet A.* 2009 Dec;149A(12):2832-7. doi: 10.1002/ajmg.a.33111.	(OMIM 103300) Moebius syndrome comprising hypoplasia of the tongue and mandible, brachydactyly of halluces, cranial nerve palsies with bilateral facial paralysis and an inability to execute horizontal eye movements. Gastroschisis	high-resolution array-based comparative genomic hybridization did not reveal any causative submicroscopic copy number changes. Testing for uniparental disomy of chromosomes 7, 14, 15, 16, and 20 was normal	None
Heinrich J.K.R.	Prenatal Genomic Profiling of Abdominal Wall Defects through Comparative Genomic Hybridization: Perspectives for a New Diagnostic Tool *Fetal Diagn Ther.* 2007;22(5):361-4. Epub 2007 Jun 5.	All of the seven fetuses studied displayed a normal G-band karyotype. Six fetuses displayed a normal disomic profile through CGH and one sample has displayed ish cgh enh 3q26]qter result (ICSN). The fetus with this imbalance of chromosome 3 was re-classified as a ruptured omphalocele, instead of gastroschisis, after birth.		None
Shi Y.	Left-sided gastroschisis with placenta findings: Case report and literature review *IJCEP* 2012 5:3 (243-246)	Large left-sided gastroschisis with pulmonary hypoplasia, scoliosis, ventricular septal defect and absence of gallbladder.	Postmortem comparative genomic hybridization micro array did not identify a specific genetic abnormality.	None

Dy M.	TPP1 deficiency: rare cause of isolated childhood-onset progressive ataxia *Neurology* 2015;85(14):1259-1261	Gastroschisis. Devel opment was normal except for stuttering (age 3). Fine motor difficulties began at age 4. Abnormalities of gait, balance, coordination, and difficulties with aca- demic performance were noted at age 6. Neurocognitive assessment (age 8) identified impaired visual processing, visual memory, and attention, and expres- sive/ receptive language skills in the below average to average range.	Whole-exome sequencing revealed compound heterozygous mutations in TPP1 (common splice, c.509-1G.C and c.1029G.C, p.Glu343Asp). TPP1 activity was significantly reduced in blood and fibroblasts	heterozygous mutations in TPP1

Search query: (gastroschisis [tiab] AND (array OR CGH OR genes OR genetic OR CNV OR deletion OR duplication OR mutation)
Search date: 28-07-2016 Total articles: 142

APPENDIX 1C

Malcards.org and genecards.org search

Symbole	Description	Implication	Article
ACHE	acetylcholinesterase (Yt blood group)	GeneCards inferred via : Publications, Disorders (show sections)	Amniotic fluiacetylcholinesterase is found in gastroschisis but not omphalocele. Alterations of enteric nerve plexus in experimental gastroschisis: is there a delay in the maturation?
HOXB5	homeobox B5	GeneCards inferred via : Disorders (show sections)	
BMP1	bone morphogenetic protein 1	GeneCards inferred via : Publications (show sections)	Mutational analysis of the BMP-1 gene in patients with gastroschisis
ADD1	adducin 1 (alpha)	GeneCards inferred via : Publications (show sections)	Selected gene polymorphisms and their interaction with maternal smoking, as risk factors for gastroschisis.
CST3	cystatin C	GeneCards inferred via : Publications (show sections)	Amnioexchange for fetuses with gastroschisis: is it effective?
MPO	myeloperoxidase	GeneCards inferred via : Publications (show sections)	Amnioexchange for fetuses with gastroschisis: is it effective?
NOS1	nitric oxide synthase 1 (neuronal)	GeneCards inferred via : Publications (show sections)	The effect on the intestines of continuous release...y system: an experimental study in a chick embryo gastroschisis model.
NPPA	natriuretic peptide A	GeneCards inferred via : Publications (show sections)	Selected gene polymorphisms and their interaction with maternal smoking, as risk factors for gastroschisis
AFP	alpha-fetoprotein	GeneCards inferred via : Disorders (show sections)	
F2	coagulation factor II (thrombin)	GeneCards inferred via : Publications (show sections)	Genetic predispositions for thromboembolism as a possible aetiology for gastroschisis.
F5	coagulation factor V (proaccelerin, labile factor)	GeneCards inferred via : Publications (show sections)	Genetic predispositions for thromboembolism as a possible aetiology for gastroschisis.

ICAM1	Intercellular adhesion molecule 1	GeneCards inferred via : Publications (show sections)	Selected gene polymorphisms and their interaction with maternal smoking, as risk factors for gastroschisis.
MTHFR	methylenetetrahydrofolate reductase (NAD(P)H)	GeneCards inferred via : Publications (show sections)	Genetic predispositions for thromboembolism as a possible aetiology for gastroschisis.
NOS3	nitric oxide synthase 3 (endothelial cell)	GeneCards inferred via : Publications (show sections)	Selected gene polymorphisms and their interaction with maternal smoking, as risk factors for gastroschisis.
IL6	interleukin 6 (interferon, beta 2)	GeneCards inferred via : Publications (show sections)	Amnioexchange for fetuses with gastroschisis: is it effective?
AEBP1	AE binding protein 1	GeneCards inferred via : Publications, Disorders (show sections)	AEBP1 gene variants in infants with gastroschisis.
SLPI	secretory leukocyte peptidase inhibitor	GeneCards inferred via : Publications (show sections)	Amnioexchange for fetuses with gastroschisis: is it effective?
BMP6	bone morphogenetic protein 6	GeneCards inferred via : Publications (show sections)	Amnioexchange for fetuses with gastroschisis: is it effective?
NSD1	Nuclear Receptor Binding SET Domain Protein 1		?
CDKN1C	Cyclin-Dependent Kinase Inhibitor 1C (P57, Kip2)		?
CYP1A2	Cytochrome P450, Family 1, Subfamily A, Polypeptide 2		Maternal smoking, xenobiotic metabolizing enzyme gene variants, and gastroschisis risk.
CYP1A1	Cytochrome P450, Family 1, Subfamily A, Polypeptide 1		Maternal smoking, xenobiotic metabolizing enzyme gene variants, and gastroschisis risk.
NAT2	N-Acetyltransferase 2 (Arylamine N-Acetyltransferase)		Maternal smoking, xenobiotic metabolizing enzyme gene variants, and gastroschisis risk.
MYBPC1	Myosin Binding Protein C, Slow Type		*ymptoms for diseases linked to the geneMYBPC1* distal arthrogryposis: gastroschisis
MYH3	Myosin, Heavy Chain 3, Skeletal Muscle, Embryonic		distal arthrogryposis: gastroschisis
MYBPC2	Myosin Binding Protein C, Fast Type		distal arthrogryposis: gastroschisis
AFD1	Acrofacial Dysostosis 1, Nager Type		acrofacial dysostosis 1, nager type: gastroschisis

TNNT3	Troponin T Type 3 (Skeletal, Fast)	distal arthrogryposis: gastroschisis
TNNI2	Troponin I Type 2 (Skeletal, Fast)	distal arthrogryposis: gastroschisis
MYH8	Myosin, Heavy Chain 8, Skeletal Muscle, Perinatal	distal arthrogryposis: gastroschisis
TPM2	Tropomyosin 2 (Beta)	distal arthrogryposis: gastroschisis
CFL2	Cofilin 2 (Muscle)	distal arthrogryposis: gastroschisis
SF3B4	Splicing Factor 3b, Subunit 4, 49kDa	acrofacial dysostosis 1, nager type: gastroschisis
TUBA8	Tubulin, Alpha 8	distal arthrogryposis: gastroschisis
TAT	Tyrosine Aminotransferase	hanhart syndrome: gastroschisis
PIEZO2	Piezo-Type Mechanosensitive Ion Channel Component 2	distal arthrogryposis: gastroschisis
WNT3	Wingless-Type MMTV Integration Site Family, Member 3	tetra-amelia syndrome: gastroschisis
ECEL1	Endothelin Converting Enzyme-Like 1	distal arthrogryposis: gastroschisis

Search term: gastroschisis, search date 28-7-2016

APPENDIX 1D

London Medical databases

Phenotype	Inherited	Genes identified	Location (CNV/gene)
arthrogryposis affects all four limbs in approximately two thirds of patients, the upper limbs predominantly in a quarter, and the lower limbs predominantly in the rest. (..) Amyoplasia and gastroschisis are occasionally associated.	Uncertain	-	2q14?; 5q14?; 5q23?
Asternia - cardiac, diaphragmatic, and abdominal defects	Uncertain	ALDH1A2, PORCN,	-
Asternia - cardiac, diaphragmatic, and abdominal defects	Uncertain	PORCN, ALDH1A2	-
ruck syndrome - osteogenesis imperfecta; contractures	Autosomal recessive	FKBP10, PLOD2	17p12, 17q21
ruck syndrome - osteogenesis imperfecta; contractures	Autosomal recessive	PLOD2, FKBP10	17p12, 17q21
Chromosome 16 - maternal disomy	Disomy	-	16
Crane-Heise - clefting; skeletal anomalies	Autosomal recessive	-	-
Goltz (focal dermal hypoplasia)	X-linked dominant	PORCN	Xp22;9q32-9q34?
Rosenak (1991) - tetraamelia; pulmonary hypoplasia	Autosomal recessive	WNT3	17q21
Schizencephaly	Autosomal dominant	COL4A1, EMX2	10q26; 8q24?; 5q21-23?
Schizencephaly	Autosomal dominant	EMX2, COL4A1	10q26; 8q24?; 5q21-23?
Smith-Lemli-Opitz syndrome type I	Autosomal recessive	SLOS	11q12-11q13
Search term: gastroschisis, search date: January 2016			

PART II

Antenatal ultrasound markers to predict neonatal outcome

Chapter

5

Reference curves for the normal fetal small bowel and colon diameters; their usefulness in fetuses with suspected dilated bowel

Chiara C.M.M. Lap, Charlotte S. Voskuilen, Lourens R. Pistorius, Eduard J.H. Mulder, Gerard H.A. Visser, Gwendolyn T.R. Manten

(Submitted)

ABSTRACT

Objectives: To establish reference curves of normal fetal small bowel and colon diameters and to assess the clinical applicability.

Method: Serial longitudinal ultrasound examinations at four-weekly intervals between 20 to 41 weeks of gestation in 39 low-risk fetuses. The largest loop of the small bowel and colon was identified. The bowel lumen short axis was measured. Linear mixed modeling was used to determine individual developmental trajectories. Twenty-eight fetuses with suspected bowel dilatation were analysed relative to the reference curves.

Results: Development of the small bowel and colon diameters was best described by a linear and cubic model, respectively. The intra-observer and inter-observer concordance were >0.94. In cases with suspected bowel dilatation, normal fetal outcome occurred if the bowel dilatation was transient. Progressive increase of fetal bowel diameter was associated with pathology after birth. Cases with small bowel pathology had a Z-score >8 after 25 weeks of gestation.

Conclusion: We provided the first ultrasound reference curves for normal fetal small bowel and colon diameters. Progressive increase of the fetal bowel diameter Z-score was highly predictive of intestinal abnormalities after birth. Longitudinal follow-up of dilated fetal bowel is important to distinguish normality from disease.

INTRODUCTION

The presence of dilated bowel loops on prenatal ultrasound may be a marker for fetal bowel obstruction and is found in various intestinal disorders, including bowel atresia, midgut volvulus, and meconium ileus.[1] Prenatal diagnosis of these conditions provides an opportunity for parental counselling, close monitoring during pregnancy and for delivery in a centre with a paediatric surgery unit. Some cases may benefit from iatrogenic preterm delivery, for example intestinal volvulus that may lead to severe bowel necrosis and fetal demise.[2] However, prenatal bowel dilatation can also be transient and even if the dilatation persists until delivery it is possible that no abnormalities are found at postnatal evaluation.[3-5] Parental counselling regarding fetal dilated bowel may therefore be challenging.

To identify pathologically dilated bowel, knowledge of the physiological and gestational age related increase in diameter of small bowel and colon is needed. To date there is no standardised method to assess the fetal bowel diameter. Furthermore, only limited data has been published on reference values for fetal intestinal measurements. None of these studies have used longitudinal data[6-8] and some studies only used post mortem specimens.[9,10]

The aim of our study was to establish reference curves of the normal fetal small bowel and colon diameters using longitudinal prospective data and to assess if these curves can be used to identify pathologically dilated bowel disease.

METHODS

Prospective longitudinal reference curves of fetal bowel diameter

To construct reference ranges of normal fetal bowel development, we included thirty-nine healthy pregnant women in a prospective longitudinal study.

In all women gestational age was determined by measurement of crown-rump length in the first trimester of pregnancy. A second trimester anomaly scan did not reveal any anomalies. We only included cases with an estimated fetal weight between the 10th and 90th percentiles[11] in the absence of risk factors that might affect fetal growth, such as previous intra-uterine growth restriction, maternal disease, or maternal use of medication. The study was reviewed and approved by the local Medical Ethics Committee of the University Medical Center Utrecht and informed consent was obtained from all participants.

Ultrasound examinations were carried out at four-weekly intervals starting at 20 weeks of gestation. All examinations were done by one observer (CL), using a General Electric Voluson 730 or E8 (General Electric Healthcare, London) ultrasound machine, with a 4-8 MHz transabdominal trans-

ducer. Biometry (including fetal head circumference, abdominal circumference and femur length) was performed, followed by ultrasound evaluation of the fetal bowel. The largest loops of the small bowel and colon were identified in a coronal plane of the fetal abdomen. For both small bowel and colon, the short axis of the bowel lumen was measured (from inner to inner bowel wall) (Figure 1).

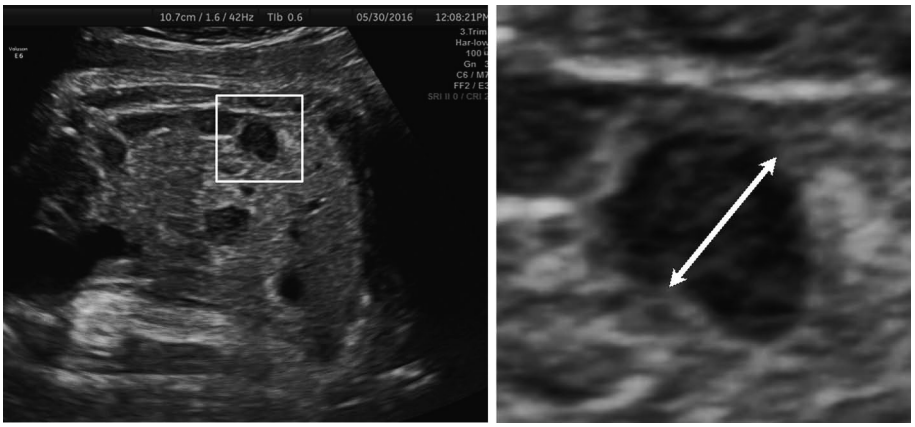

Figure 1. Identification of the largest loop of the colon (coronal plane) at 35 weeks of gestation. Measurement of the short axis of the bowel lumen (inner to inner bowel wall).

Data management and statistical analysis were performed with SPSS for Windows (version 21.0, IBM/SPSS Inc., Chicago, IL, USA). The serial measurements available for each fetus were analysed with multilevel (mixed-effects) modeling to determine the individual developmental trajectories of the small bowel and colon diameters. The first level comprises the variation between gestational ages within fetuses and the second level the variation between individual fetuses. We explored linear, quadratic, and cubic functions of gestational age for the two intestinal variables. The means and 95% prediction intervals (PIs) of the diameters of the small bowel and colon for consecutive gestational ages were calculated. The intra-observer agreement was calculated with intra-class correlation coefficient (ICC) based on two measurements in 39 cases by one observer and the inter-observer agreement was calculated with ICC based on 39 repeated measurements by two observers (GM, LP) blinded for type of bowel and outcome.

Assessment of clinical applicability

To assess the diagnostic applicability of the developed reference curves we identified cases with suspected dilated bowel using the prenatal ultrasound database of the Wilhelmina Children's Hospital, Utrecht, a tertiary referral hospital. Ultrasound examinations were performed between 1st of January 2007 and 31st of December 2013. The suspicion of dilated bowel was based on the subjective assessment of the sonographer.

Fetuses with ultrasound findings suggestive of duodenal atresia (double bubble sign), additional extra-gastrointestinal anomalies or with chromosomal abnormalities were excluded. Stored ultrasound images were reviewed for each patient. The short axis of the largest dilated bowel loop was remeasured in the images using Image J version 1.48 (NIH, USA). If more examinations were available, serial ultrasound images were reviewed to assess whether the dilatation resolved, persisted, or increased over time. Hospital charts were reviewed for maternal, perinatal, and neonatal characteristics. If patients did not receive further care at our centre, the referral hospitals were contacted in order to retrieve follow-up data. In each case we calculated Z-scores of the small bowel or colon diameter relative to the study reference curves.

RESULTS

Prospective longitudinal reference curves of fetal bowel diameter

A total of 198 ultrasound examinations were performed in 39 uneventful pregnancies. The first ultrasound was performed at 20 weeks of gestation. Repeat scans were performed at four-week interval (median 4.0; IQR 4.0-4.4 weeks) until labor. Delivery occurred at a median gestational age of 40 weeks 6 days (range 36 weeks 4 days - 41 weeks 6 days). Median birth weight was 3520 grams (range 2600 - 4700 grams; Dutch reference curves Z-scores[12] mean 0.07 ±0.96). None of the cases had bowel pathology diagnosed within one month after birth. The median number of scans per pregnancy was 5 (range 4-6). Measurements of small bowel and colon diameters were obtained in 63% and 98% of cases, respectively. The intra-observer and inter-observer ICC for small bowel was 0.94 and 0.96, respectively. For colon the ICC was 0.96 for both intra- and inter-observer measurements.

The development of small bowel diameter and colon diameter was best described by a linear model and a cubic model, respectively, as shown in Figure 2. The regression equations for the small bowel and colon modeled as a function of gestational age are given in Appendix 1. At 40 weeks of gestation, mean small bowel diameter was 5.1 mm and mean colon diameter was 14.5 mm (Table 1).

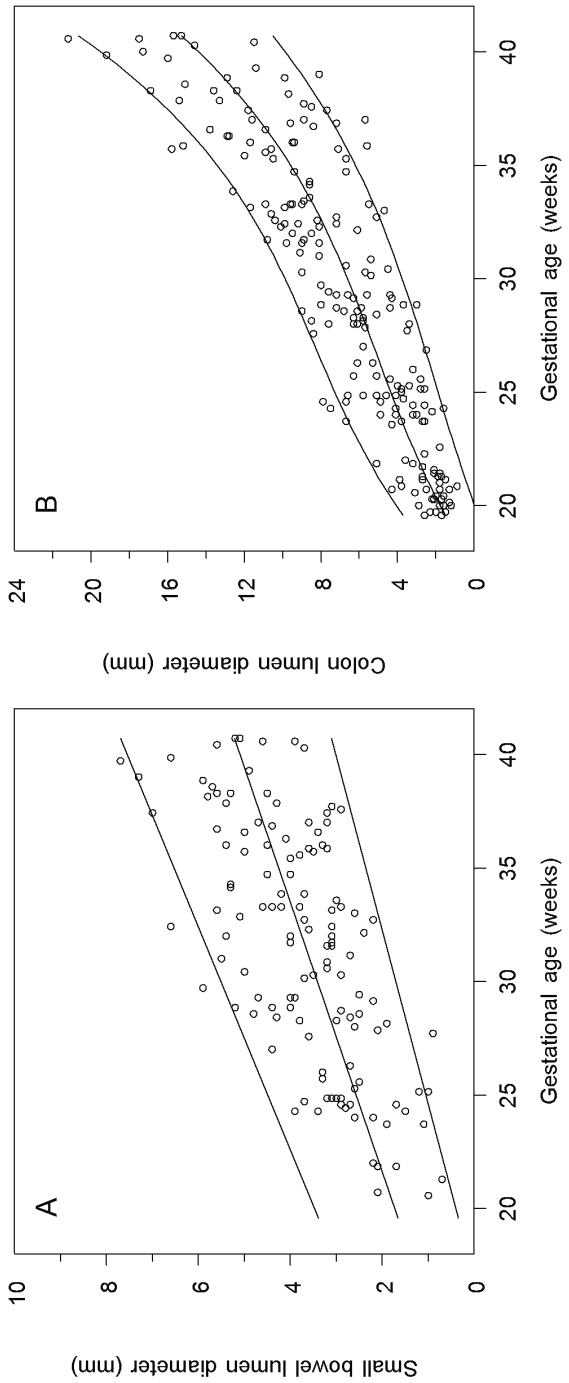

Figure 2. Reference charts of small bowel diameter (A) and colon diameter (B) Showing raw data (◦) and fitted 50th percentile and 95% prediction ranges.

Table 1. Small bowel and colon diameters according to gestational age

	Small bowel diameter (mm)		Colon diameter (mm)	
Weeks of gestation	Mean	95% prediction interval	Mean	95% prediction interval
20	1.7	0.4-3.5	1.8	0.0-4.0
22	2.1	0.7-3.9	2.9	0.8-5.5
24	2.4	0.9-4.3	3.9	1.5-6.7
26	2.7	1.2-4.7	4.8	2.2-7.8
28	3.1	1.4-5.1	5.7	3.0-8.8
30	3.4	1.7-5.5	6.6	3.7-9.8
32	3.8	2.0-5.9	7.7	4.6-11.0
34	4.1	2.2-6.3	8.9	5.6-12.5
36	4.4	2.5-6.7	10.4	6.8-14.3
38	4.8	2.8-7.1	12.3	8.2-16.5
40	5.1	3.0-7.6	14.5	9.8-19.4

Assessment of clinical applicability

We identified 28 cases with suspected isolated dilated bowel loops. In Figure 3 Z-scores of inner diameter of fetal bowel of these cases are presented relative to the study reference curves.

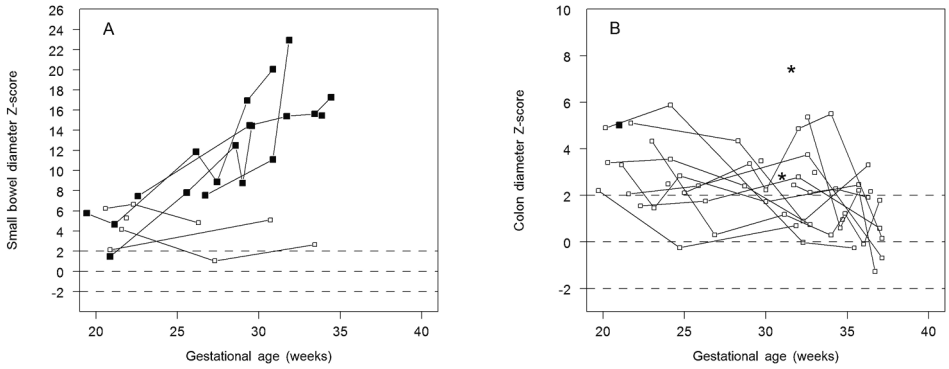

Figure 3. Fetal small bowel (A) and colon (B) inner diameter according to gestational age in fetuses with (¾, n=8) and without (■, n=20) bowel pathology.

Z-scores were calculated relative to the study nomograms in each case. Upper and lower horizontal lines indicate Z-scores of 2 and -2 respectively, i.e. the range of ± 2 SD's from the mean values represented by a Z-score of 0. Two cases (*) were antenatally suspected of colon dilatation and are presented in Figure 3B but turned out to have small bowel pathology after birth.

In Figure 3 cases with suspected small bowel dilatation (Figure 3A) and suspected colon dilatation (Figure 3B) are presented. Only 26% of fetuses with suspected dilated bowel were found to have intestinal abnormalities shortly after birth.

All cases with small bowel pathology after birth (n=7) had a Z-score >8 after 25 weeks of gestation. In cases with two or more consecutive ultrasound examinations progressive dilatation was found in all cases with postnatal bowel pathology. In cases without bowel pathology after birth, the bowel diameter decreased to a Z-score below 4 after 35 weeks of gestation (Figure 3). In twelve cases with repeated measurements the bowel diameter was not progressive. None of these cases presented with intestinal abnormalities after birth. Additional polyhydramnios was seen in seven cases. In five cases bowel pathology was diagnosed after birth.

The antenatal and postnatal findings of the cases with postnatal bowel pathology are described in Table 2. Five out of eight cases had additional polyhydramnios. Two cases (Table 2, case 3 and case 7) were antenatally suspected of colon dilatation and are presented in Figure 3B, but turned out to have small bowel pathology after birth. There was one case (Table 2, case 8) that was suspected of colon dilatation before birth and this was confirmed postnatally. Unfortunately there were no consecutive measurements of these three cases. Seven cases had small bowel obstructions. There was one intrauterine fetal death at 31 weeks' gestation (case 1). Autopsy showed dysmorphic facial features (depressed nasal bridge, downward slanting palpebral fissures) and a duodenal web, causing severe dilatation of the proximal duodenum. The cause of death could not be established. Case 2 and 3 presented with meconium ileus at birth and were diagnosed with cystic fibrosis. Case 4 was born with a jejunal atresia and had concomitant congenital biliary atresia. Surgical porto-enterostomy was not successful and she died at fifteen months of age awaiting liver transplantation. Case 5, an infant born with jejunal and ileal atresia and antenatal volvulus, had multiple anastomotic leaks after primary surgery. Adequate intestinal function could not be established and he died at four months of age. Case 6 had intra-uterine small bowel perforations resulting in meconium peritonitis. Postnatal surgery showed extended bowel necrosis. Despite surgical attempts to preserve bowel function, she died eighteen hours after birth. A monochorionic twin pregnancy with one child (case 7) with antenatal suspected bowel dilatation and polyhydramnios presented with atresia, volvulus and peritonitis. Successful ileostomy with end-to-end anastomosis was performed. There was only one case with colon pathology after birth; Case 8 had a blind-ending ascending colon in which surgical anastomosis was successful. In the group without neonatal bowel pathology, one infant was diagnosed with biliary atresia at three weeks of age. She had a successful liver transplantation and is doing well now at five years of age.

Table 2. Summary of cases with bowel pathology

Case nr	Gestational age at last ultrasound examination	Appearances	Postnatal diagnosis	Outcome
1	30w 6d	Dilated bowel (24mm), polyhydramion	Intra uterine fetal death at 31 weeks' gestation, autopsy showed a duodenal web, causing severe dilatation of the proximal duodenum	
2	31w 6d	Dilated bowel loops (28 mm)	Meconium ileus, volvulus, small bowel necrosis	Ileal resection, cystic fibrosis
3	31w 0d	Dilated bowel (12 mm), meconium plug, echogenic bowel, polyhydramnion	Meconium ileus, meconiumperitonitis	Ileal resection, cystic fibrosis
4	33w 4d	Dilated bowel (21 mm)	Malrotation and jejunal atresia, biliary atresia	Jejunal resection, failed porto-enterostomy, died due to liver failure
5	34w 3d	Dilated bowel (24 mm), polyhydramnion	Ileal and jejunal atresia with volvulus	Jejunal and ileal resection, died 4 months of age
6	29w 4d	Dilated bowel (18 mm), polyhydramnion	Meconium peritonitis, small bowel necrosis	Jejunal and ileal resection, died 18 hours after birth
7	31w 4d	Dilated bowel (20 mm), polyhydramnion	Ileal atresia, volvulus, meconium peritonitis	Ileal resection, now well
8	21w 0d	Echolucent abdominal structure (8.6 mm)	Colonic atresia	Ileocolic anastomosis, now well

w, weeks; d, days.

DISCUSSION

We provide the first ultrasound reference curves of the fetal small bowel and colon diameters based on repeated measurements on individuals. The charts were derived from longitudinal data obtained from prospective investigations between 20 and 40 weeks of gestation. The mean colon diameter at 40 weeks gestation was 14.5 mm, with a maximum of 19.4 mm. For small bowel the mean diameter at 40 weeks gestation was 5.1 mm with a maximum of 7.6 mm.

Our results for colon diameter are in line with the findings of two other studies in which a maximal inner diameter of 18 mm was found.[6,8] In one of these studies an increase in mean colon diameter from 3.5 to 13.5 mm between 20 and 40 weeks of gestation was found.[8] We are aware of only one

study on ultrasound assessment of the small bowel diameter across gestation.[7] These authors reported an increase from 1 to 4.4 mm in the course of gestation, with a maximum of 8 mm at term. Neither standard deviations nor prediction intervals were given. All previous reference charts for small bowel and colon diameter were constructed using cross-sectional data.[6-8] Malas et al. studied the development of colon, jejunum and ileum in a post mortem series of 131 fetuses.[9,10] The authors only provided the outer-to-outer bowel wall diameters. For colon diameter they found an increase from 3 to 15 mm between 20 and 40 weeks of gestation. The diameter of the small intestine was determined as an average of 7 mm at term, which is higher than in our series. This difference may be explained by the fact that the post mortem measurement of a loop of bowel without smooth muscle tone can be significantly different from the diameter of a loop of bowel in a living fetus.

In our retrospective study only 26% of fetuses with suspected dilated bowel were found to have intestinal abnormalities at birth. Our study shows that fetal intestinal dilatation can resolve during gestation; 56% of fetuses with repeated measurements had a resolution of intestinal dilatation on consecutive ultrasound examinations. Resolution of dilated bowel should be considered reassuring for normal neonatal outcome, since none of those fetuses were found to have intestinal pathology after birth. In the cases with transient bowel dilatation there was one infant diagnosed with biliary atresia; a condition only seen in 1 in 19.000 livebirths.[13] To our knowledge transient antenatal bowel dilatation has not been described in association with biliary atresia. It would be interesting to investigate its potential as a screening tool for biliary atresia.

In all cases with progressive dilatation of the small bowel, pathology of the small bowel was confirmed after birth. A large small bowel diameter (Z-score >8) after 25 weeks of gestation was also associated with small bowel pathology. The type of bowel disease diagnosed after birth varied however. In all these cases surgical treatment was necessary in early postnatal life. This stresses the importance of antenatal diagnosis of bowel pathology to ensure immediate paediatric (surgical) care after birth.

Polyhydramnios is a risk factor for fetal bowel obstruction.[5] In our case series of patients with suspected bowel pathology, five out of eight cases with postnatal bowel pathology had polyhydramnios. However, polyhydramnios was also seen in two cases without bowel pathology after birth. Hence polyhydramnios is not a reliable indicator for bowel obstruction.

The incidence of abnormalities after birth in our retrospective series is lower than that reported in a previous study by Ruiz et al.[3] They described postnatal bowel pathology in 8 of 15 fetuses (53%) with bowel dilatation on prenatal ultrasound. This difference is possibly explained by underreporting of cases with normal postnatal outcome, since there were five cases lost to follow-up in their series.

The strength of our study of normal reference curves is its prospective and longitudinal design. The bowel measurements were performed according to a strict protocol. We are aware that distinguishing the small bowel from colon can be difficult. However, the coronal plane of the fetal abdomen helps to distinguish the small bowel from the colon by its anatomic position. In addition,

identification of haustra of the colon becomes easier in the third trimester. This confirms -again- the importance of repeated measurements.

The cohort used to test the applicability of our study was limited by retrospective design. The measurements were performed before the prospective study was done and therefore not standardised. Identification of small bowel or colon was not preformed according to our proposed protocol. However, we remeasured the bowel dilatation and calibrated the images in order to improve the standardisation of measurements. Unfortunately, repeated measurements were not available for all cases with postnatal colon pathology. Therefore, no definite conclusions can be drawn about the development of colon dilatation over time. Further research in cases with suspected colon dilatation using the normal colon curves is necessary in order to test the clinical applicability of the reference curves of the colon.

In conclusion, we have provided ultrasound reference curves for the normal fetal small bowel and colon diameters. These reference curves may be useful in the prenatal counselling of parents carrying a fetus with dilated bowel loops. Transiently dilated bowel on prenatal ultrasound predicts a normal fetal outcome. Progressive increase of the fetal bowel diameter, on the other hand, is highly predictive of intestinal abnormalities after birth. Longitudinal follow-up of dilated bowel is important to distinguish normality from disease.

REFERENCES

1. Shawis R, Antao B. Prenatal bowel dilatation and the subsequent postnatal management. *Early Hum Dev*. 2006;82(5):297-303. S0378-3782(06)00065-X [pii].
2. Takacs ZF, Meier CM, Solomayer EF, Gortner L, Meyberg-Solomayer G. Prenatal diagnosis and management of an intestinal volvulus with meconium ileus and peritonitis. *Arch Gynecol Obstet*. 2014;290(2):385-387. 10.1007/s00404-014-3223-7 [doi].
3. Ruiz MJ, Thatch KA, Fisher JC, Simpson LL, Cowles RA. Neonatal outcomes associated with intestinal abnormalities diagnosed by fetal ultrasound. *J Pediatr Surg*. 2009;44(1):71-4; discussion 74-5. 10.1016/j.jpedsurg.2008.10.010 [doi].
4. Borsellino A, Zaccara A, Nahom A, Trucchi A, Aite L, Giorlandino C, Bagolan P. False-positive rate in prenatal diagnosis of surgical anomalies. *J Pediatr Surg*. 2006;41(4):826-829. 10.1016/j.jpedsurg.2005.12.024.
5. Virgone C, D'antonio F, Khalil A, Jonh R, Manzoli L, Giuliani S. Accuracy of prenatal ultrasound in detecting jejunal and ileal atresia: Systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2015;45(5):523-529. 10.1002/uog.14651 [doi].
6. Nyberg DA, Mack LA, Patten RM, Cyr DR. Fetal bowel. normal sonographic findings. *J Ultrasound Med*. 1987;6(1):3-6.
7. Parulekar SG. Sonography of normal fetal bowel. *J Ultrasound Med*. 1991;10(4):211-220.
8. Zalel Y, Perlitz Y, Gamzu R, Peleg D, Ben-Ami M. In-utero development of the fetal colon and rectum: Sonographic evaluation. *Ultrasound Obstet Gynecol*. 2003;21(2):161-164. 10.1002/uog.26 [doi].
9. Malas MA, Aslankoc R, Ungor B, Sulak O, Candir O. The development of jejunum and ileum during the fetal period. *Early Hum Dev*. 2003;74(2):109-124. S0378378203000859 [pii].
10. Malas MA, Aslankoc R, Ungor B, Sulak O, Candir O. The development of large intestine during the fetal period. *Early Hum Dev*. 2004;78(1):1-13. 10.1016/j.earlhumdev.2004.03.001 [doi].
11. Verburg BO, Steegers EA, De Ridder M, Snijders RJ, Smith E, Hofman A, Moll HA, Jaddoe VW, Witteman JC. New charts for ultrasound dating of pregnancy and assessment of fetal growth: Longitudinal data from a population-based cohort study. *Ultrasound Obstet Gynecol*. 2008;31(4):388-396. 10.1002/uog.5225 [doi].
12. Perinatale zorg in Nederland.. 2006.
13. Hartley JL, Davenport M, Kelly DA. Biliary atresia. *Lancet*. 2009;374(9702):1704-1713. 10.1016/S0140-6736(09)60946-6 [doi].

Chapter

6

Isolated abdominal wall defect with complete liver herniation without a covering or remnant membrane: an ominous sign: case report and review of literature

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ABSTRACT

Complete liver herniation in abdominal wall defects without a membrane is rare and its prognosis is not well documented. We present a case diagnosed at 12 weeks of gestation. At 27 weeks a Caesarean section was performed for fetal distress. The infant proved impossible to ventilate and died. In literature sixteen similar cases are described of whom fourteen died in the neonatal period and two in infancy. This suggests that herniation of the complete liver in isolated abdominal wall defects without a remnant membrane is lethal and counselling should be provided accordingly.

CASE REPORT

A 26-year-old primigravida was referred at 12 weeks' gestation to a tertiary care centre with an ultrasound diagnosis of fetal gastroschisis. She had a body mass index of 22 and had suffered from anorexia until 12 years previously. Fetal ultrasound examination revealed a large abdominal wall defect with evisceration of bowel, liver and gallbladder (Figure 1). No additional abnormalities were found. The patient chose to continue the pregnancy and declined fetal karyotyping.

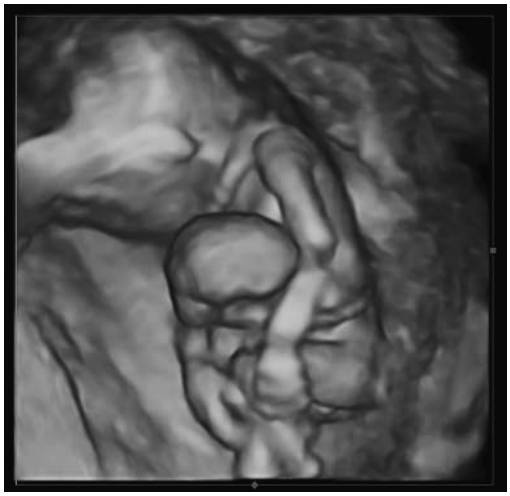

Figure 1. Fetus with an anterior abdominal wall defect with herniation of the complete liver and bowel without a covering membrane. Threedimensional surface rendering ultrasound obtained at 16 weeks of gestation.

At 27 6/7 weeks gestation she was referred to our tertiary hospital with severe intra uterine growth restriction (IUGR) and absent end diastolic flow in the umbilical artery. She reported normal fetal movement.

We confirmed a large abdominal wall defect to the right side of the umbilical cord. The complete liver, gallbladder and intestine were herniated through the defect into the amniotic cavity. The thoracic circumference was normal for the gestational age and the heart was normally positioned. The defect of the abdominal wall was more suggestive for gastroschisis than ruptured omphalocele since no membrane could be identified by ultrasound and the defect was positioned at the right side of the umbilical cord. Apart from the abdominal wall defect, no other abnormalities were detected, making the diagnosis of a body stalk abnormality or limb body wall syndrome unlikely.

Doppler evaluation showed absent end diastolic flow in the umbilical artery and normal Doppler waveforms of the middle cerebral artery. The amount of amniotic fluid was normal. She was admit-

ted to the hospital and a course of prenatal steroids was given. Fetal heart rate monitoring was performed twice a day.

Three days later an emergency Caesarean section was carried out for signs of brainsparing (Vmax MCA < 2SD) and cardiotocographic signs of fetal distress. A female infant was delivered with a birth weight of 640 gram and Apgar scores of 2 and 2 at 1 and 5 minutes, respectively. The neonate proved impossible to ventilate despite intubation directly after birth. After 25 minutes the resuscitation was stopped and the neonate died 40 minutes after birth.

The trimmed placental weight was normal for gestational age (360 grams). The umbilical cord showed inflammation of neutrophilic granulocytes in the wall of all three vessels. The umbilical cord coiling index was 0.32 (normal range 0.1 - 0.3). There was an increased variation of chorionic villus size with several trophoblastic pseudo-inclusions. Several small groups of avascular villi were found in keeping with fetal vessel thrombosis. There were no signs of villitis or vasculitis.

Autopsy revealed a female infant of 640 grams (p3-10) with an abdominal wall defect from the diaphragm to the umbilical cord insertion with extra abdominal bowel, stomach, spleen, liver and gallbladder. The head circumference (21.5 cm) and crown-rump (20 cm), femur (4.1 cm) and foot (4.4 cm) length were all below the third centile. Liver, spleen and kidney weights were normal. The weights of the heart (3.0 gram), thymus (1.0 gram), adrenal glands 1.gram) and lungs (10.5) were low (appropriate for 21-22 weeks of gestation), the lung to body weight ratio was 0.016 (>0.015).[1] Microscopic evaluation of the lungs showed normal development for the gestational age. The liver showed severe fibrosis and collapse of reticulin suggestive of hepatocyte atrophy.

The brain was of normal size, weight and maturation and showed global signs of recent hypoxic ischemic damage. The periventricular, brainstem and cerebellum white matter showed signs of ischemic damage occurring at least several days before birth.

Postmortem cytogenetics analysis unfortunately failed because the samples were contaminated. MLPA (multiplex ligation-dependent probe amplification) of the placenta showed no signs of trisomy 13,18, 21 or monosomy X.

DISCUSSION

Isolated abdominal wall defects are either gastroschisis or omphalocele. These two entities can be distinguished by the presence of a membrane covering extruding organs and a central insertion of the umbilicus in omphalocele or the absence of a membrane and umbilicus insertion lateral to the defect in gastroschisis The omphalocelic membrane can rupture during labour. Some authors presume the membrane can also rupture and diminish in early pregnancy.[2] No cases have been described to our knowledge in which the membrane was first seen by ultrasound and ruptured before

labour, which raises the questions of which forces would cause antenatal rupture, and whether this entity actually exists at all. One could wonder if the cases labeled as prelabour ruptured omphalocele, in which no membrane can be identified postnatally, were not in fact cases of gastroschisis with herniation of the complete liver.

In gastroschisis the liver is seldom completely herniated. The neonatal survival rate of gastroschisis is over 90%.[3] However, this is based on cases without liver herniation. The prognosis of children with gastroschisis and herniation of the complete liver is unknown. Some authors believe that true gastroschisis never involves the liver. They define an abdominal wall defect with liver herniation without an identifiable membrane as antenatally ruptured omphalocele.[2] Our literature search therefore included gastroschisis cases with complete herniation of the liver and cases defined as ruptured omphalocele with evisceration of the complete liver without a membrane. Cases with additional structural or chromosomal abnormalities were excluded since this could influence prognosis.

Thirty-three cases with descriptions of herniation of the liver without covering or remnant membrane were described, nineteen cases were diagnosed with gastroschisis and fourteen cases were diagnosed with ruptured omphalocele. Seventeen of these thirty-three cases were excluded from the review because the position of the liver, partial or completely extra abdominal, was not described. As shown in Table 1, there were sixteen remaining cases with complete herniation of the liver, fourteen cases died in the neonatal period. The two last cases died at 101 and 365 days respectively, after a life completely dependent on mechanical ventilation.

The evidence suggests that this condition is lethal (0 survival out of 16 cases 95% confidence interval for survival 0 – 19%), and most often caused by respiratory failure (7 cases out of 13 cases where the cause of death was described).

The respiratory insufficiency in these cases is believed to be comparable with the mechanism of pulmonary hypoplasia that is often seen in giant omphaloceles containing liver. Low intra-abdominal pressure and lateral shift of the abdominal muscles gives the thorax a grey hound shape; long and narrow with a decreased radius of curvature of the diaphragm.[2,4] As a result the fetal thorax is always in an 'inhalation' position with decreased respiratory movements. These movements are important for thoracic musculature development, fluid shifts in the lungs and pulmonary growth.

Intra-uterine growth restriction, which was also seen in the case described, might further worsen the prognosis of the children with a non-membrane covered extra-abdominal liver. IUGR is seen in the majority of gastroschisis cases in contrast to giant omphalocele[5] and is believed to be the result of protein loss due to chronic inflammation of the bowel.[6]

We suggest that the chronic stretching of the umbilical vein and venous duct in the liver may have caused liver damage, explaining the liver fibrosis in our case. This results in chronic ischemia and pulmonary hypertension and exacerbates IUGR.

Absent diastolic flow in the umbilical cord, signs of brainsparing and IUGR are commonly seen in placental bed pathology. The latter could not be confirmed in our case. Interestingly, the cord coil-

ing index was too high. This is associated with thrombosis in fetal placental vessels, chronic fetal hypoxia and IUGR (similarly as seen in our case).[7]

Table 1. Studies reporting cases of isolated abdominal wall defect with herniation of bowel and complete liver without a covering or ruptured membrane

Author	Diagnosed with	GA at birth (weeks)	Weight (gram)	Deceased	Days lived	Cause of death
McClellan et al. 2011 [8]	GS	30	700	Yes	6	Renal failure
McClellan et al. 2011 [8]	GS	36	2000	Yes	9	Pulmonary hypoplasia and hypertension, liver disease
McClellan et al. 2011 [8]	GS	35	1200	Yes	13	Herpes simplex virus sepsis
Opitz et al. 2008[9]	GS	30	1720	Yes	26	Silo complication
Santiago-Munoz et al. 2007 [10]	GS	NA	NA	Yes	1	NA
Santiago-Munoz et al. 2007 [10]	GS	NA	NA	Yes	1	NA
Santiago-Munoz et al. 2007 [10]	GS	NA	NA	Yes	1	NA
Eggink et al. 2006 [11]	GS	Term	3000	Yes	101	Sepsis
Vegunta et al. 2005 [12]	GS	NA	1455	Yes	12	Renal failure
Brantberg 2004 [13]	GS	29	1600	Yes	1	Hydrops and hydrothorax
Clausner et al. 1996 [14]	GS	NA	NA	Yes	365	pulmonary hypoplasia, lived on mechanical ventilation
Argyle 1989 [15]	GS	32	1750	Yes	1	Pulmonary hypoplasia
Lee1969 [16]	GS	32	1500	Yes	1	Vesico abdominal disproportion
Patel et al. 2009 [17]	RGO	<34	NA	Yes	<7	Respiratory sepsis and multiorgan failure
Patel et al. 2009 [17]	RGO	<34	NA	Yes	<7	Respiratory sepsis and multiorgan failure
Rijhwani et al. 2005 [18]	RGO	30	862	Yes	3	Respiratory failure and sepsis

GS, gastroschisis; RGO, ruptured giant omphalocele; GA, gestation age; NA, not available; F, female; M, male

In conclusion an abdominal wall defect with herniation of the complete liver without a (remnant) membrane, either defined as gastroschisis or antenately ruptured omphalocele is rare but nearly always lethal and counselling should be provided accordingly.

REFERENCES

1. Wigglesworth JS, Desai R. Use of DNA estimation for growth assessment in normal and hypoplastic fetal lungs. *Arch Dis Child*. 1981;56(8):601-605.
2. Kamata S, Usui N, Sawai T, Nose K, Fukuzawa M. Prenatal detection of pulmonary hypoplasia in giant omphalocele. *Pediatr Surg Int*. 2008;24(1):107-111. 10.1007/s00383-007-2034-3.
3. Ajayi FA, Carroll PD, Shellhaas C, Foy P, Corbitt R, Osawe O, Caniano DA, O'Shaughnessy R. Ultrasound prediction of growth abnormalities in fetuses with gastroschisis. *J Matern Fetal Neonatal Med*. 2011;24(3):489-492. 10.3109/14767058.2010.500428.
4. Hershenson MB, Brouillette RT, Klemka L, Raffensperger JD, Poznanski AK, Hunt CE. Respiratory insufficiency in newborns with abdominal wall defects. *J Pediatr Surg*. 1985;20(4):348-353.
5. Payne NR, Simonton SC, Olsen S, Arnesen MA, Pfleghaar KM. Growth restriction in gastroschisis: Quantification of its severity and exploration of a placental cause. *BMC Pediatr*. 2011;11(1):90. 10.1186/1471-2431-11-90.
6. Carroll SG, Kuo PY, Kyle PM, Soothill PW. Fetal protein loss in gastroschisis as an explanation of associated morbidity. *Am J Obstet Gynecol*. 2001;184(6):1297-1301. 10.1067/mob.2001.114031.
7. de Laat MW, van Alderen ED, Franx A, Visser GH, Bots ML, Nikkels PG. The umbilical coiling index in complicated pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2007;130(1):66-72. 10.1016/j.ejogrb.2006.01.018.
8. McClellan EB, Shew SB, Lee SS, Dunn JC, Deugarte DA. Liver herniation in gastroschisis: Incidence and prognosis. *J Pediatr Surg*. 2011;46(11):2115-2118. 10.1016/j.jpedsurg.2011.07.010.
9. Opitz JM, Pysher TJ. Invited editorial comment: Further reflections on gastroschisis. *Am J Med Genet C Semin Med Genet*. 2008;148C(3):192-198. 10.1002/ajmg.c.30177.
10. Santiago-Munoz PC, McIntire DD, Barber RG, Megison SM, Twickler DM, Dashe JS. Outcomes of pregnancies with fetal gastroschisis. *Obstet Gynecol*. 2007;110(3):663-668. 10.1097/01.AOG.0000277264.63736.7e.
11. Eggink BH, Richardson CJ, Malloy MH, Angel CA. Outcome of gastroschisis: A 20-year case review of infants with gastroschisis born in Galveston, Texas. *J Pediatr Surg*. 2006;41(6):1103-1108. 10.1016/j.jpedsurg.2006.02.008.
12. Vegunta RK, Wallace LJ, Leonardi MR, Gross TL, Renfroe Y, Marshall JS, Cohen HS, Hocker JR, Macwan KS, Clark SE, Ramiro S, Pearl RH. Perinatal management of gastroschisis: Analysis of a newly established clinical pathway. *J Pediatr Surg*. 2005;40(3):528-534. 10.1016/j.jpedsurg.2004.11.037.
13. Brantberg A, Blaas HG, Salvesen KA, Haugen SE, Eik-Nes SH. Surveillance and outcome of fetuses with gastroschisis. *Ultrasound Obstet Gynecol*. 2004;23(1):4-13. 10.1002/uog.950.
14. Clausner A, Lukowitz A, Rump K, Berger S, Wurfel A. Treatment of congenital abdominal wall defects - A 25-year review of 132 patients. *Pediatr Surg Int*. 1996;11(2-3):76-81.
15. Argyle JC. Pulmonary hypoplasia in infants with giant abdominal wall defects. *Pediatr Pathol*. 1989;9(1):43-55.
16. Lee SH, Park KS. A gastroschisis with antenatal eviceration of entire liver, intestine and stomach. *Yonsei Med J*. 1969;10(2):196-197.
17. Patel G, Sadiq J, Shenker N, Impey L, Lakhoo K. Neonatal survival of prenatally diagnosed exomphalos. *Pediatr Surg Int*. 2009;25(5):413-416. 10.1007/s00383-009-2357-3.
18. Rijhwani A, Davenport M, Dawrant M, Dimitriou G, Patel S, Greenough A, Nicolaides K. Definitive surgical management of antenatally diagnosed exomphalos. *J Pediatr Surg*. 2005;40(3):516-522. 10.1016/j.jpedsurg.2004.11.028.

Chapter

7

Ultrasound markers predicting complex gastroschisis and adverse outcome; a longitudinal prospective nationwide cohort study

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(Article in preparation)

ABSTRACT

Objective: To identify antenatal ultrasound markers differentiating between complex and simple gastroschisis and to investigate which variables are related to morbidity after birth.

Methods: Serial longitudinal ultrasound examinations at four-weekly intervals between 20 and 37 weeks were performed in isolated fetal gastroschisis cases. The primary outcome was simple or complex (bowel atresia, volvulus, perforation or necrosis) gastroschisis at birth. Fetal biometry, the occurrence of polyhydramnios, intra- and extra-abdominal bowel diameters and the Pulsatility Index (PI) of the superior mesenteric artery were assessed and compared to reference ranges. Linear mixed modeling was used to compare the individual trajectories of both simple and complex cases. The last measurements before delivery of the intra- and extra-abdominal bowel diameters (< or ≥15mm and < or ≥20m) were used to compare mortality, time to full enteral feeding (TFEF) and length of hospital stay (LOS).

Results: Between 2010 and 2014, 101 cases of isolated fetal gastroschisis were included. Three intra uterine deaths occurred, at 22, 32 and 33 weeks of gestation. Seventy-nine (80.6%) liveborn infants had simple and 19 (19.4%) had complex gastroschisis. There were 3 neonatal deaths, one in the simple and 2 in the complex group. TFEF and LOS were significantly longer in the complex cases compared to the simple group ($P<0.001$, and $P<0.001$, respectively). There was no correlation between abdominal circumference, estimated fetal weight and complex gastroschisis. The PI of the intra- and extra-abdominal superior mesenteric artery also did not differentiate between simple and complex cases. However, in both groups the PI was significantly lower than in controls. Both intra- and extra-abdominal bowel diameter were larger in complex cases than in simple ones and multilevel analysis showed a significant group main effect for both variables ($P<0.001$ and $P<0.05$, respectively). Identification of complex cases based on bowel diameter, remains, however, difficult. TFEF and LOS were significantly longer in cases with an intra-abdominal diameter of more than 15 mm at the last measurement before birth ($P=0.009$ and $P=0.013$, respectively).

Conclusions: In this large prospective longitudinal study we found that prognosis of complex gastroschisis is poorer than that of simple cases. In both groups the PI of the intra- and extra-abdominal superior mesenteric artery is substantially lower than in controls, but this measurement does not differentiate between the two gastroschisis groups. Only the intra-abdominal bowel diameter differentiates between simple and complex cases, although its predictive value is relatively low.

INTRODUCTION

Nowadays gastroschisis is diagnosed antenatally in >90% of cases.[1] Although survival rate of live born infants to initial hospital discharge is good (>90%)[2-6], the risk of intrauterine fetal death (IUFD) is still 7 times higher than in the normal population[7] and morbidity occurs in 30% of the liveborns (Chapter 2). The bowel condition at birth is an important prognostic factor for neonatal outcome.[8] Compared to the gastroschisis cases without additional intestinal abnormalities (simple gastroschisis), children born with complex gastroschisis (atresia, volvulus, perforation or necrosis of the bowel)[9], have an increased risk of mortality and of prolonged hospitalisation, long term use of total intravenous nutrition, additional ventilation days, multiple surgical procedures and postoperative complications.[9-11]

If intestinal complications could be predicted antenatally, this could lead to an improvement of parental counselling as well as the identification of those patients that might benefit from obstetric interventions, like premature induction of labour. In addition, if the presence of bowel atresia before birth could be predicted, this would significantly help the surgeon to diagnose atresia early and plan a repair, since atresia is often missed at the first surgery (in 40% of cases).[12-14] Various attempts have been made to correlate antenatal ultrasound findings with neonatal outcome. Reports are conflicting because of the small size of study populations, retrospective study designs and non-standardised methods and timing of ultrasound examination.[15,16] A recent meta-analysis, mainly based on retrospective studies, showed that intra-abdominal bowel dilatation and polyhydramnios are the most promising markers for bowel atresia.[16] However, definitions of dilatation and polyhydramnios were not given.[16]

We have conducted a prospective longitudinal multi-centre study with fetal ultrasound assessment and surveillance according to a standard protocol, in order to assess markers related to outcome. In addition to bowel dilatation and polyhydramnios, we studied the velocimetry of the superior mesenteric artery and fetal biometry, including abdominal circumference (AC) as potential markers for complex gastroschisis and to predict neonatal outcome.

METHODS

Recruitment/eligibility criteria

In the Netherlands all women pregnant of a foetus with gastroschisis are referred to one of the seven university medical centres with a paediatric surgery department. This study was conducted at all

seven centres as a prospective longitudinal observational nationwide cohort study. If gastroschisis was confirmed by ultrasound and no other extra-gastrointestinal congenital disorder (potentially influencing the outcome) was suspected, patients were eligible for participation. Cases found to be non-isolated until after birth were excluded post-hoc. This study protocol was approved by the Medical Review Ethics Committee (Reference number: 10-076/C).

Ultrasound examination

Between 18-22 weeks of gestation, an anomaly scan was performed intended to detect structural anomalies. In cases with gastroschisis, ultrasound follow-up evaluation was performed at 24, 28, 30, 32, 34, 35 and 36 weeks of gestation. During the examination, fetal biometry, the occurrence of polyhydramnios, pulsatility index (PI) of the umbilical artery, bowel diameter measurements and PI of the superior mesenteric artery were performed. All examinations were done by trained ultrasonographers using a General Electric Voluson 730 or E8 (General Electric Healthcare, London) ultrasound machine, with a 4-8 MHz transabdominal transducer. Polyhydramnios was defined as an amniotic fluid index (AFI) ≥24 cm.[17] Bowel diameters were measured at the short axis of the bowel lumen (inner to inner wall) of the most dilated bowel segment, both intra- and extra-abdominally. Intra-abdominal superior mesenteric artery measurements were obtained in a sagittal or axial plane of the fetal abdomen after its origin from the aorta, just above the renal arteries (with an angle of insonation preferably below 30°).[18] The extra-abdominal superior mesenteric artery was identified and measured direct distally to the abdominal wall defect.

The AC and estimated fetal weight (EFW) values of both simple and complex cases were expressed as Z-scores and compared to well-established reference data.[19,20] The occurrence of polyhydramnios during pregnancy was compared between simple and complex cases.

The intra-abdominal and extra-abdominal bowel diameters of both the simple and complex cases were compared to the longitudinal reference data of the colon that we measured in 39 uncomplicated pregnancies (data under review, Chapter 5). Additionally, we analysed whether intra-abdominal and extra-abdominal diameters of ≥15 or ≥20 mm, at the last measurement before delivery were predictors for complex or simple gastroschisis, neonatal mortality, longer time to full enteral feeding (TFEF) and longer length of hospital stay (LOS). These cut-off values were based on the mean (14.5 mm) and 95%-confidence interval (max 19.4 mm) of the colon diameter of our normal reference range (Chapter 5, Table 1).

The raw PI measurements of the superior mesenteric artery of both categories (simple and complex) were compared to the reference ranges described by Ebbing et al. and expressed as standard deviation scores (SDS) or Z-scores.[18]

Fetal monitoring and labour

Cardiotocography surveillance was performed from 34 weeks of gestation at least twice a week till delivery in a home monitoring or outpatient setting. Delivery was planned in one of the participating centres from 37 weeks gestation onwards by induction of labour.[21] Caesarean delivery was only performed for obstetric reasons, such as fetal distress or failure to progress in labour.

Neonatal care

Primary operative abdominal wall repair of gastroschisis was attempted in all cases based on the condition of the child, the exteriorized viscera volume and the judgment of the surgeon, neonatologist and anaesthetist. If the viscera could not be reduced primarily, a silo bag was placed. In case of silo placement, elective closure of the abdominal wall was planned in the subsequent days. We categorised gastroschisis cases as simple or complex based on the gastrointestinal tract condition at birth. Antenatal atresia, volvulus, necrosis or perforation of the bowel at birth was defined as complex gastroschisis.[9,22] The primary outcome measure was simple or complex gastroschisis. Secondary outcome measures were perinatal and postnatal mortality, TFEF expressed in days i.e. the complete cessation of total parenteral nutrition (TPN), and LOS.

Statistical analysis

Statistical analysis was performed using the statistical software package SPSS (version 23, SPSS Inc., Chicago, IL, USA). Results were summarized with the use of standard descriptive statistics: counts and percentages for categorical variables, and means with standard deviations (SD) or medians with a minimum and maximum value for continuous variables. The normality of the continuous variables was assessed by Kolmogorov-Smirnov test and Q-Q plot. The two categories (simple and complex) were compared for equivalence in clinical characteristics using standard statistical tests. For continuous data with skewed distribution the Mann-Whitney U test was used. The unpaired-t-test was used for comparison of variables for which the assumption of normal distribution was retained. Comparison of categorical variables was performed using either Chi-square test or the Fisher's exact test, where appropriate. The Yates' continuity of correction factor was added to the Chi-square test when testing two variables with each two categories (2x2 contingency table). Linear mixed modelling was performed to analyse the regression of serial measurements on the same subject over time. This was done for the biometric variables (Z-scores), intestinal intra- and extra-abdominal diameters, and PI values of the umbilical artery and superior mesenteric artery (Z-scores). Models with linear and quadratic components of gestational age (centred at 15 weeks) were explored and compared using the Bayesian Information Criterion (BIC). With all tests, a P-value of <0.05 was considered statistically significant. Birth weight was expressed as a Z-score according to Dutch norm charts, adjusted for parity, fetal sex, and gestational age. Neonates were classified as small for gestational age (SGA) defined as birth weight below the 10th percentile (P10) based on The Netherlands Perinatal Registry data/ Dutch reference curves.[23]

RESULTS

Between April 2010 and August 2014, 101 cases with isolated gastroschisis were included in the study. There was one dichorionic twin pregnancy with one affected fetus. Maternal baseline characteristics for the 101 included cases are presented in Table 1.

Table 1. Maternal baseline characteristics of all isolated gastroschisis cases.

	N	n	
Age (yr)	101	-	26.6 ± 5.5
Primiparous	101	71	70.3 %
BMI (kg/m^2)	93	-	22.7 ± 3.6
Smoking€	90	34	37.7 %
Recreational drugs use∑	88	14	15.9 %

Yr, years; BMI, body mass index
Data given as mean (standard deviation) or number (%)
€, During first trimester pregnancy
∑, Including cocaine, marihuana and amphetamines

Intra uterine fetal death

There were three cases of IUFD. One infant was stillborn at 33 3/7 weeks of gestation (birth weight 1725 gram (P50)); autopsy confirmed an isolated simple gastroschisis. Karyotyping showed no abnormalities; pathological investigation of the placenta was suggestive of an intrauterine infection. Another IUFD occurred at 22 weeks of gestation (birth weight 270 gram (<P10)); array analysis detected a 2.5Mb deletion in 15q11.2 involving several genes associated with epilepsy and behavioural disorders[24]; histological examination showed a small placenta (<P10), suspected for circumvallate placenta and chorioamnionitis with a high umbilical cord coiling index (0.6). Additional investigation of the hereditary pattern of the deletion or autopsy were not permitted by the parents. Apart from the severe IUGR, other causes for the IUFD were not found. The third IUFD occurred at 31 4/7 weeks of gestation; placental investigation showed a normal placental weight without signs of infection or infarction. Autopsy was not performed and birth weight was not registered; there was no evident cause of the IUFD.

Complex and simple gastroschisis outcome

Seventy-nine (80.6%) liveborns were classified as having simple and nineteen (19.4%) as having complex gastroschisis (Table 2). The most common additional gastro-intestinal disorder was atresia of the bowel, accounting for 18 out of 19 (94.7%) complex cases. Small additional congenital abnormalities were unilateral clubfoot (n=1) and hydronephrosis (n=6).

The maternal characteristics showed no significant differences between the two groups, except for the use of recreational drugs, which was higher in the complex cases (6/18 (33.3%) versus 8/70

(11.4%); (P=0.03)). Table 2 shows the outcome of the 98 liveborn cases divided into simple and complex cases. The gestational age at birth of fetuses with complex gastroschisis, 36.0 weeks (32.3-37.6 weeks) was lower than in the simple cases, 36.7 weeks (range 31.9-38.3) (P=0.03). Spontaneous onset of delivery occurred more often in the complex group (57.9% versus 26.2%, P=0.014) All other perinatal outcome variables showed no significant difference between the two groups.

There were three postnatal deaths: one in the simple group (1.3%) and two in the complex (11.1%) group. One case with simple gastroschisis died at 48 days after birth of respiratory insufficiency due to severe atelectasis and pneumonia, pulmonary hypertension and a severe hydrocephalus after a subdural hematoma. One case with complex gastroschisis died 128 days after birth due to multi-organ failure after repeated operations for small bowel perforation and recurrent Klebsiella sepsis. A third case with complex gastroschisis died 254 days after delivery due to a persistent sepsis caused by a duodenum perforation after adhesiolysis.

Time to full enteral feeding and LOS were threefold longer in the complex gastroschisis group compared to the simple group (TFEF: median and range: 87 days (13-236) and 27 days (8-183), respectively, P<0.001; LOS: 98.5 days (31-203) and 37.5 days (12-155), respectively, P<0.001). The complex group also needed more often repeated surgical interventions (P<0.001).

Ultrasound evaluation

In Appendix Table 1 the mean number per fetus of longitudinal measurements of the different variables is given. All variables had a similar mean number of measurements between the two groups. Polyhydramnios (AFI<24 cm) occurred in six cases of the simple group (7.6%) and in three of the complex group (15.7%) (P=0.37). Two neonates with polyhydramnios died after birth, one in the complex and one in the simple group. Neonatal mortality was increased in the cases with polyhydramnios, 2 out 9, as compared to 1 out of 88 without polyhydramnios (P=0.02). The TFEF and LOS were equally distributed between cases with and without polyhydramnios (P=0.90 and P=0.83, respectively). The PI of the umbilical artery was identical to that in the control group and did not differ between simple and complex cases (data not shown).

Both simple and complex gastroschisis cases had a smaller AC and lower EFW than controls (Fig 1A and B). Multilevel analysis of the AC and EFW showed no significant Group-by-Gestational age interaction effects, neither significant Group main effects when comparing simple with complex cases (Figures 1A and B; Appendix Table 2). This resulted in model-predicted mean trajectories that were not different between the simple and complex groups (Figures 1A and B).

Table 2. Perinatal outcome liveborns

	Simple gastroschisis (n=79)			Complex gastroschisis (n=19)			P-value
	N	n		N	n		
GA at birth (wk) (median, range)	79	-	36.7 (31.9-38.3)	19	-	36.0 (32.3-37.6)	0.03
Onset of delivery	79			19			0.004
- Spontaneously		21	26.6%		11	57.9%	
- Induction		46	58.2%		3	15.8%	
- Elective Caesarean section		12	15.2%		5	26.3%	
Route of delivery	79			19			0.06
- Spontaneously		57	72.2%		11	57.9%	
- Instrumental delivery		2	2.5%		3	15.8%	
- Caesarean section		20	25.3%		5	26.3%	
Birth weight (grams)	79	-	2484±460	19	-	2372±403	0.33
Birth weight Z-score	79	-	-0.53 (0.79)	19	-	-0.37 (0.92)	0.27
Birth weight <P10	79	12	15.2%	19	4	21.1%	0.51
Male gender	79	40	50.6%	19	12	63.2%	0.44
Apgar at 5 min <7	79	4	5.0%	19	1	5.3%	1.00
Primary closure	78	50	64.1%	19	11	57.9%	0.61
Repeated surgeries[¥]	79	35	44.3%	19	17	89.5%	<0.001
Bowel condition at birth							
Atresia				19	18	94.47%	
Antenatal volvulus				19	1	5.3%	
Necrosis				19	3	15.8%	
Perforation				19	3	15.8%	
Intestinal complications							
NEC	79	1	1.3%	19	1	5.3%	0.35
Postnatal perforation	79	1	1.3%	19	0	0%	
Postnatal stricture	79	3	3.8%	19	4	21.1%	0.025
Non-intestinal complications							
Cholestatic icterus	79	23	29.1%	19	14	73.7%	<0.001
Line sepsis	79	27	34.2%	19	12	63.2%	0.035
Wound infections	79	9	11.4%	19	4	21.0%	0.27
Respiratory problems	79	14	17.7%	19	3	15.8%	1.00
Neurological problems	79	10	12.7%	19	1	5.3%	0.69
Mortality	79	1	1.3%	19	2	10.5%	0.10
TFEF (d)[$]	73		27 (8-183)	16		87 (13-236)	<0.001
LOS (d)[€]	76		37.5 (12-155)	16		98.5 (31-203)	<0.001

GA, gestational age; CS, Caesarean section; (wk), weeks; NEC, necrotizing enterocolitis; TFEF, time to full enteral feeding, (d),days; LOS, length of hospital stay;

Data given as mean (standard deviation), median (range) or number (%)

¥, Repeated surgery after first closure

$, 4 patients in simple group and 3 in the complex group and were discharged to home with parenteral nutrition and TFEF was unknown the discharge date was chosen as TFEF

€, 4 patients in the simple group and 1 in the complex were transferred to a regional hospital without a definitive discharge date to home, their transfer date was chosen as discharge date.

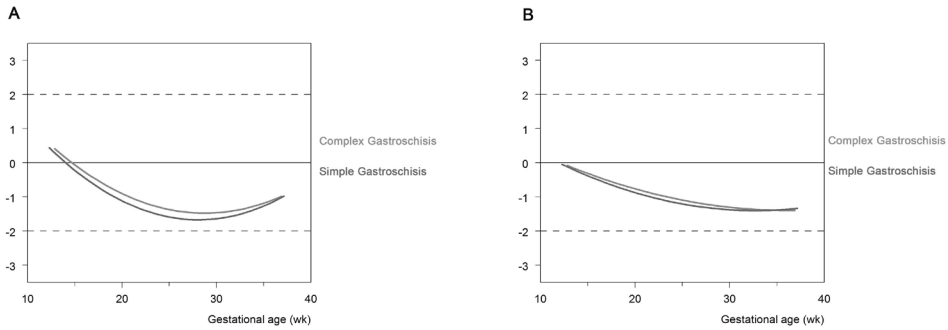


Figure 1A and B. Distribution of the abdominal circumference (AC) (A) and estimated fetal weight (EFW) (B) .
Expressed as Z-scores and presented relative to normal population reference lines (-2 SDS, 0 SDS, and +2 SDS). Model-predicted median lines for the simple and complex gastroschisis groups are included based on linear mixed modelling.

Simple gastroschisis cases had an intra-abdominal bowel diameter that was identical to that in controls, but extra-abdominal bowel diameters were generally increased (Figure 2A and B). Complex cases had both increased intra- and extra-abdominal bowel diameters, with values exceeding the 97.7 centile of controls in just over half of the cases regarding the intra-abdominal diameters and in over 70% of third trimester measurements regarding the extra-abdominal bowel diameter. Multilevel analysis of the intra- and extra-abdominal bowel diameter showed a significant Group main effect for both variables, when simple and complex cases were compared ($P<0.001$ and $P<0.05$, respectively). No significant Group-by-Gestational age interaction effects were found (Appendix Table 2). This resulted in model-predicted mean trajectories that were significantly different between the simple and complex groups (Figure 2A and B).

In Table 3 the 15mm and 20mm cut-off values of the intra-abdominal and extra-abdominal bowel diameters are shown at the last measurement before delivery. An intra-abdominal bowel diameter >20mm occurred more often in complex cases (26.3% versus 6.8%, $P=0.030$). These cut-off values did not discriminate between simple and complex cases for the extra-abdominal bowel measurements. However, there were only a few complex cases with consistently large bowel diameters and in other cases these diameters varied with time, whereby diameters tended to become normal near term. This is illustrated in Figure 3A, which shows the individual trajectories of the intra-abdominal bowel diameters for the complex cases. A somewhat better identification of complex cases may be achieved by using higher cut-off values. For instance, with a cut-off value for the intra-abdominal bowel diameter of 10 mm at 20 weeks, 20 mm at 30 weeks and 30 mm at 40 weeks, 8 out of 19 complex cases had more than one value above this cut-off value, in contrast to only one out of 81 simple cases.

Time to full enteral feeding and LOS was significantly higher in those cases with an intra-abdominal diameter of more than >15mm or >20mm (Table 3), for the combined group.

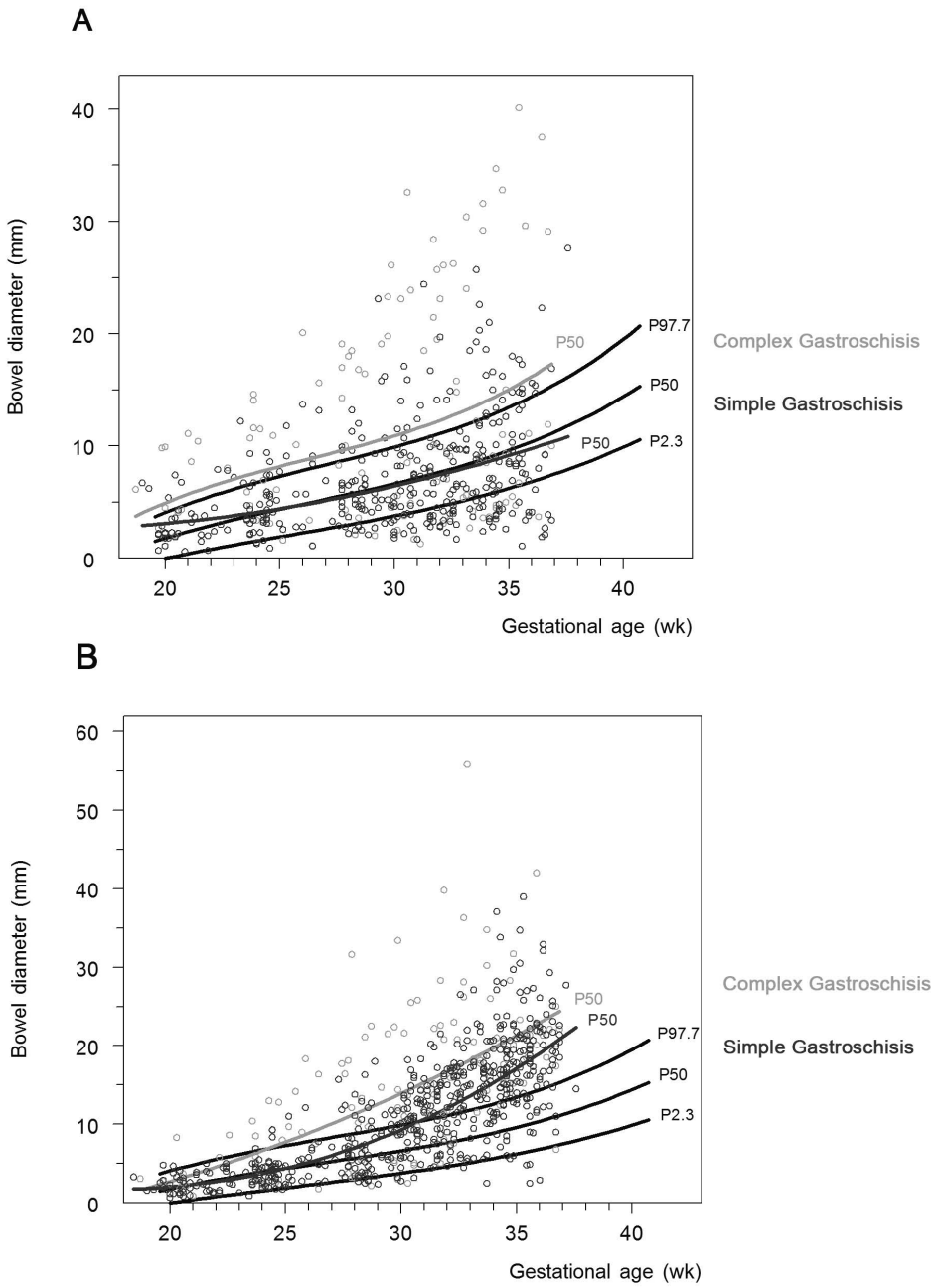


Figure 2A and B. Intra- (A) and extra- (B) abdominal bowel diameters of simple and complex gastroschisis cases. The model predicted lines (P50) of the simple and complex cases are included based on linear mixed modelling. The reference lines of the normal colon diameter (P2.3, P50, P97.7) are included (black lines).

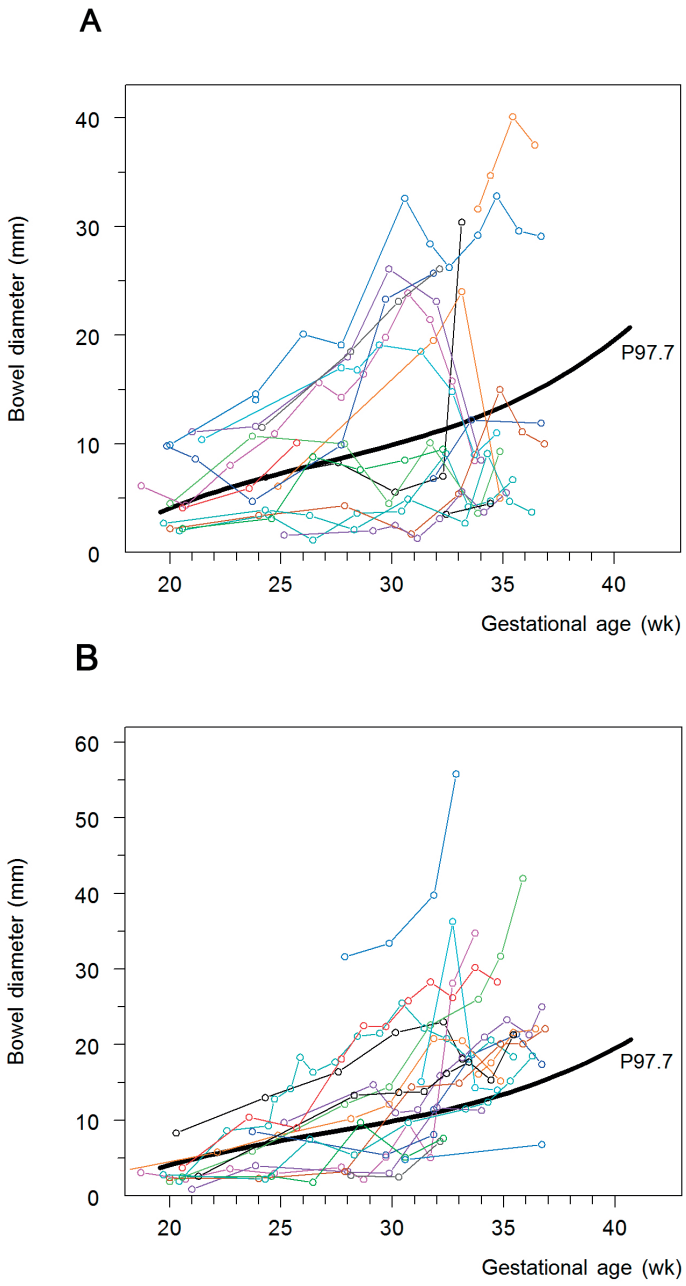


Figure 3A and B. Individual trajectories of the intra-abdominal (A) and extra-abdominal (B) bowel diameter measurements in the complex gastroschisis cases.
The reference line (P97.7) of the normal colon diameter is included.

Table 3A. Last measurement during gestation of the intra-abdominal bowel diameter

Variable	Intra-abdominal bowel diameter					
	Diameter <15 mm	Diameter ≥15 mm	P	Diameter <20 mm	Diameter ≥20mm	P
Simple (n) #	59	15	0.55	69	5	0.03
Complex (n)#	14	5		14	5	
Neonatal mortality* #	2	0	1.00	2	0	1.00
Alive #	71	20		81	10	
All cases (n) ¥	66	19		76	9	
TFEF median (range)	29 (8-183)	50 (24-236)	0.009	29 (8-183)	70 (27-236)	0.004
All cases (n) ¥	69	19		79	9	
LOS median (range)	42 (12-190)	64 (29-203)	0.013	42 (12-190)	95 (30-203)	0.004
Simple (n) ¥	54	15		64	5	
TFEF (median-range)	24 (8-183)	35 (24-135)	0.011	25.5 (8-183)	55 (27-81)	0.058
Simple (n) ¥	58	14		68	4	
LOS (median-range)	35 (12-155)	45.5 (29-154)	0.049	37 (12-155)	61 (30-95)	0.179
Complex (n) ¥	12	4		12	4	
TFEF (median-range)	74 (13-165)	143.5 (70-236)	0.078	74 (13-165)	143.5 (70-236)	0.078
Complex (n) ¥	11	5		11	5	
LOS (median-range)	93 (31-190)	129 (70-203)	0.090	93 (31-190)	129 (70-203)	0.090

Complex, complex gastroschisis; simple, simple gastroschisis; (n), number; TFEF, time to full enteral feeding expressed in days; LOS, length of hospital stay expressed in days;
#, Liveborn cases
¥, Liveborn cases, neonatal deaths excluded
*, one deceased case, no bowel measurements available
If cases were discharged to home with parenteral nutrition and the TFEF was unknown the discharge date was chosen as TFEF.

Table 3B. Last measurement during gestation of the extra-abdominal bowel diameter

Variable	Extra-abdominal bowel diameter					
	Diameter <15 mm	Diameter ≥15 mm	P	Diameter <20 mm	Diameter ≥20mm	P
Simple (n) #	22	55	0.78	43	34	1.00
Complex ((n) #	6	13		11	8	
Neonatal mortality* #	0	2	1.00	1	1	1.00
Alive #	28	66		53	41	
All cases (n) ¥	26	62		49	39	
TFEF median (range)	42 (11-236)	29 (8-183)	0.346	36 (11-236)	29 (8-183)	0.548
All cases (n) ¥	27	64		51	40	
LOS median (range)	47 (20-203)	42 (12-190)	0.309	42 (19-203)	45.5 (12-190)	0.924
Simple (n) ¥	21	51		40	32	
TFEF median (range)	36 (11-118)	25.0 (8-183)	0.187	28 (11-118)	26 (8-183)	0.434
Simple (n) ¥	21	54		41	34	
LOS median (range)	42 (20-154)	35.5 (12-155)	0.399	36.0 (19-154)	39 (12-155)	0.852
Complex (n) ¥	5	11		9	7	
TFEF median (range)	90 (13-236)	84 (41-165)	0.743	90 (13-236)	84 (41-165)	0.606
Complex (n) ¥	6	10	0.875	10	6	
LOS median (range)	105 (31-203)	98.5 (48-190)		98.5 (31-203)	105.5 (48-190)	0.792

Complex, complex gastroschisis; simple, simple gastroschisis; (n), number; TFEF, time to full enteral feeding expressed in days; LOS, length of hospital stay expressed in days;
#, Liveborn cases
¥, Liveborn cases, neonatal deaths excluded
*, one deceased case, no bowel measurements available
If cases were discharged to home with parenteral nutrition and the TFEF was unknown the discharge date was chosen as TFEF.

For simple and complex cases individually similar trends were found, although not significant. Such associations were not found for the extra-abdominal cut-off values.

Doppler measurements of the superior mesenteric artery, both intra- and extra-abdominal, are shown in Appendix Table 2 and Figure 4A and B. The majority of the PI measurements showed values below the median values (P50) of the reference ranges: for intra- and extra-abdominal PI this held for 83% and 89% of measurements, respectively. Lowest PI values were found for the extra-abdominal PI. These numbers were similarly distributed between the simple and complex groups. Multilevel analysis showed neither significant Group-by-Gestational age interaction effects, nor significant Group main effects. This resulted in model-predicted mean trajectories that were not different between the simple and complex groups (Table 3).

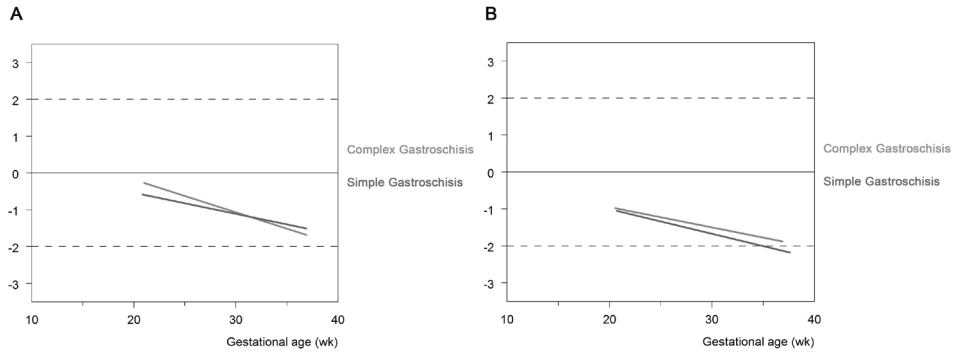


Figure 4A and B. Distribution of the pulsatility index (PI) of the intra-abdominal superior mesenteric artery (A) and the PI of the extra-abdominal superior mesenteric superior artery (B).
Expressed as Z-scores and presented relative to normal population reference lines (-2 SDS, 0 SDS, and +2 SDS). Model-predicted lines for the complex and simple gastroschisis groups are included based on linear mixed modelling.

The three IUFDs were analysed separately. In the two third trimester deaths the PI of the internal mesenteric artery was found to be very low in de weeks before intrauterine demise (Appendix Figure 1). None of the other variables, AC, EFW, PI of the umbilical artery, bowel diameters and PI of the external mesenteric superior artery, showed consistent differences with the liveborn cases of the simple or complex gastroschisis groups (data not shown).

DISCUSSION

Main findings

This is the largest prospective longitudinal study investigating antenatal markers to predict complex gastroschisis. Complex gastroschisis was associated with a higher morbidity and a slightly higher perinatal mortality than simple gastroschisis. Both intra- and extra-abdominal bowel diameters were larger than in simple cases, but antenatal prediction remains difficult given the large overlap between simple and complex cases and large fluctuations in diameters. Doppler measurements of the superior mesenteric artery showed a significantly lower resistance to flow in both simple and complex cases, but did not differentiate between both groups. Abdominal circumference, estimated fetal weight, pulsatility index of the umbilical artery and amniotic fluid volume were also not useful in this respect. In the combined group (simple and complex) polyhydramnios was associated with increased neonatal mortality but not with neonatal morbidity. Intra-abdominal bowel dilatation was correlated with a longer TFEF and LOS.

In a recent meta-analysis on prenatal ultrasound and outcomes in gastroschisis[16], based on 8 retrospective and one prospective study, bowel atresia was found to be correlated to the intra-abdominal bowel dilatation, (odds ratio: 5.48, 95%-CI 3.1-9.8), which is in agreement with our findings. The cut-off values used for abnormal intra-abdominal bowel diameter were either not stated[11,25,26], or varied widely from to 6-18 mm[27-30] and gestational age at scanning was often not reported. This makes the implications for clinical practice difficult. In our study cut-off values of ≥15 or ≥20 mm of the intra-abdominal bowel diameter at the last ultrasound before delivery, showed a significant difference between simple and complex cases. However, this would only identify 26% of the complex cases. In part this may be due to the fact that values sometimes tended to normalise at the end of gestation (Figure 3A). Also others have described large fluctuations in bowel diameter with time in gastroschisis cases.[31] Only with larger cut-off values for the intra abdominal bowel diameter, increasing from 10 mm at 20 weeks to 30 mm at 40 weeks, we were able to identify 8 out of 19 complex cases, with one false-positive.
A relationship between extra-abdominal bowel dilation and atresia was not found in earlier studies[16] and also we found a large overlap between simple and complex cases.

In search of potential markers for vascular obstruction we studied the PI of the superior mesenteric artery, which was on average significantly lower than in controls, especially with advancing gestation. It may be hypothesized that this decreased vascular resistance may be caused by vaso-dilatation due to progressive chronic inflammation of the bowel. Lower serum protein concentration caused by albumin leakage, eventually leading to hypovolemia and subsequently hypoperfusion, may also play a role.[32] Our results do not support the theory suggesting vascular constriction at the level of the abdominal wall as a cause of intestinal damage in fetal gastroschisis.[33,34]
Only three previous studies have studied superior mesenteric artery Doppler velocimetry in fetal gastroschisis. Martilloti et al.[31] performed a retrospective study in which they found a higher incidence of perturbed mesenteric circulation in complex cases. The measurement method and the definition of abnormal Doppler was not described. Volumenie et al. analysed the influence of amnio-infusion on the Doppler velocimetry of superior mesenteric artery in 17 gastroschisis cases and reported a significant positive correlation between the extra-abdominal PI before amnio-infusion and maximal bowel dilation (r=0.54) and length of the NICU-stay; other correlations with neonatal outcome were not found.[35] Abuhamad et al. conducted a prospective, longitudinal study to determine whether Doppler velocimetry of the superior mesenteric artery could predict adverse neonatal outcome in 25 infants with gastroschisis. They found that about 50% of cases had a PI below the normal range, with no difference between simple and complex cases, which is in line with our findings.[36] Blood flow velocimetry of both intra- and extra-abdominal superior mesenteric artery did not differentiate between good and poor neonatal outcome, which is also in agreement with our findings. Appar-

ently Doppler velocimetry of the superior mesenteric artery does not differentiate between simple and complex gastroschisis cases and is also unlikely to be related to neonatal morbidity. The two third trimester IUFDs in our series showed very low PI values in the intra-abdominal mesenteric artery in the weeks before fetal demise. This may have been the result of excessive inflammation, but we realize that this is highly speculative.

We did not find a correlation between the AC or the EFW during gestation and complex gastroschisis or adverse outcome. This is in accordance with previous studies.[16]
In fetuses with an obstruction of the proximal small bowel, there is generally polyhydramnios.[37] Several studies have also found a correlation between polyhydramnios and fetal bowel obstruction in gastroschisis cases and also meta-analysis by Antonio et al, based on 5 studies, polyhydramnios was associated with bowel atresia.[16] The definition of polyhydramnios differed between these studies. We did not find a correlation between polyhydramnios and bowel atresia, but polyhydramnios occurred in two of the three cases that died in the neonatal period. Conclusions based on these small numbers should be made with caution.

Strengths and limitations

The major strength of this study is its prospective and longitudinal study design, whereby ultrasonographers were blinded for outcome. The ultrasound evaluations were performed according to a standardised protocol in a large sample size, thus making it possible to display the antenatal individual course of the ultrasound markers of interest. Another advantage of this study is the use of universal, objective and contemporary primary outcomes for risk-categorization according to Molik et al.[9], making it possible to reproduce this study.
One of the limitations of our study is the missing data. However, as the missing values were random with no differences between simple and complex cases, the data sample is still representative of the gastroschisis population. Different from a previously performed study by our group (Chapter 6), we did not try to distinguish the colon from the small bowel. In gastroschisis the normal anatomic markers of the bowel are missing and the haustra of the colon cannot be recognized anymore. To our opinion, it is therefore impossible to differentiate between small bowel and colon in these cases. One could speculate that the clinical consequences of a dilated colon may be less worrisome than of the small bowel, knowing that atresia of the colon seldomly occurs in gastroschisis.[12]
Not all ultrasound markers previously described in literature were assessed in this study. Gastric dilatation or abnormal stomach size may be a prognostic marker for neonatal death[16] and absence of a lumen in the extra-abdominal loops may be a sign of complex or (in particular closing) gastroschisis.[31]

CONCLUSION

In conclusion, this study confirms the importance of classification of cases into simple and complex for the prediction of outcome, which is poorer in the latter group. Based on this large prospective longitudinal study we conclude that only the intra abdominal bowel dilation appears to be associated with complex gastroschisis especially. However, high cut-off values have to be applied to identify some of those cases reliably. Altogether and unfortunately, the predictive value of the bowel diameter seems limited.

REFERENCES

1. Garne E, Loane M, Dolk H, De Vigan C, Scarano G, Tucker D, Stoll C, Gener B, Pierini A, Nelen V, Rosch C, Gillerot Y, Feijoo M, Tincheva R, Queisser-Luft A, Addor MC, Mosquera C, Gatt M, Barisic I. Prenatal diagnosis of severe structural congenital malformations in Europe. *Ultrasound Obstet Gynecol*. 2005;25(1):6-11. 10.1002/uog.1784.
2. Bradnock TJ, Marven S, Owen A, Johnson P, Kurinczuk JJ, Spark P, Draper ES, Knight M. Gastroschisis: One year outcomes from national cohort study. *BMJ*. 2011;343(7832):1036.
3. Fillingham A, Rankin J. Prevalence, prenatal diagnosis and survival of gastroschisis. *Prenat Diagn*. 2008;28(13):1232-1237. 10.1002/pd.2153.
4. Abdel-Latif ME, Bolisetty S, Abeywardana S, Lui K, Australian and New Zealand Neonatal Network. Mode of delivery and neonatal survival of infants with gastroschisis in Australia and New Zealand. *J Pediatr Surg*. 2008;43(9):1685-1690. 10.1016/j.jpedsurg.2008.03.053.
5. Salihu HM, Emusu D, Aliyu ZY, Pierre-Louis BJ, Druschel CM, Kirby RS. Mode of delivery and neonatal survival of infants with isolated gastroschisis. *Obstet Gynecol*. 2004;104(4):678-683. 10.1097/01.AOG.0000139513.93115.81.
6. Sharp M, Bulsara M, Gollow I, Pemberton P. Gastroschisis: Early enteral feeds may improve outcome. *J Paediatr Child Health*. 2000;36(5):472-476.
7. South AP, Stutey KM, Meinzen-Derr J. Meta-analysis of the prevalence of intrauterine fetal demise in gastroschisis. *Am J Obstet Gynecol*. 2013;2(209):114e1-13. 10.1016/j.ajog.2013.04.032; 10.1016/j.ajog.2013.04.032.
8. Cowan KN, Puligandla PS, Laberge JM, Skarsgard ED, Bouchard S, Yanchar N, Kim P, Lee S, McMillan D, von Dadelszen P, Canadian Pediatric Surgery Network. The gastroschisis prognostic score: Reliable outcome prediction in gastroschisis. *J Pediatr Surg*. 2012;47(6):1111-1117. 10.1016/j.jpedsurg.2012.03.010; 10.1016/j.jpedsurg.2012.03.010.
9. Molik KA, Gingalewski CA, West KW, Rescorla FJ, Scherer LR, Engum SA, Grosfeld JL. Gastroschisis: A plea for risk categorization. *J Pediatr Surg.* 2001;36(1):51-55. 10.1053/jpsu.2001.20004.
10. Bergholz R, Boettcher M, Reinshagen K, Wenke K. Complex gastroschisis is a different entity to simple gastroschisis affecting morbidity and mortality-a systematic review and meta-analysis. *J Pediatr Surg*. 2014;49(10):1527-1532. 10.1016/j.jpedsurg.2014.08.001 [doi].
11. Emil S, Canvasser N, Chen T, Friedrich E, Su W. Contemporary 2-year outcomes of complex gastroschisis. *J Pediatr Surg*. 2012;47(8):1521-1528. 10.1016/j.jpedsurg.2011.12.023; 10.1016/j.jpedsurg.2011.12.023.
12. Snyder CL, Miller KA, Sharp RJ, Murphy JP, Andrews WA, Holcomb GW,3rd, Gittes GK, Ashcraft KW. Management of intestinal atresia in patients with gastroschisis. *J Pediatr Surg*. 2001;36(10):1542-1545. 10.1053/jpsu.2001.27040.
13. Phillips JD, Raval MV, Redden C, Weiner TM. Gastroschisis, atresia, dysmotility: Surgical treatment strategies for a distinct clinical entity. *J Pediatr Surg*. 2008;43(12):2208-2212. 10.1016/j.jpedsurg.2008.08.065.
14. Kronfli R, Bradnock TJ, Sabharwal A. Intestinal atresia in association with gastroschisis: A 26-year review. *Pediatr Surg Int*. 2010;26(9):891-894. 10.1007/s00383-010-2676-4.
15. Page R, Ferraro ZM, Moretti F, Fung KF. Gastroschisis: Antenatal sonographic predictors of adverse neonatal outcome. *J Pregnancy*. 2014;2014:239406. 10.1155/2014/239406 [doi].
16. D'Antonio F, Virgone C, Rizzo G, Khalil A, Baud D, Cohen-Overbeek TE, Kuleva M, Salomon LJ, Flacco ME, Manzoli L, Giuliani S. Prenatal risk factors and outcomes in gastroschisis: A meta-analysis. *Pediatrics*. 2015;136(1):e159-69. 10.1542/peds.2015-0017 [doi].
17. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 101: Ultrasonography in pregnancy. *Obstet Gynecol.* 2009;113(2 Pt 1):451-461. 10.1097/AOG.0b013e31819930b0 [doi].

18. Ebbing C, Rasmussen S, Godfrey KM, Hanson MA, Kiserud T. Fetal superior mesenteric artery: Longitudinal reference ranges and evidence of regulatory link to portal liver circulation. *Early Hum Dev.* 2009;85(4):207-213. 10.1016/j.earlhumdev.2008.09.412 [doi].

19. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. *Am J Obstet Gynecol*. 1985;151(3):333-337. 0002-9378(85)90298-4 [pii].

20. Verburg BO, Steegers EA, De Ridder M, Snijders RJ, Smith E, Hofman A, Moll HA, Jaddoe VW, Witteman JC. New charts for ultrasound dating of pregnancy and assessment of fetal growth: Longitudinal data from a population-based cohort study. *Ultrasound Obstet Gynecol.* 2008;31(4):388-396. 10.1002/uog.5225 [doi].

21. Sparks TN, Shaffer BL, Page J, Caughey AB. Gastroschisis: Mortality risks with each additional week of expectant management. *Am J Obstet Gynecol*. 2016. S0002-9378(16)30648-2 [pii].

22. Abdullah F, Arnold MA, Nabaweesi R, Fischer AC, Colombani PM, Anderson KD, Lau H, Chang DC. Gastroschisis in the United States 1988-2003: Analysis and risk categorization of 4344 patients. *J Perinatol*. 2007;27(1):50-55. 10.1038/sj.jp.7211616.

23. Visser GH, Eilers PH, Elferink-Stinkens PM, Merkus HM, Wit JM. New dutch reference curves for birthweight by gestational age. *Early Hum Dev.* 2009;85(12):737-744. 10.1016/j.earlhumdev.2009.09.008; 10.1016/j.earlhumdev.2009.09.008.

24. Doornbos M, Sikkema-Raddatz B, Ruijvenkamp CA, Dijkhuizen T, Bijlsma EK, Gijsbers AC, Hilhorst-Hofstee Y, Hordijk R, Verbruggen KT, Kerstjens-Frederikse WS, van Essen T, Kok K, van Silfhout AT, Breuning M, van Ravenswaaij-Arts CM. Nine patients with a microdeletion 15q11.2 between breakpoints 1 and 2 of the prader-willi critical region, possibly associated with behavioural disturbances. *Eur J Med Genet.* 2009;52(2-3):108-115. 10.1016/j.ejmg.2009.03.010 [doi].

25. Huh NG, Hirose S, Goldstein RB. Prenatal intraabdominal bowel dilation is associated with postnatal gastrointestinal complications in fetuses with gastroschisis. *Am J Obstet Gynecol.* 2010;202(4):396.e1-396.e6. 10.1016/j.ajog.2009.10.888.

26. Brantberg A, Blaas HG, Salvesen KA, Haugen SE, Eik-Nes SH. Surveillance and outcome of fetuses with gastroschisis. *Ultrasound Obstet Gynecol*. 2004;23(1):4-13. 10.1002/uog.950.

27. Contro E, Fratelli N, Okoye B, Papageorghiou A, Thilaganathan B, Bhide A. Prenatal ultrasound in the prediction of bowel obstruction in infants with gastroschisis. *Ultrasound Obstet Gynecol*. 2010;35(6):702-707. 10.1002/uog.7514.

28. Kuleva M, Khen-Dunlop N, Dumez Y, Ville Y, Salomon LJ. Is complex gastroschisis predictable by prenatal ultrasound? *BJOG Int J Obstet Gynaecol*. 2012;119(1):102-109.

29. Goetzinger KR, Tuuli MG, Longman RE, Huster KM, Odibo AO, Cahill AG. Sonographic predictors of postnatal bowel atresia in fetal gastroschisis. *Ultrasound Obstet Gynecol*. 2013;4(43):420-425. 10.1002/uog.12568; 10.1002/uog.12568.

30. Ghionzoli M, James CP, David AL, Shah D, Tan AW, Iskaros J, Drake DP, Curry JI, Kiely EM, Cross K, Eaton S, De Coppi P, Pierro A. Gastroschisis with intestinal atresia--predictive value of antenatal diagnosis and outcome of postnatal treatment. *J Pediatr Surg*. 2012;47(2):322-328. 10.1016/j.jpedsurg.2011.11.022.

31. Martillotti G, Boucoiran I, Damphousse A, Grignon A, Dube E, Moussa A, Bouchard S, Morin L. Predicting perinatal outcome from prenatal ultrasound characteristics in pregnancies complicated by gastroschisis. *Fetal Diagn Ther.* 2016;39(4):279-286. 10.1159/000440699 [doi].

32. Carroll SG, Kuo PY, Kyle PM, Soothill PW. Fetal protein loss in gastroschisis as an explanation of associated morbidity. *Am J Obstet Gynecol*. 2001;184(6):1297-1301. 10.1067/mob.2001.114031.

33. Langer JC, Bell JG, Castillo RO, Crombleholme TM, Longaker MT, Duncan BW, Bradley SM, Finkbeiner WE, Verrier ED, Harrison MR. Etiology of intestinal damage in gastroschisis, II. timing and reversibility of histological changes, mucosal function, and contractility. *J Pediatr Surg*. 1990;25(11):1122-1126.

34. Langer JC, Longaker MT, Crombleholme TM, Bond SJ, Finkbeiner WE, Rudolph CA, Verrier ED, Harrison MR. Etiology of intestinal damage in gastroschisis. I: Effects of amniotic fluid exposure and bowel constriction in a fetal lamb model. *J Pediatr Surg*. 1989;24(10):992-997.

35. Volumenie JL, de Lagausie P, Guibourdenche J, Oury JF, Vuillard E, Saizou C, Luton D. Improvement of mesenteric superior artery doppler velocimetry by amnio-infusion in fetal gastroschisis. *Prenat Diagn*. 2001;21(13):1171-1174.

36. Abuhamad AZ, Mari G, Cortina RM, Croitoru DP, Evans AT. Superior mesenteric artery doppler velocimetry and ultrasonographic assessment of fetal bowel in gastroschisis: A prospective longitudinal study. *Am J Obstet Gynecol*. 1997;176(5):985-990.

37. Virgone C, D'antonio F, Khalil A, Jonh R, Manzoli L, Giuliani S. Accuracy of prenatal ultrasound in detecting jejunal and ileal atresia: Systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2015;45(5):523-529. 10.1002/uog.14651 [doi].

APPENDIX TABLE 1

Measurement characteristics for biometric and Doppler variables

Variable	Simple (n=79)	Complex (n=19)	T-test/Chi-sq P-value
Number of measurements (n)			
Abdominal circumference; total 747	600	147	---
Estimated fetal weight; total 734	592	142	---
Umbilical artery. PI; total 767	610	157	---
Intra-abd. bowel diameter; total 473	357	116	---
Extra-abd. bowel diameter; total 681	550	131	---
Superior mesenteric art. intra-abd. PI; total 445	374	71	---
Superior mesenteric art. extra-abd. PI; total 409	340	69	---
Mean number of measurements (m; SD)			
Abdominal circumference; R 3-12	7.6 (1.9); n=79	7.8 (2.3); n=19	0.78
Estimated fetal weight; R 3-12	7.5 (1.9); n=79	7.6 (2.3); n=19	0.97
Umbilical art. PI; R 2-15	7.7 (2.4); n=79	8.4 (3.2); n=19	0.41
Intra-abd. bowel diameter; R 1-12	4.8 (2.1); n=77	6.1 (3.0); n=19	0.080
Extra-abd. diameter; R 2-16	7.1 (2.1); n=78	6.9 (3.5); n=19	0.77
Superior mesenteric art. intra-abd. PI; R 1-10	5.0 (2.2); n=79	3.7 (2.6); n=19	0.12
Superior mesenteric art. extra-abd. PI; R 1-9	4.3 (2.3); n=79	3.6 (2.0); n=19	0.25
GA at first measurement (wk); (m; SD)			
Abdominal circumference;	19.2 (3.9); n=79	18.8 (5.0); n=19	0.73
Estimated fetal weight;	19.9 (3.2); n=79	19.9 (4.1); n=19	0.98
Intra-abd. bowel diameter;	23.6 (3.5); n=74	23.3 (4.6); n=19	0.77
Extra-abd. bowel diameter;	22.7 (3.4); n=77	23.8 (5.1); n=19	0.37
Superior mesenteric art. intra-abd. PI;	23.2 (4.2); n=72	24.0 (3.7); n=16	0.47
Superior mesenteric art. extra-abd. PI;	23.3 (3.5); n=71	24.4 (4.2); n=17	0.26
GA at final measurement (wk); (m; SD)			
Abdominal circumference;	35.0 (1.6); n=79	34.5 (1.6); n=19	0.23
Estimated fetal weight;	35.0 (1.6); n=79	34.5 (1.7); n=19	0.19
Intra-abd. bowel diameter;	34.4 (2.1); n=71	34.2 (2.6); n=18	0.70
Extra-abd. bowel diameter;	35.4 (1.5); n=77	34.8 (1.7); n=19	0.10
Mesenteric art intra-abd. PI;	34.6 (2.1); n=71	33.3 (2.5); n=14	0.043
Mesenteric art extra-abd. PI;	34.6 (2.4); n=65	33.4 (2.4); n=15	0.067

m, mean; SD, standard deviation; R, range; GA, gestational age (wk); wk, weeks; abd., abdominal; PI, pulsatility index; AC, abdominal circumference; art., artery;

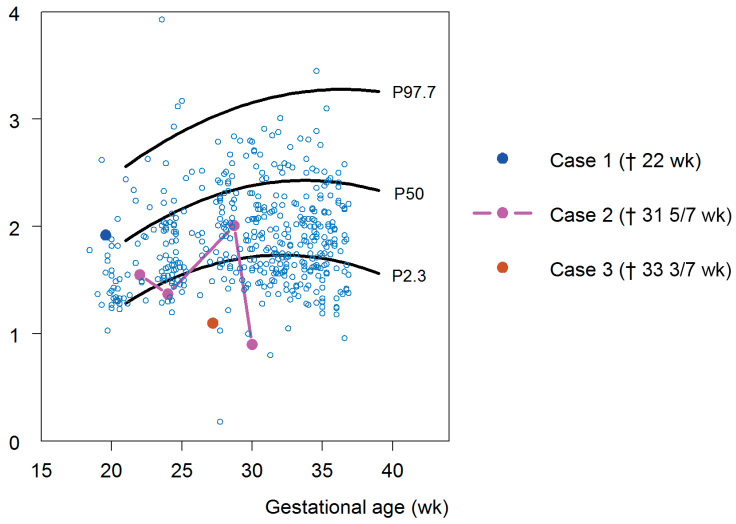
APPENDIX TABLE 2

Model estimates for biometric and Doppler Z-scores (mean and standard error). Gestational age (GA) centred at 15 weeks. Multilevel analysis.

Variable	**Intercept** (mean and SE)	**GA-linear** (mean and SE)	**GA-squared** (mean and SE)	**Group (Simple)** (mean and SE)	**Group-by-GA interactions**
Biometry					
Abdominal circumference Z-score	-0.35 (0.13) $	-0.204 (0.017) *	0.0077 (0.0007) *	0.46 (0.22) &	n.s.
Estimated fetal weight Z-score	-0.49 (0.09) *	-0.101 (0.012) *	0.0027 (0.0005) *	0.30 (0.15) &	n.s.
Bowel diameters					n.s.
Intra-abdominal bowel diameter (mm; ln)	0.43 (0.18) &	0.13 (0.03) *	-0.0022 (0.0010) &	0.46 (0.13) #	n.s.
Extra-abdominal bowel diameter (mm; sqrt)	0.79 (0.17) *	0.093 (0.03) *	0.0036 (0009) *	0.42 (0.14) $	n.s.
Doppler					n.s.
Superior mesenteric artery Intra-abdominal PI Z-score	-0.32 (0.24) n.s.	-0.053 (0.014) *	n.s.	0.04 (0.26) n.s.	n.s.
Superior mesenteric artery Extra-abdominal PI Z-score	-0.67 (0.30) n.s.	-0.067 (0.02) *	n.s.	0.09 (0.25) n.s.	n.s.

SE, Standard error; GA, Gestational age; PI, pulsatility Index; ln, natural logarithm; Sqrt, square root; n.s., not significant;
*, P <0.0001
#, P <0.001
$, P <0.005
&, P <0.05

APPENDIX FIGURE 1



Pulsatility Index (PI) of the intra-abdominal superior mesenteric artery including all measurements of the live born infants (light blue) and the measurements of the intra uterine fetal deaths (IUFD).
Case 1 (dark blue) IUFD at 22 weeks, Case 2 (pink) IUFD at 31 5/7 weeks, case 3 (brown) IUFD a 33 3/7 weeks of gestation.

PART III

Summary and general discussion

Chapter

8

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

Nowadays, gastroschisis is almost always diagnosed prenatally during routine first and second trimester ultrasound examinations.[1] The pathogenesis of gastroschisis is still poorly understood and counselling the parents expecting a child with gastroschisis is challenging. The risk of sudden intra uterine fetal death (IUFD) is still 7 times higher than in the normal pregnancies.[2] Although survival of the liveborn is good[3-5], surgical and neonatal intensive care is needed in early life with morbidity occurring in one third of the children. Not much is known about the long-term outcome of these children.

Given the many uncertainties regarding aetiology, diagnostic tools and prognosis of gastroschisis, we conducted a series of studies, to

Part I

- Provide better information on short and long-term prognosis of a child with an isolated gastroschisis.
- Assess the value of genetic testing and morphological examination in a cohort of patients with gastroschisis.

Part II

- Investigate potential antenatal ultrasound markers that could better predict neonatal outcome and may influence obstetric management in timing of delivery.

The information in the presented studies can be relevant for clinicians who are counselling future parents and who will treat and follow the child born with gastroschisis, most notably perinatologists, neonatologists, paediatric surgeons and general practitioners.
As the results have already been discussed in detail throughout the chapters of the thesis, this final chapter intends to give a high-level overview of the most relevant results. It also aims to discuss what the implication of these results is for the clinical situation.

PART I

Short-term prognosis of a child with isolated gastroschisis

Due to the implementation of total parenteral feeding and improvements in surgical techniques as well as in neonatal intensive care, the survival rate of infants with gastroschisis has increased to approximately 90-95%.[3-5] The condition of the intestines at birth in particular is a significant prognostic marker for neonatal morbidity and long-term outcome.[6] In 2001 Molik et al. concluded that the group of infants with gastroschisis can be divided into two categories: simple and complex gastroschisis.[7] The term 'simple' gastroschisis refers to the newborns without additional intestinal complications at birth, while the term 'complex' gastroschisis refers to newborns with additional intestinal abnormalities including atresia, volvulus, perforation and/or necrosis.

A recent meta-analysis comparing outcome of simple and complex gastroschisis found an increased incidence of mortality (RR: 5.39 (2.42, 12.01 95%-CI)) in the complex gastroschisis cases.[8] The time to full enteral feedings (TFEF) and the length of hospital stay (LOS) was also longer for the complex group. This meta-analysis involved studies including gastroschisis cases with additional congenital disorders such as cardiac abnormalities and amyoplasia, which are more common in complex gastroschisis.[9] These additional disorders may significantly influence the TFEF, LOS and risk of mortality.[10] In addition, in this meta-analysis[8] only the mean differences of TFEF and LOS between complex and simple cases were presented, whereas the actual duration, given in quantitative data of both entities is important in counselling with respect to prognosis.

Therefore, in **Chapter 2** we aimed to determine outcome of children born with *isolated* gastroschisis in order to give the prognosis of the sole entity of gastroschisis in an international cohort of liveborn cases from the Netherlands and Sao Paolo, Brazil. Moreover, we compared our findings with the systematically reviewed literature of studies on isolated gastroschisis cases born in the Western world. Our primary objective was to investigate the TFEF in isolated cases of gastroschisis, since this reflects the condition of the child and its bowel. Our second objective was to investigate length of mechanical ventilation, LOS and mortality. In addition, we investigated the difference in these outcomes between simple and complex gastroschisis. The cohort study included 204 liveborns with isolated gastroschisis. The median TFEF, duration of ventilation and LOS were, 26 days (range 6-515), 2 days (range 0-90) and 33 days (range 11-515), respectively. Overall mortality was 10.8%. TFEF and LOS were significantly longer ($P<0.0001$) and mortality was four times higher in the complex group (30.0% versus 7.5%) compared to the simple group. In Brazil 94.1% of infants were delivered by Caesarean section and in the Netherlands only 38.1%. There were no differences between both groups in TFEF, mortality and LOS suggesting that time and route of delivery did not influence

outcome. This is in line with findings of previous studies on obstetric and neonatal management in gastroschisis.[11-14]
Seventeen studies, including the current study, were part of the meta-analysis comprising a total of 1652 patients. The mean TFEF was 35.3 ± 4.4 days, length of ventilation was 5.5 ± 2.0 days, LOS was 46.4 ± 5.2 days and overall mortality was 5.3%. The outcomes of simple compared to complex cases were only described (or additionally supplied by the author) in five studies, including the current one.[15-18] TFEF, ventilation time, LOS were significant longer and the mortality rate was 3.64 (1.95 – 6.83 95%-CI) times higher in complex cases.

The study presented in **Chapter 2** showed that the presence of complex gastroschisis drastically changes outcome even when gastroschisis is isolated. But also in simple gastroschisis cases, intensive care during the first days of life is necessary for survival. Whether this influences further development of these children with gastroschisis was the question of interest for the next chapter of this thesis.

Long-term outcome

The interventions and events in early life, in addition to the generally late preterm birth and growth restriction in the majority of gastroschisis children, are likely to have long-term effects on neuro-developmental outcome. Most studies have only focussed on the outcome during hospitalisation. The few studies on neurodevelopmental outcome of children with gastroschisis mostly regarded pre-scholars. The studies of pre-scholars invariably reported cognitive outcomes to be in the normal range.[19-23] Deficits might, however, only become apparent after the child has entered school, when higher cognitive demands are required.
In **Chapter 3** we compared the outcome of 16 children born with gastroschisis and treated at the University Medical Center Groningen, the Netherlands, with a control group of 32 children matched for gender, gestational age, birth weight, and corrected for socioeconomic status (SES) and being small for gestational age (SGA). Neuropsychological tests included intelligence, memory, attention, visual perception, motor skills, visuomotor skills and parental report of executive functioning.
Median verbal intelligence quotient and global executive functioning scores of children born with gastroschisis were poorer than of controls (95 (inter quartile range (IQR) 88-100) vs. 104 (IQR 98-113), P=0.001, and 29 (IQR 6.8-63.8) vs. 5.0 (IQR 2.8-19.8), P=0.03, respectively). Children with gastroschisis were more often classified as borderline or abnormal than controls regarding response inhibition (odds ratio (OR) 20.4; 95%-confidence interval (95%-CI) 2.4-171.5), selective visual attention (OR 40.4; 95%-CI 5.9-275.4), sustained auditory attention (OR 88.1; 95%-CI 5.8-1342.8), and fine motor skills (50% vs. 0%). Fifty-eight per cent of the children born with gastroschisis repeated a grade and 19% required special education compared to 19% and 0%, respectively, of the control group. These associations persisted after adjustment for SGA and SES. The auditory verbal memory, visuomotor skills and behavioural problems were comparable to controls.

Only two others studies have previously assessed outcome of school aged gastroschisis survivors, but none of these studies had a control group.[24,25] Harris et al.[24] assessed intellectual ability[27,28] and neurological status, such as hearing, vision and behavioural status[29], of 39 children born with gastroschisis (median age 10 years with range 5-17 years) and compared the results with normative means, thus without correction for comorbidity, such as prematurity and low birth weight. Giudici et al.[25] performed a follow-up study, including screening for neurodevelopmental problems using the Neurology-Psychomotor Developmental Index (NPDI)[26], at 3 years interval, of 17 gastroschisis survivors from birth until the age of six years. They found that, as children became older, the proportion of deficits increased, which is consistent with our hypothesis of poorer outcome in school age than in pre-school age children with gastroschisis. They did not specify which domains of the NPDI were affected.
In contrast with Harris et al., we found a lower average TIQ in the gastroschisis group than the control group, which seemed rather related to a lower average VIQ. However, our lower IQ-scores represented subtle differences, since the clinical classification of IQ-scores did not differ between the gastroschisis and the control groups, which is consistent with Harris et al. Similar to Harris et al., gastroschisis children had an increased risk for impaired attention, i.e. selective visual attention and sustained auditory attention and executive functioning in school age gastroschisis cases was poorer compared with matched controls.

The investigated domains and tools differed between the three studies and the effect of additional gastrointestinal tract disorders (complex gastroschisis), of number of operations and of different surgical strategies could not be investigated, due to the low number of cases. However, we may conclude that outcome at school age of gastroschisis children is poorer than expected from studies at pre-school age. Also when corrected for gestational age, birth weight and socioeconomic status, school aged children born with gastroschisis scored significantly lower on several aspects of attention, executive functioning and fine motor skills. Special education and grade retention was more common in gastroschisis children than their age related peers. We therefore strongly recommend multidisciplinary long-term follow-up for these at-risk children.

Genetic risk factors

In **Chapter 4** we showed that not only external factors, such as the events in early life, influences the development of the child with gastroschisis, but that a genetic cause may also play a role. Young maternal age, associated with environmental factors like smoking and low economic status, is a well-recognized risk factor for gastroschisis.[30-33] However, the fact that gastroschisis is more common in Caucasians compared to African-Americans living in the same socio-economic area[34,35] and that the recurrence risk (2.4%) is increased within families[36], suggests that the aetiology of gastroschisis is multifactorial and that genetic factors contribute as well. Gastroschisis is not associated with

abnormalities at standard chromosome analysis.[37,38] Although in many other congenital disorders that are also not associated with an abnormal karyogram, the application of array has led to the identification of new monogenetic causes and target genes[39,40], this was never systematically studied in gastroschisis cases. Gastroschisis is mostly described as an isolated congenital disorder, although the incidence of associated anomalies varies from 5 to 50% between studies. This is due to different inclusion and classification criteria.[41,42] Studying major and minor morphologic findings in children with congenital anomalies allows for the detection of patterns of anomalies. They can serve as indicators of aberrant fetal development, not only referring to specific monogenetic syndromes, but also resulting from interaction between genetic and environmental disturbances.[43-46]

In **Chapter 4** we performed a clinical morphological examination and array-analysis in 21 gastroschisis cases (median age 11 years, range 4-27 years) and their parents in order to assess the value of genetic testing in these patients and to identify potential genetic causes or risk factors for gastroschisis. We found a significantly increased incidence of two or more minor morphological anomalies per patient as compared to healthy controls (89.5% versus 55.7%, P=0.004). The incidence of major morphological abnormalities was not increased, which may be due to the fact that we only studied surviving patients. The anomalies at clinical morphological examination did not lead to a syndrome diagnosis. However, the higher incidence of minor anomalies cannot be explained by a localized event like vascular disruption or clot formation, a frequently hypothesized cause of gastroschisis.[33,47,48] We did not observe a specific pattern of phenotypic abnormalities, which fits with a multifactorial aetiology and genetic heterogeneity. Developmental genes usually do not function in one site, but are expressed on different sites and times during embryogenesis. Array-analysis revealed seven inherited and one *de novo* Copy Number Variations (CNVs) in 5 cases. The *de novo* duplication was classified as a variant of unknown significance. No overlap with the CNVs region were found between cases of this study and individual gastroschisis cases described in literature or databases. Although the inherited nature of the CNVs in the other cases makes it unlikely that they are causal, it does not per definition exclude pathogenicity. CNVs are well recognized as susceptibility factors for various disorders and can have incomplete penetrance.[49-52] Because we were the first to perform array in a cohort of children with gastroschisis, interpretation of our array findings is hampered by the limited available data and the limited knowledge on the contribution of genetics in the aetiology of gastroschisis. Future systematic application of array in all children with a congenital anomality, including gastroschisis, will increase these numbers and yield sufficient data to enable the detection of rare pathogenic / risk CNVs that are present significantly more often in patients with gastroschisis, thus allowing the identification of candidate gastroschisis susceptible genes. This has been shown to be successful in isolated structural defects like cardiac anomalies, craniofacial and renal disorders only after several hundreds to thousands of patients had been analysed, allowing

determination of the prevalence of specific CNVs in cases versus healthy controls, as well as the detection of rare *de novo* causal gains or losses.[39,50]

Three cases in our series displayed neurologic disorders, including two with severe neurodevelopmental delay. The importance of genetic testing in nonsyndromic (sporadic) cases of unexplained intellectual disability or developmental delay has been outlined in previous studies, whereby array-CGH provided a diagnosis in 15-20% of cases[53] and WES a diagnosis in 33% of cases.[54]

We detected a *de novo MECP2* gene mutation explaining the neurodevelopmental impairment and regression in the first case[55] and a single nucleotide variant in the *KCNQ2* gene in the second case. *De novo* mutations in this latter gene cause an epileptic encephalopathy with poor developmental outcome[56] which is compatible with the phenotype in this case. Inheritance is currently being determined by parental analysis. One and possibly two monogenic disorders in a cohort of only 21 patients suggest that monogenetic disorders in cases with gastroschisis are underreported, especially since our inclusion criteria did not bias in favour of additional anomalies. Most pathologic mutations in congenital disorders are *de novo*. It is possible that this is also the case in gastroschisis, explaining its sporadic incidence. Monogenetic conditions are, potentially, more vulnerable for a second hit and therefore additional abnormalities are more often seen in monogenic disorders.[52]

Reports on monogenic disorders in patients with gastroschisis are rare and hard to find because the gastroschisis is almost exclusively labeled to be coincidental. We found two other reports.[57,58] Because genetics diagnosis are often made later in life, and widespread application of WES to patients diagnostics has only become available around five years ago, underreporting of monogenetic diagnosis in population-based cohort studies of gastroschisis patients is likely. The consistent finding that major unrelated malformations are present in one in six (15%) children with gastroschisis[7,37,59,60] however, now justifies systematic genetic screening and testing in cases with gastroschisis with associated dysmorphic features and / or impaired development.

PART II

Antenatal ultrasound markers to predict outcome

In part two of this thesis we investigated potential antenatal ultrasound markers to identify intestinal disorders, to improve parental counselling and to identify those patients that might potentially profit from obstetric interventions, like preterm induction of labour. In addition, if the presence of bowel atresia before birth could be predicted, then this would significantly help the surgeon to early diagnose atresia and plan a repair. In gastroschisis cases, atresia may be missed at birth during the first surgery in about 40% of cases.[61-63]

In gastroschisis, various attempts have been made to correlate antenatal ultrasound findings with neonatal outcome. Reports are conflicting because of the small size of study populations, retrospective study designs, short time of follow-up and non-standardised methods and timing of ultrasound examinations.[64,65] A recent meta-analysis, mainly based on retrospective studies, has shown that intra-abdominal bowel dilatation and polyhydramnios are the most promising markers for bowel atresia in gastroschisis cases. The cut-offs used for bowel diameter were either not stated or varied widely from to 6-18 mm and the gestational age at scanning was often not reported.[65] This has made the implications for clinical practice difficult and the authors of the systematic review rightly plead for prospective standardised studies.

Normal reference curves of the fetal bowel diameter

To identify pathologically dilated bowel, knowledge of the physiological and gestational age related increase in diameter of small bowel and colon in healthy fetuses is needed. To date there was no standardised method to assess the fetal bowel diameter. Furthermore, only limited data has been published on reference values for fetal intestinal measurements. None of these studies has used longitudinal data[66-68] and some studies only used post mortem specimens.[69,70] In **Chapter 5** we establish reference curves of normal fetal small bowel and colon diameters based on serial longitudinal ultrasound examinations at four-weeks intervals in 39 low-risk fetuses between 20 to 41 weeks of gestation. In addition, we assessed the clinical applicability of these references curves in a retrospective cohort of 28 fetuses with suspected fetal bowel dilatation.

The bowel diameter was measured according to a standard protocol; the largest loops of the small bowel and colon were identified in a coronal plane of the fetal abdomen. For both the colon and small bowel, the short axis of the bowel lumen was measured (from inner to inner bowel wall). A total of 198 ultrasound examinations were performed in 39 uneventful pregnancies. The development of small bowel diameter and colon diameter was best described by a linear model and a cubic model, respectively. The intra-observer and inter observer ICC for small bowel and colon were ≥ 0.94. The mean small bowel diameter at 40 weeks' gestation was 5.1 mm with a maximum of 7.6 mm. For colon the mean diameter at 40 weeks' gestation was 14.5 mm, with a maximum of 19.4 mm.

In the cases with suspected dilated bowel only 26% of fetuses were found to have intestinal abnormalities at birth. Our study showed that fetal intestinal dilatation could resolve during gestation; 56% of fetuses with repeated measurements had a resolution of intestinal dilatation on consecutive ultrasound examinations. Resolution of dilated bowel should be considered reassuring for normal neonatal outcome, since none of those fetuses were found to have intestinal pathology after birth. In all cases with progressive dilatation of the small bowel, pathology of the small bowel was confirmed after birth. A large small bowel diameter (Z-score >8) after 25 weeks of gestation was also associated with small bowel pathology. The type of bowel disease diagnosed after birth varied. In

all these cases surgical treatment was necessary in early postnatal life. This stresses the importance of antenatal diagnosis of bowel pathology to ensure immediate paediatric (surgical) care after birth.

Herniation of the complete liver in gastroschisis

In **Chapter 6** we describe a case of gastroschisis with a highly unusual ultrasound finding: herniation of the complete liver in the amniotic cavity. At 12 weeks of gestation an abdominal wall defect was detected with complete herniation of the liver without a covering membrane. At 27 weeks a Caesarean section was performed for supspected fetal distress. The infant proved impossible to ventilate and died. To investigate if this condition is always lethal we performed a literature search including gastroschisis cases with complete herniation of the liver and cases defined as ruptured omphalocele with evisceration of the complete liver without a membrane. Cases with additional structural or chromosomal abnormalities were excluded since this could influence prognosis. There were sixteen cases with complete herniation of the liver, fourteen cases died in the neonatal period and the other 2 after 3 months and one year, respectively, after a life completely dependent on mechanical ventilation. So, the evidence suggests that this condition is indeed lethal (0 survival out of 16 cases 95%-confidence interval for survival 0 – 19%), with most infants dying because of respiratory failure.

Antenatal ultrasound markers to predict outcome of isolated gastroschisis

Finally, in **Chapter 7** we present the results of the "Fetal Abdominal Markers Identified by Ultrasound to Predict Neonatal Gastroschisis Outcome" (FLAMINGO) study. A prospective longitudinal national multi-centre study with fetal ultrasound assessment and surveillance according to a standard protocol, to assess markers related to outcome of isolated gastroschisis cases. The primary outcome was simple or complex gastroschisis and secondary outcomes were TFEF, LOS and mortality.

This study was conducted at all seven reference centres for gastroschisis in the Netherlands. Between 18-22 weeks of gestation, an anomaly scan was performed to exclude extra-intestinal abnormalities, ultrasound follow-up evaluation was performed at 24, 28, 30, 32, 34, 35 and 36 weeks of gestation. During the examination fetal biometry, Amniotic Fluid Index (AFI), pulsatility index (PI) of the umbilical artery and superior mesenteric artery and bowel diameter measurements were assessed. Bowel diameters were measured at the short axis of the bowel lumen (inner to inner wall) of the most dilated bowel segment, both intra- and extra-abdominal. Intra-abdominal superior mesenteric artery measurements were obtained after its origin from the aorta, just above the renal arteries. The extra-abdominal superior mesenteric artery was identified and measured direct distally to the abdominal wall defect. Superior mesenteric artery PI data were compared to those of a published reference range.[71] Delivery was planned in one of the participating centres from 37 weeks' gestation onwards by induction of labour. Caesarean delivery was only performed for obstetric reasons, such as fetal distress or failure to progress in labour. Primary operative abdominal wall repair of

gastroschisis was attempted in all cases based on the judgment of the surgeon, neonatologist and anaesthetist. If the viscera could not be reduced primarily, a silo bag was placed.

Between April 2010 and August 2014, 101 cases with isolated gastroschisis were included in the study. There were 3 cases of IUFD at 22, 32 and 33 weeks of gestation. In one case chorioamnionitis was the most likely reason for fetal death, in the other cases no evident causes of death were found. Seventy-nine (80.6%) live born infants were classified as having simple and nineteen (19.4%) as having complex gastroschisis. There were three postnatal deaths: one in the simple group and two in the complex group (P=0.10). Time to full enteral feeding and hospital stay were significantly and on average three times longer in the complex group as compared to the simple group. The complex group also needed more often repeated surgical interventions (P<0.001). The most common additional gastro-intestinal disorder was atresia of the bowel, accounting for 18 out of 19 (94.7%) complex cases.

Abdominal circumference and estimated fetal weight were significantly lower in case of gastroschisis, but did not differentiate between complex and simple cases. The PI of the umbilical artery was normal in both groups. Polyhydramnios was related to neonatal mortality but did not differ between both groups.

The intra-abdominal bowel diameters in simple gastroschisis cases were on average the same as in control cases, but were above the 97.7th centile in 50% of complex cases. The extra abdominal diameters were increased in both groups with highest values in complex cases. However, differentiation between simple and complex cases based on these values remaines difficult given the large inter-individual differences and fluctuations with time. Only with high cut-off values of the intra-abdominal diameter, ranging from 10 mm at 20 weeks to 30 mm at 40 weeks we were able to identify 8 of 19 complex cases, with one false positive case. Bowel diameters ≥15mm before delivery were related to neonatal morbidity (TFEF and LOS), for the combined group.

The last variable studied was the PI in the superior mesenteric artery. This was found to be significantly decreased in gastroschisis cases without differentiation between simple and complex cases. With time values became lower, with lowest values for the PI in the extra abdominal part of the mesenteric artery. In one other longitudinal study in 25 gastroschisis cases similar data on the PI of the mesenteric artery were found.[72] It may be hypothesized that this decreased vascular resistance is caused by vaso-dilatation due to progressive chronic inflammation of the bowel. Lower serum protein concentration caused by albumin leakage, eventually leading to hypovolemia and subsequently hypoperfusion, may also play a role.[73] Our results do not support the theory suggesting vascular constriction at the level of the abdominal wall as a cause of intestinal damage in fetal gastroschisis.[74,75] Both third trimester fetal deaths in our study had a very low PI in the intra-abdominal superior mesenteric artery, which may suggest excessive inflammation, but this is highly speculative. Unfortunately, we were not able to find significant antenatal ultrasound markers that can differentiate complex gastroschisis cases from simple ones, apart from a possible association between

enlarged intra abdominal bowel lumen diameters. When intra abdominal bowel lumen is dilated ≥15 mm in the third trimester there is an increased risk of complex gastroschischis and prolonged TFEF and LOS.

CLINICAL IMPLICATIONS

Part I

- The results of **Chapter 2** provide useful information for the counselling of parents expecting a child with isolated gastroschisis. Quantitative ranges in outcome of the liveborn with isolated gastroschisis regarding TFEF, mechanical ventilation time, LOS and mortality are given. This study also confirms the differences in outcome between simple and complex isolated gastroschisis.
- In **Chapter 3** we showed that children born with gastroschisis seem to have an increased risk of an impaired functional development, when corrected for prematurity, growth restriction and social economic status. Grade retention was more common in gastroschisis children than in their age related peers. We therefore strongly recommend multidisciplinary long-term follow-up of these at-risk children.
- In **Chapter 4** we showed that not only external factors, such as events in early life, influence the development of the child with gastroschisis, but that (novo-)genetic disorders may also play a role. The results of this study justify syndrome evaluation and genetic analysis in cases with gastroschisis, especially when children have additional congenital malformations or developmental delay.

Part II

- In **Chapter 5** we established a standard method to measure the fetal bowel diameter and have provided normal reference curves of the small bowel and colon. These curves can be used to identify dilated bowel.
- We showed that repeated measurements of a suspected dilated fetal bowel during gestation is important to distinguish a pathologically dilated bowel from a transiently dilated bowel (**Chapter 5**).
- Based on a case report and additional literature search we conclude that the unusual appearance of complete herniation of the liver in gastroschisis is bound to be lethal. This can be used in the counselling and obstetric management of these cases (**Chapter 6**).

- Our prospective longitudinal FLAMINGO-study showed that gastroschisis is associated with a lower resistance to flow in both the intra- and extra-abdominal part of the superior mesenteric artery. This may be related to bowel inflammation (**Chapter 7**).
- The only variable that differentiated between simple and complex gastroschisis cases was the diameter of the intra-abdominal bowel lumen. However, high cut-off values from 10 mm at 20 weeks till 30 mm at 40 weeks may have to be used to identify a part of the complex cases reliably.

FUTURE DIRECTIONS

- Close follow up children born with gastroschisis during (pre-) school age and regular assessment of their development may detect problems early in life. Early interventions may improve their outcome, but this needs to be established in future studies.
- Genetic testing using array and WES in children with gastroschisis may give further inside of the genetic role in its aetiology.
- Fetal monitoring using CTG was performed in the FLAMINGO-study from 34 weeks of gestation. Whether this may predict and prevent sudden intra uterine fetal death needs to be established.
- Unfortunately the sensitivity of the investigated antenatal ultrasound markers in **Chapter 7** were not high enough to diagnose complex gastroschisis antenatally reliably. Other markers that may be assessed, are: a) gastric dilatation; this may be a prognostic marker for neonatal death,[8] b) absence of a lumen in the extra abdominal loops, which may be a sign of complex (or in particular closing) gastroschisis, c) 3D ultrasound assessment of the fetal intestine, which may give a better indication of the volumes of the eviscerated fetal intestine.
- If antenatal markers with a high specificity and sensitivity for complex gastroschisis cases will be found than the timing of delivery of complex gastroschisis should be investigated. In complex and simple cases combined, delivery as early as 37 weeks has shown to minimize pre- and postnatal mortality.[76] Preterm delivery has been suggested to protect the exteriorized bowel from severe damage due to exposure to amniotic fluid and compression. Morbidity due to intrauterine bowel damage must outweigh morbidity caused by prematurity. Since only 19% of gastroschisis patients are born with severe bowel damage (complex gastroschisis), elective preterm delivery of all gastroschisis cases could cause unnecessary morbidity due to prematurity. Complex gastroschisis may benefit from a different obstetric management with close fetal surveillance and even preterm delivery in order to protect the bowel from severe damage caused by venous compression, ischemia and chronic inflammation.[77,78]

REFERENCES

1. Garne E, Loane M, Dolk H, De Vigan C, Scarano G, Tucker D, Stoll C, Gener B, Pierini A, Nelen V, Rosch C, Gillerot Y, Feijoo M, Tincheva R, Queisser-Luft A, Addor MC, Mosquera C, Gatt M, Barisic I. Prenatal diagnosis of severe structural congenital malformations in Europe. *Ultrasound Obstet Gynecol*. 2005;25(1):6-11. 10.1002/uog.1784.
2. South AP, Stutey KM, Meinzen-Derr J. Meta-analysis of the prevalence of intrauterine fetal demise in gastroschisis. *Am J Obstet Gynecol*. 2013;2(209):114e1--13. 10.1016/j.ajog.2013.04.032; 10.1016/j.ajog.2013.04.032.
3. Martillotti G, Boucoiran I, Damphousse A, Grignon A, Dube E, Moussa A, Bouchard S, Morin L. Predicting perinatal outcome from prenatal ultrasound characteristics in pregnancies complicated by gastroschisis. *Fetal Diagn Ther*. 2016;39(4):279-286. 10.1159/000440699 [doi].
4. Vachharajani AJ, Dillon PA, Mathur AM. Outcomes in neonatal gastroschisis: An institutional experience. *Am J Perinatol*. 2007;24(8):461-465.
5. Bradnock TJ, Marven S, Owen A, Johnson P, Kurinczuk JJ, Spark P, Draper ES, Knight M. Gastroschisis: One year outcomes from national cohort study. *BMJ*. 2011;343(7832):1036.
6. Cowan KN, Puligandla PS, Laberge JM, Skarsgard ED, Bouchard S, Yanchar N, Kim P, Lee S, McMillan D, von Dadelszen P, Canadian Pediatric Surgery Network. The gastroschisis prognostic score: Reliable outcome prediction in gastroschisis. *J Pediatr Surg*. 2012;47(6):1111-1117. 10.1016/j.jpedsurg.2012.03.010; 10.1016/j.jpedsurg.2012.03.010.
7. Molik KA, Gingalewski CA, West KW, Rescorla FJ, Scherer LR, Engum SA, Grosfeld JL. Gastroschisis: A plea for risk categorization. *J Pediatr Surg*. 2001;36(1):51-55. 10.1053/jpsu.2001.20004.
8. Bergholz R, Boettcher M, Reinshagen K, Wenke K. Complex gastroschisis is a different entity to simple gastroschisis affecting morbidity and mortality-a systematic review and meta-analysis. *J Pediatr Surg*. 2014;49(10):1527-1532. 10.1016/j.jpedsurg.2014.08.001 [doi].
9. Arnold MA, Chang DC, Nabaweesi R, Colombani PM, Bathurst MA, Mon KS, Hosmane S, Abdullah F. Risk stratification of 4344 patients with gastroschisis into simple and complex categories. *J Pediatr Surg*. 2007;42(9):1520-1525. 10.1016/j.jpedsurg.2007.04.032.
10. Akhtar J, Skarsgard ED, Canadian Pediatric Surgery Network (CAPSNet). Associated malformations and the "hidden mortality" of gastroschisis. *J Pediatr Surg*. 2012;47(5):911-916. 10.1016/j.jpedsurg.2012.01.044.
11. Logghe HL, Mason GC, Thornton JG, Stringer MD. A randomized controlled trial of elective preterm delivery of fetuses with gastroschisis. *J Pediatr Surg*. 2005;40(11):1726-1731. 10.1016/j.jpedsurg.2005.07.047.
12. Segel SY, Marder SJ, Parry S, Macones GA. Fetal abdominal wall defects and mode of delivery: A systematic review. *Obstet Gynecol*. 2001;98(5 Pt 1):867-873.
13. Abdel-Latif ME, Bolisetty S, Abeywardana S, Lui K, Australian and New Zealand Neonatal Network. Mode of delivery and neonatal survival of infants with gastroschisis in Australia and New Zealand. *J Pediatr Surg*. 2008;43(9):1685-1690. 10.1016/j.jpedsurg.2008.03.053.
14. Ross AR, Eaton S, Zani A, Ade-Ajayi N, Pierro A, Hall NJ. The role of preformed silos in the management of infants with gastroschisis: A systematic review and meta-analysis. *Pediatr Surg Int*. 2015;31(5):473-483. 10.1007/s00383-015-3691-2 [doi].
15. Garcia L, Brizot M, Liao A, Silva MM, Tannuri AC, Zugaib M. Bowel dilation as a predictor of adverse outcome in isolated fetal gastroschisis. *Prenat Diagn*. 2010;30(10):964-969. 10.1002/pd.2596.
16. Kuleva M, Salomon LJ, Benoist G, Ville Y, Dumez Y. The value of daily fetal heart rate home monitoring in addition to serial ultrasound examinations in pregnancies complicated by fetal gastroschisis. *Prenat Diagn*. 2012;32(8):789-796. 10.1002/pd.3903; 10.1002/pd.3903.
17. Emil S, Canvasser N, Chen T, Friedrich E, Su W. Contemporary 2-year outcomes of complex gastroschisis. *J Pediatr Surg*. 2012;47(8):1521-1528. 10.1016/j.jpedsurg.2011.12.023; 10.1016/j.jpedsurg.2011.12.023.

18. Frybova B, Vlk R, Kokesova A, Rygl M. Isolated prenatal ultrasound findings predict the postnatal course in gastroschisis. *Pediatr Surg Int.* 2015;31(4):381-387. 10.1007/s00383-015-3675-2 [doi].
19. Payne NR, Gilmore L, Svobodny S, Perdue NR, Hoekstra RE, Olsen S, Moore JR. A cross-sectional, case-control follow-up of infants with gastroschisis. *J Neonatal-Perinat Med*. 2010;3(3):207-215.
20. South AP, Marshall DD, Bose CL, Laughon MM. Growth and neurodevelopment at 16 to 24 months of age for infants born with gastroschisis. *J Perinatol.* 2008;28(10):702-706. 10.1038/jp.2008.71.
21. Gorra AS, Needelman H, Azarow KS, Roberts HJ, Jackson BJ, Cusick RA. Long-term neurodevelopmental outcomes in children born with gastroschisis: The tiebreaker. *J Pediatr Surg*. 2012;47(1):125-129. 10.1016/j.jpedsurg.2011.10.028.
22. Minutillo C, Rao SC, Pirie S, McMichael J, Dickinson JE. Growth and developmental outcomes of infants with gastroschisis at one year of age: A retrospective study. *J Pediatr Surg*. 2013;48(8):1688-1696. 10.1016/j.jpedsurg.2012.11.046; 10.1016/j.jpedsurg.2012.11.046.
23. van Manen M, Hendson L, Wiley M, Evans M, Taghaddos S, Dinu I. Early childhood outcomes of infants born with gastroschisis. *J Pediatr Surg*. 2013;48(8):1682-1687. 10.1016/j.jpedsurg.2013.01.021; 10.1016/j.jpedsurg.2013.01.021.
24. Harris EL, Hart SJ, Minutillo C, Ravikumara M, Warner TM, Williams Y, Nathan EA, Dickinson JE. The long-term neurodevelopmental and psychological outcomes of gastroschisis: A cohort study. *J Pediatr Surg*. 2016;51(4):549-553. 10.1016/j.jpedsurg.2015.08.062 [doi].
25. Giudici L, Bokser VS, Maricic MA, Golombek SG, Ferrario CC. Babies born with gastroschisis and followed up to the age of six years faced long-term morbidity and impairments. *Acta Paediatr*. 2016;105(6):e275-80. 10.1111/apa.13374 [doi].
26. Lejarraga H, Menendez AM, Menzano E, Guerra L, Biancato S, Pianelli P, Fattore MJ, De Raco P, Schejter V, Contreras MM, Glomba C, Bellusci C, Lusnig A, Rautenstrauch C, Paris V, Galeana A, Feinsilber V, Garay ML, Alves L, Del Pino M, Andrews M, Pagano A, Larigoitia D. PRUNAPE: Screening for psychomotor development problems at primary care level. *Arch Argent Pediatr*. 2008;106(2):119-125. 10.1590/S0325-00752008000200005 [doi].
27. Wechsler D, ed. *Wechsler Intelligence Scale for Children.* Fourth Edition Australin Standerdised Edition (WISC-IV Australian) ed. Pearson; 2005.
28. Wechsler D, ed. *Wechsler Preschool & Primary Scale of Intelleigence- Australian Standardised Edition (WPPSI-III Australian).* Third Edition ed. Pearson; 2004.
29. YouthinMind: Strengths and difficulties questionnaire..
30. Drongowski RA, Smith RK,Jr, Coran AG, Klein MD. Contribution of demographic and environmental factors to the etiology of gastroschisis: A hypothesis. *Fetal Diagn Ther.* 1991;6(1-2):14-27.
31. Torfs CP, Velie EM, Oechsli FW, Bateson TF, Curry CJ. A population-based study of gastroschisis: Demographic, pregnancy, and lifestyle risk factors. *Teratology*. 1994;50(1):44-53. 10.1002/tera.1420500107.
32. Haddow JE, Palomaki GE, Holman MS. Young maternal age and smoking during pregnancy as risk factors for gastroschisis. *Teratology*. 1993;47(3):225-228. 10.1002/tera.1420470306.
33. Lubinsky M. Hypothesis: Estrogen related thrombosis explains the pathogenesis and epidemiology of gastroschisis. *Am J Med Genet A*. 2012;158A(4):808-811. 10.1002/ajmg.a.35203; 10.1002/ajmg.a.35203.
34. Salihu HM, Pierre-Louis BJ, Druschel CM, Kirby RS. Omphalocele and gastroschisis in the state of New York, 1992-1999. *Birth Defects Res A Clin Mol Teratol*. 2003;67(9):630-636. 10.1002/bdra.10113.
35. Williams LJ, Kucik JE, Alverson CJ, Olney RS, Correa A. Epidemiology of gastroschisis in metropolitan Atlanta, 1968 through 2000. *Birth Defects Res A Clin Mol Teratol.* 2005;73(3):177-183. 10.1002/bdra.20114.
36. Kohl M, Wiesel A, Schier F. Familial recurrence of gastroschisis: Literature review and data from the population-based birth registry "mainz model". *J Pediatr Surg*. 2010;45(9):1907-1912. 10.1016/j.jpedsurg.2010.05.003.

37. Mastroiacovo P, Lisi A, Castilla EE, Martinez-Frias ML, Bermejo E, Marengo L, Kucik J, Siffel C, Halliday J, Gatt M, Anneren G, Bianchi F, Canessa MA, Danderfer R, de Walle H, Harris J, Li Z, Lowry RB, McDonell R, Merlob P, Metneki J, Mutchinick O, Robert-Gnansia E, Scarano G, Sipek A, Potzsch S, Szabova E, Yevtushok L. Gastroschisis and associated defects: An international study. *Am J Med Genet A*. 2007;143(7):660-671. 10.1002/ajmg.a.31607.

38. Hwang PJ, Kousseff BG. Omphalocele and gastroschisis: An 18-year review study. *Genet Med*. 2004;6(4):232-236.

39. Southard AE, Edelmann LJ, Gelb BD. Role of copy number variants in structural birth defects. *Pediatrics*. 2012;129(4):755-763. 10.1542/peds.2011-2337 [doi].

40. Chen X, Shen Y, Gao Y, Zhao H, Sheng X, Zou J, Lip V, Xie H, Guo J, Shao H, Bao Y, Shen J, Niu B, Gusella JF, Wu BL, Zhang T. Detection of copy number variants reveals association of cilia genes with neural tube defects. *PLoS One*. 2013;8(1):e54492. 10.1371/journal.pone.0054492 [doi].

41. Rankin J, Dillon E, Wright C. Congenital anterior abdominal wall defects in the north of England, 1986-1996: Occurrence and outcome. *Prenat Diagn*. 1999;19(7):662-668.

42. Stoll C, Alembik Y, Dott B, Roth MP. Omphalocele and gastroschisis and associated malformations. *Am J Med Genet A*. 2008;146A(10):1280-1285. 10.1002/ajmg.a.32297.

43. Merks JH, Ozgen HM, Koster J, Zwinderman AH, Caron HN, Hennekam RC. Prevalence and patterns of morphological abnormalities in patients with childhood cancer. *JAMA*. 2008;299(1):61-69. 10.1001/jama.2007.66; 10.1001/jama.2007.66.

44. Ozgen H, Hellemann GS, Stellato RK, Lahuis B, van Daalen E, Staal WG, Rozendal M, Hennekam RC, Beemer FA, van Engeland H. Morphological features in children with autism spectrum disorders: A matched case-control study. *J Autism Dev Disord*. 2011;41(1):23-31. 10.1007/s10803-010-1018-7; 10.1007/s10803-010-1018-7.

45. Gorlin R, Cohen M, Hennekam R. S*yndromes of the Head and Neck*. 4th ed. Oxford England: Oxford University Press; 2001.

46. Marden PM, Smith DW, Mcdonald MJ. Congenital anomalies in the newborn infant, including minor variations. a study of 4,412 babies by surface examination for anomalies and buccal smear for sex chromatin. *J Pediatr*. 1964;64:357-371.

47. Hoyme HE, Jones MC, Jones KL. Gastroschisis: Abdominal wall disruption secondary to early gestational interruption of the omphalomesenteric artery. *Semin Perinatol*. 1983;7(4):294-298.

48. Lubinsky MS. Association of prenatal vascular disruptions with decreased maternal age. *Am J Med Genet*. 1997;69(3):237-239.

49. Hanemaaijer NM, Sikkema-Raddatz B, van der Vries G, Dijkhuizen T, Hordijk R, van Essen AJ, Veenstra-Knol HE, Kerstjens-Frederikse WS, Herkert JC, Gerkes EH, Leegte LK, Kok K, Sinke RJ, van Ravenswaaij-Arts CM. Practical guidelines for interpreting copy number gains detected by high-resolution array in routine diagnostics. *Eur J Hum Genet*. 2012;20(2):161-165. 10.1038/ejhg.2011.174 [doi].

50. Bianco AM, Girardelli M, Tommasini A. Genetics of inflammatory bowel disease from multifactorial to monogenic forms. *World J Gastroenterol*. 2015;21(43):12296-12310. 10.3748/wjg.v21.i43.12296 [doi].

51. Jarick I, Volckmar AL, Putter C, Pechlivanis S, Nguyen TT, Dauvermann MR, Beck S, Albayrak O, Scherag S, Gilsbach S, Cichon S, Hoffmann P, Degenhardt F, Nothen MM, Schreiber S, Wichmann HE, Jockel KH, Heinrich J, Tiesler CM, Faraone SV, Walitza S, Sinzig J, Freitag C, Meyer J, Herpertz-Dahlmann B, Lehmkuhl G, Renner TJ, Warnke A, Romanos M, Lesch KP, Reif A, Schimmelmann BG, Hebebrand J, Scherag A, Hinney A. Genome-wide analysis of rare copy number variations reveals PARK2 as a candidate gene for attention-deficit/hyperactivity disorder. *Mol Psychiatry*. 2014;19(1):115-121. 10.1038/mp.2012.161 [doi].

52. Girirajan S, Rosenfeld JA, Cooper GM, Antonacci F, Siswara P, Itsara A, Vives L, Walsh T, McCarthy SE, Baker C, Mefford HC, Kidd JM, Browning SR, Browning BL, Dickel DE, Levy DL, Ballif BC, Platky K, Farber DM, Gowans GC, Wetherbee JJ, Asamoah A, Weaver DD, Mark PR, Dickerson J, Garg BP, Ellingwood SA, Smith R, Banks VC,

Smith W, McDonald MT, Hoo JJ, French BN, Hudson C, Johnson JP, Ozmore JR, Moeschler JB, Surti U, Escobar LF, El-Khechen D, Gorski JL, Kussmann J, Salbert B, Lacassie Y, Biser A, McDonald-McGinn DM, Zackai EH, Deardorff MA, Shaikh TH, Haan E, Friend KL, Fichera M, Romano C, Gecz J, DeLisi LE, Sebat J, King MC, Shaffer LG, Eichler EE. A recurrent 16p12.1 microdeletion supports a two-hit model for severe developmental delay. *Nat Genet*. 2010;42(3):203-209. 10.1038/ng.534 [doi].

53. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA, Feuk L, Friedman JM, Hamosh A, Jackson L, Kaminsky EB, Kok K, Krantz ID, Kuhn RM, Lee C, Ostell JM, Rosenberg C, Scherer SW, Spinner NB, Stavropoulos DJ, Tepperberg JH, Thorland EC, Vermeesch JR, Waggoner DJ, Watson MS, Martin CL, Ledbetter DH. Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet*. 2010;86(5):749-764. 10.1016/j.ajhg.2010.04.006 [doi].
54. Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, Braxton A, Beuten J, Xia F, Niu Z, Hardison M, Person R, Bekheirnia MR, Leduc MS, Kirby A, Pham P, Scull J, Wang M, Ding Y, Plon SE, Lupski JR, Beaudet AL, Gibbs RA, Eng CM. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. *N Engl J Med*. 2013;369(16):1502-1511. 10.1056/NEJMoa1306555 [doi].
55. Grozeva D, Carss K, Spasic-Boskovic O, Tejada MI, Gecz J, Shaw M, Corbett M, Haan E, Thompson E, Friend K, Hussain Z, Hackett A, Field M, Renieri A, Stevenson R, Schwartz C, Floyd JA, Bentham J, Cosgrove C, Keavney B, Bhattacharya S, Italian X-linked Mental Retardation Project, UK10K Consortium, GOLD Consortium, Hurles M, Raymond FL. Targeted next-generation sequencing analysis of 1,000 individuals with intellectual disability. *Hum Mutat*. 2015;36(12):1197-1204. 10.1002/humu.22901 [doi].
56. Kato M, Yamagata T, Kubota M, Arai H, Yamashita S, Nakagawa T, Fujii T, Sugai K, Imai K, Uster T, Chitayat D, Weiss S, Kashii H, Kusano R, Matsumoto A, Nakamura K, Oyazato Y, Maeno M, Nishiyama K, Kodera H, Nakashima M, Tsurusaki Y, Miyake N, Saito K, Hayasaka K, Matsumoto N, Saitsu H. Clinical spectrum of early onset epileptic encephalopathies caused by KCNQ2 mutation. *Epilepsia*. 2013;54(7):1282-1287. 10.1111/epi.12200 [doi].
57. Quelin C, Loget P, Verloes A, Bazin A, Bessieres B, Laquerriere A, Patrier S, Grigorescu R, Encha-Razavi F, Delahaye S, Jouannic JM, Carbonne B, D'Herve D, Aubry MC, Mace G, Harvey T, Ville Y, Viot G, Joye N, Odent S, Attie-Bitach T, Wolf C, Chevy F, Benlian P, Gonzales M. Phenotypic spectrum of fetal smith-lemli-opitz syndrome. *Eur J Med Genet*. 2012;55(2):81-90. 10.1016/j.ejmg.2011.12.002; 10.1016/j.ejmg.2011.12.002.
58. Dy ME, Sims KB, Friedman J. TPP1 deficiency: Rare cause of isolated childhood-onset progressive ataxia. *Neurology*. 2015;85(14):1259-1261. 10.1212/WNL.0000000000001876 [doi].
59. Feldkamp ML, Botto LD, Byrne JL, Krikov S, Carey JC. Clinical presentation and survival in a population-based cohort of infants with gastroschisis in utah, 1997-2011. *Am J Med Genet A*. 2015. 10.1002/ajmg.a.37437 [doi].
60. Stoll C, Alembik Y, Dott B, Roth MP. Risk factors in congenital abdominal wall defects (omphalocele and gastroschisi): A study in a series of 265,858 consecutive births. *Ann Genet*. 2001;44(4):201-208.
61. Snyder CL, Miller KA, Sharp RJ, Murphy JP, Andrews WA, Holcomb GW,3rd, Gittes GK, Ashcraft KW. Management of intestinal atresia in patients with gastroschisis. *J Pediatr Surg*. 2001;36(10):1542-1545. 10.1053/jpsu.2001.27040.
62. Phillips JD, Raval MV, Redden C, Weiner TM. Gastroschisis, atresia, dysmotility: Surgical treatment strategies for a distinct clinical entity. *J Pediatr Surg*. 2008;43(12):2208-2212. 10.1016/j.jpedsurg.2008.08.065.
63. Kronfli R, Bradnock TJ, Sabharwal A. Intestinal atresia in association with gastroschisis: A 26-year review. *Pediatr Surg Int*. 2010;26(9):891-894. 10.1007/s00383-010-2676-4.
64. Page R, Ferraro ZM, Moretti F, Fung KF. Gastroschisis: Antenatal sonographic predictors of adverse neonatal outcome. *J Pregnancy*. 2014;2014:239406. 10.1155/2014/239406 [doi].
65. D'Antonio F, Virgone C, Rizzo G, Khalil A, Baud D, Cohen-Overbeek TE, Kuleva M, Salomon LJ, Flacco ME, Manzoli L, Giuliani S. Prenatal risk factors and outcomes in gastroschisis: A meta-analysis. *Pediatrics*. 2015;136(1):e159-69. 10.1542/peds.2015-0017 [doi].

66. Nyberg DA, Mack LA, Patten RM, Cyr DR. Fetal bowel. normal sonographic findings. *J Ultrasound Med*. 1987;6(1):3-6.

67. Parulekar SG. Sonography of normal fetal bowel. *J Ultrasound Med*. 1991;10(4):211-220.

68. Zalel Y, Perlitz Y, Gamzu R, Peleg D, Ben-Ami M. In-utero development of the fetal colon and rectum: Sonographic evaluation. *Ultrasound Obstet Gynecol*. 2003;21(2):161-164. 10.1002/uog.26 [doi].

69. Malas MA, Aslankoc R, Ungor B, Sulak O, Candir O. The development of jejunum and ileum during the fetal period. *Early Hum Dev*. 2003;74(2):109-124. S0378378203000859 [pii].

70. Malas MA, Aslankoc R, Ungor B, Sulak O, Candir O. The development of large intestine during the fetal period. *Early Hum Dev*. 2004;78(1):1-13. 10.1016/j.earlhumdev.2004.03.001 [doi].

71. Ebbing C, Rasmussen S, Godfrey KM, Hanson MA, Kiserud T. Fetal superior mesenteric artery: Longitudinal reference ranges and evidence of regulatory link to portal liver circulation. *Early Hum Dev*. 2009;85(4):207-213. 10.1016/j.earlhumdev.2008.09.412 [doi].

72. Abuhamad AZ, Mari G, Cortina RM, Croitoru DP, Evans AT. Superior mesenteric artery doppler velocimetry and ultrasonographic assessment of fetal bowel in gastroschisis: A prospective longitudinal study. *Am J Obstet Gynecol*. 1997;176(5):985-990.

73. Carroll SG, Kuo PY, Kyle PM, Soothill PW. Fetal protein loss in gastroschisis as an explanation of associated morbidity. *Am J Obstet Gynecol*. 2001;184(6):1297-1301. 10.1067/mob.2001.114031.

74. Langer JC, Bell JG, Castillo RO, Crombleholme TM, Longaker MT, Duncan BW, Bradley SM, Finkbeiner WE, Verrier ED, Harrison MR. Etiology of intestinal damage in gastroschisis, II. timing and reversibility of histological changes, mucosal function, and contractility. *J Pediatr Surg*. 1990;25(11):1122-1126.

75. Langer JC, Longaker MT, Crombleholme TM, Bond SJ, Finkbeiner WE, Rudolph CA, Verrier ED, Harrison MR. Etiology of intestinal damage in gastroschisis. I: Effects of amniotic fluid exposure and bowel constriction in a fetal lamb model. *J Pediatr Surg*. 1989;24(10):992-997.

76. Sparks TN, Shaffer BL, Page J, Caughey AB. Gastroschisis: Mortality risks with each additional week of expectant management. *Am J Obstet Gynecol*. 2016. S0002-9378(16)30648-2 [pii].

77. Moir CR, Ramsey PS, Ogburn PL, Johnson RV, Ramin KD. A prospective trial of elective preterm delivery for fetal gastroschisis. *Am J Perinatol*. 2004;21(5):289-294. 10.1055/s-2004-829864.

78. Gelas T, Gorduza D, Devonec S, Gaucherand P, Downham E, Claris O, Dubois R. Scheduled preterm delivery for gastroschisis improves postoperative outcome. *Pediatr Surg Int*. 2008;24(9):1023-1029. 10.1007/s00383-008-2204-y.

Chapter

9

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Gastroschisis is een aangeboren defect van de buikwand dat zich rechts naast de navel bevindt. Een deel van de dunne darm en het colon (dikke darm) zijn door het defect buiten de buikholte (in het vruchtwater) gelegen. Regelmatig komt het voor dat ook een gedeelte van de maag, blaas en, milt en soms ook gonaden en de lever betrokken zijn in de gastroschisis. Deze organen zijn niet bedekt met een buikvlies, wat wel het geval is bij de omphalocèle (buikwand defect van de navel waarbij de organen bedekt zijn met een vlies).

In Nederland is de prevalentie van gastroschisis ongeveer 1.1 per 10.000 levend geboren kinderen. Tegenwoordig wordt de diagnose bijna altijd antenataal (voor de geboorte) gesteld tijdens het structureel echoscopisch onderzoek in het tweede trimester van de zwangerschap.[1]
De hulpverlener die de diagnose gastroschisis vaststelt heeft ook de uitdagende taak om aan de ouders uit te leggen wat deze diagnose voor hun ongeboren kind en voor hen betekent. Meestal wordt dit in samenspraak gedaan met de kinderchirurg, die de hersteloperatie na de geboorte zal verrichten.
De overleving van een pasgeborene met gastroschisis is de afgelopen drie decennia enorm verbeterd (>90%) door de ontwikkelingen en toepassing van parenterale voeding bij de neonaten en de innovaties in chirurgische technieken en neonatale intensive care.[2-4] Toch zijn er nog veel onduidelijkheden rondom deze aangeboren afwijking (**hoofdstuk 1**). De oorzaak van deze ontwikkelingsstoornis is nog onbekend. De kans op een intra-uteriene sterfte is 7x hoger ten opzichte van een laag-risico zwangerschap[5] en de kans op morbiditeit (ziekte) is groot (30%). Kinderen moeten soms na hun geboorte meerdere malen worden geopereerd in een korte periode en zijn vaak langdurig opgenomen. Tot op heden is er weinig bekend over de lange termijn uitkomsten van kinderen met gastroschisis.
Gezien de grote onduidelijkheden over de etiologie (oorzaak) van gastroschisis, verschillen in korte en lange termijn prognose en het voorspellen hiervan hebben we verschillende onderzoeken uitgevoerd met als doel:

Deel I van dit proefschrift

- Betere informatie te verkrijgen over de korte en lange termijn prognosen van kinderen geboren met een geïsoleerde (zonder extra-abdominale afwijkingen) gastroschisis.
- Het onderzoeken van de toegevoegde waarde van genetisch en morfologisch onderzoek (studie naar grote en kleine afwijkingen van de lichaamsstructuur) bij kinderen met gastroschisis.

Deel II van dit proefschrift

– Het identificeren van mogelijke echografische markers die een voorspellende waarde hebben over de postnatale uitkomst en die mogelijk het antenatale beleid kunnen beïnvloeden om zo de neonatale uitkomst te verbeteren.

De resultaten van deze studies kunnen een handvat zijn voor de counselend arts van de toekomstige ouders, maar ook voor de behandelend arts van het kind, zowel vlak na de geboorte als ook in het verdere leven. In deze samenvatting zullen wij de belangrijkste bevindingen uiteenzetten en deze bespreken in het licht van de huidige literatuur.

Korte termijn gevolgen van geïsoleerde gastroschisis

De aan- of afwezigheid van beschadiging aan de darmen bij de geboorte blijkt een belangrijke factor te zijn voor de prognose van een kind met gastroschisis.[6] In 2001 stelden Molik et al. voor om gastroschisis in te delen in simpele en complexe gastroschisis.[7] Bij een simpele gastroschisis zijn er geen andere darmafwijkingen. Bij een complexe gastroschisis is dit wel het geval en worden één of meer van de volgende darmafwijkingen gevonden: een darmatresie (aangeboren gedeeltelijke of volledige afsluiting van de darm), -perforatie, -necrose (gedeeltelijk afgestorven darm) of volvulus (darm draaiing).

In een recent verschenen meta-analyse werden een verhoogde sterfte (RR: 5,39 (2,42, 12,01 95% betrouwbaarheidsinterval (95%-BI)), langere ziekenhuisopname (LOS) en langdurige parenterale voeding (voeding via het infuus) (TPN) geconstateerd in de complexe gastroschisis groep.[8] De studies die in deze meta-analyse waren opgenomen bevatten ook kinderen met niet geïsoleerde gastroschisis. Dat wil zeggen, kinderen met gastroschisis met daarbij aangeboren afwijkingen buiten het maag-darmkanaal (extra-intestinaal) zoals hartafwijkingen en amyoplasie (zeldzame aangeboren aanlegstoornis van de spieren met dwangstand van de ledematen). Extra-intestinale afwijkingen komen vaker voor bij kinderen met een complexe gastroschisis[9] en kunnen de prognose significant nadelig beïnvloeden. Daarnaast werden in deze meta-analyse alleen de relatieve verschillen in TFEF (duur TPN) en LOS (duur van de ziekenhuisopname) tussen simpele en complexe gastroschisis gegeven terwijl de wérkelijke duur van beide uitkomsten juist zo van belang is voor de counselling. In **hoofdstuk 2** stelden we ons daarom ten doel de prognose van geïsoleerde gastroschisis te onderzoeken in een retrospectief internationaal cohort van 204 levend geboren kinderen uit Nederland en Brazilië. Vervolgens vergeleken we onze bevindingen in een systematisch review en meta-analyse. De primaire uitkomst was de duur van parenterale voeding (TFEF), omdat dit een goede weerspiegeling is van de conditie van de darmen. Enterale voeding wordt alleen verdragen indien de darmen goed functioneren. De secundaire uitkomstmaten waren de lengte van mechanische beademing, de duur van de ziekenhuisopname en sterfte. Daarnaast onderzochten we de verschillen in uitkomst tussen kinderen met een simpele en complexe gastroschisis.

De mediane duur van de TFEF, mechanische beademing en LOS was respectievelijk, 26 dagen (range 6-515), 2 dagen (range 0-90) en 33 dagen (range 11-515). Het sterftepercentage was 10,8%. TFEF en LOS waren significant langer (P <0,0001) en de kans op sterfte was 4x hoger in de complexe groep ten opzichte van de simpele groep (30,0% versus 7,5%). In Brazilië worden kinderen met gastroschisis standaard per sectio Caesarea (keizersnede) geboren; het percentage sectio's was dan ook significant hoger (94,1%) in de Braziliaanse groep ten opzichte van de kinderen uit Nederland (38,1%), waar we, ook bij gastroschisis, streven naar een vaginale baring. Desalniettemin waren er geen verschillen tussen beide landen in TFEF, LOS en mortaliteit. Dat suggereert dat de modus partus geen invloed heeft op de uitkomst en dat is in overeenstemming met de bevindingen van eerdere studies, waarbij geen verschil werd gevonden tussen de uitkomsten na vaginale baring of keizersnede.[10-13]

In totaal werden 17 studies (met totaal 1652 patiënten), inclusief onze cohortstudie, geschikt bevonden voor de meta-analyse. De gemiddelde TFEF was 35,3 ± 4,4 dagen, de duur van de mechanische beademing was 5,5 ± 2,0 dagen, LOS was 46,4 ± 5,2 dagen en de totale mortaliteit was 5,3%. De uitkomsten van simpele in vergelijking tot complexe gastroschisis werden slechts in 5 studies, inclusief de onze, beschreven. TFEF, mechanische beademing en LOS waren significant langer en het sterftecijfer was 3,64 (1,95-6,83 95%-BI) keer hoger in de complexe gastroschisis groep.

Met deze studie hebben we laten zien dat aanwezigheid van een complexe gastroschisis de uitkomst drastisch verandert, ook als de aandoening geïsoleerd is. Maar ook bij simpele gastroschisis is intensieve zorg in de eerste levensdagen noodzakelijk. De vraag of dit invloed heeft op de verdere ontwikkeling is het onderwerp van het volgende hoofdstuk.

Lange termijn gevolgen

De interventies in het vroege leven en ook het feit dat een aanzienlijk gedeelte van de kinderen met gastroschisis te vroeg wordt geboren en een laag geboortegewicht heeft, zijn allemaal risicofactoren voor een gestoorde groei en neuropsychologische ontwikkeling. Eerdere studies waren vooral gericht op de klinische uitkomsten van deze kinderen tijdens de ziekenhuisopname. De weinige studies die de neuropsychologische ontwikkeling van de kinderen hebben bestudeerd, betreffen vooral kinderen jonger dan 6 jaar.[14-18] Deze onderzoeken vonden een min of meer normale ontwikkeling. Milde ontwikkelingsstoornissen komen echter vaak pas aan het licht als er meer van de cognitieve vaardigheden wordt geëist. Veelal is dat pas vanaf het moment dat het kind moet leren lezen en schrijven.

In **hoofdstuk 3** vergeleken we de onderzoeksresultaten van 16 kinderen, geboren met gastroschisis en behandeld in het Universitair Medisch Centrum Groningen, met een controlegroep van 32 kinderen zonder een congenitale afwijking, "gematcht" naar geslacht, zwangerschapsduur bij geboorte, geboortegewicht, en gecorrigeerd voor een te laag gewicht voor de zwangerschapsduur en een lage sociaaleconomische status van beide ouders.

Intelligentie, geheugen, aandacht, visuele perceptie, motorische vaardigheden en visuomotorische vaardigheden (het kunnen omzetten van visuele waarnemingen in een motorische handeling) werden getest. Het executief functioneren (de hogere regel- en controle functies van de hersenen, zoals het doelgericht uitvoeren van taken) werd aan de hand van vragenlijsten voor ouders bepaald.

De mediane scores van het verbale IQ en het executieve functioneren van de kinderen geboren met gastroschisis, waren slechter dan die van de controlegroep (respectievelijk 95 (interquartielafstand (IQR) 88-100) vs. 104 (IQR 98-113), P = 0,001, en 29 (IQR 6,8-63,8) versus 5,0 (IQR 2,8- 19,8) P = 0,03). Kinderen met gastroschisis werden vaker geclassificeerd als subklinisch of klinisch afwijkend dan de controle-kinderen op respons inhibitie (odds ratio (OR) 20,4; 95%-BI 2,4-171,5), selectieve visuele aandacht (OR 40,4; 95%-BI 5,9-275,4), aanhoudende auditieve aandacht (OR 88,1; 95%-BI 5,8-1342,8) en fijne motoriek (50% versus 0%). Achtenvijftig procent van de kinderen geboren met gastroschisis doubleerden een klas en 19% volgde speciaal onderwijs in vergelijking met 19% en 0% van de controlegroep. Deze verschillen bleven bestaan na correctie voor geboortegewicht (percentiel) en sociaaleconomische status. Het auditief en verbaal geheugen en de visuomotorische vaardigheden waren vergelijkbaar met de controlegroep. Gedragsproblemen verschilden niet tussen de groepen. Voor zo ver bekend zijn er slechts twee andere studies, die de uitkomsten van schoolgaande gastroschisis-kinderen hebben onderzocht. Geen van deze studies gebruikte een controlegroep.[19,20] Giudici et al.[20] volgden 17 gastroschisis kinderen tot de leeftijd van zes jaar. Zij toonden aan dat naarmate het kind ouder werd, er meer ontwikkelingsstoornissen aan het licht kwamen. Zo vonden zij bij 11 van de 17 kinderen (65%) een afwijkende Neurologie-Psychomotorische Developmental Index (NPDI)[21], waarvan zes kinderen (35%) speciaal onderwijs volgden. Helaas werd in deze studie niet aangegeven welke domeinen van de NPDI het betrof. Harris et al.[19] onderzochten o.a. intelligentie en neurologische ontwikkeling en gedrag[22-24] van 39 kinderen, geboren met gastroschisis (mediane leeftijd 10 jaar, (spreiding 5-17 jaar)), en vergeleken de resultaten met landelijke normaalwaarden. Het werkgeheugen was de enige subschaal die significant lager was in de gastroschisis groep. Ook leken deze kinderen een verhoogd risico op gedragsproblemen en gestoorde ouder-kind relatie te hebben.

Hoewel de onderzoeksstrategieën en -domeinen verschillen tussen de drie studies en de verschillen tussen simpele en complexe gastroschisis niet konden worden onderzocht, kunnen we wel concluderen dat de neuropsychologische ontwikkeling van kinderen met gastroschisis op schoolgaande leeftijd slechter is dan verwacht mag worden op basis van de uitkomsten van onderzoeken bij deze kinderen op jongere leeftijd. Ook als we corrigeren voor zwangerschapsduur, geboortegewicht en sociaaleconomische status scoren kinderen met gastroschisis significant lager op aandacht, executief functioneren en fijne motorische vaardigheden. Speciaal onderwijs is vaker geïndiceerd bij kinderen met gastroschisis dan bij hun gezonde leeftijdsgenootjes. Wij pleiten daarom voor een

goede, multidisciplinaire follow up van deze kinderen, om zo vroegtijdig problemen op te sporen en de gepaste hulp te kunnen aanbieden.

Genetische risicofactoren

In **hoofdstuk 4** hebben we aangetoond dat naast externe factoren zoals de gebeurtenissen in het vroege leven, ook genetische factoren een rol kunnen spelen in de ontwikkeling van het kind met gastroschisis. Jonge maternale leeftijd, lage sociaaleconomische status en roken zijn bekende risicofactoren voor gastroschisis.[25-28] Maar het feit dat gastroschisis vaker voorkomt bij blanken in vergelijking met Afro-Amerikanen uit dezelfde sociaal-economische omgeving[25-28] en dat het herhalingsrisico van gastroschisis binnen families (2,4%) verhoogd is[29], suggereert dat de etiologie van gastroschisis multifactorieel is en dat genetische factoren mogelijk ook bijdragen tot het krijgen van de aandoening.

Gastroschisis is niet geassocieerd met chromosomale afwijkingen bij standaard karyotypering.[30,31] Bij andere congenitale afwijkingen waarbij het chromosomenpatroon ook normaal is, heeft de toepassing van array's geleid tot het ontdekken van nieuwe monogene (één verandering (mutatie) in één gen) oorzaken en van kandidaat genen (genen die mogelijke betrokken zijn bij een genetische aandoening).[32,33] Bij gastroschisis is tot op heden nog geen systematisch array-onderzoek verricht. Gastroschisis wordt meestal beschreven als een geïsoleerde aangeboren aandoening, maar de incidentie van additionele afwijkingen varieert van 5 tot 50%.[34,35] Deze variatie is waarschijnlijk gebaseerd op een verschil in definitie van de additionele afwijking.

Onderzoek naar grote en kleine dysmorfieën (bijzondere uiterlijke kenmerken) bij kinderen met een congenitale afwijking kan inzicht geven in het ontstaan van de afwijking, zoals een onderliggend samenhangend mechanisme dat de kenmerken veroorzaakt. Dit geldt niet alleen voor monogene ziektebeelden maar ook bij ziektebeelden die een gevolg zijn van een gestoorde interactie tussen omgevingsfactoren en genetische factoren.[36-39]

In **hoofdstuk 4** voerden we een klinisch morfologisch onderzoek en array-analyse uit bij 21 kinderen en hun ouders om de waarde van genetisch onderzoek bij deze patiënten te evalueren en om mogelijke genetische oorzaken of risicofactoren voor gastroschisis te identificeren. We vonden een significant verhoogde incidentie van twee of meer kleine morfologische afwijkingen per patiënt in vergelijking met gezonde controles (89,5% versus 55,7% P = 0,004). De incidentie van grote morfologische afwijkingen was niet verhoogd. Dit kan mogelijk verklaard worden door het feit dat wij alleen overlevenden hebben bestudeerd. De afwijkingen bij klinisch morfologisch onderzoek leidden niet tot een syndroomdiagnose. Maar de hoge aantallen milde afwijkingen bij kinderen met gastroschisis kunnen niet worden verklaard door een geïsoleerd vasculair incident in de buikwand; één van de meest genoemde hypotheses van het ontstaan van gastroschisis.[28,40,41] We hebben geen specifiek patroon van fenotypische afwijkingen gevonden, wat ook niet te verwachten is bij een

multifactoriële etiologie en heterogenetische oorzaak, want ontwikkelingsgenen hebben vaak een functie op verschillende momenten en locaties tijdens de embryogenese.
Door middel van array-analyse werden zeven overgeërfde en een *de novo* copy number variations (CNVs) in 5 casus gevonden. De *de novo* duplicatie werd geclassificeerd als een waarvan de klinische relevantie onbekend is. Er werd geen overlap gevonden tussen de CNV-regionen binnen ons gastroschisis cohort en gastroschisis casus beschreven in de literatuur. Omdat 4 CNVs overgeërfd waren van gezonde ouders is het onwaarschijnlijk dat deze CNVs de oorzaak zijn van gastroschisis. Maar dat hoeft een pathologische rol in de ontwikkeling van gastroschisis niet per se uit te sluiten. CNVs staan bekend als risicofactoren voor verschillende aandoeningen en ze kunnen een incomplete erfelijke penetrantie hebben.[42-45] Als in de toekomst array onderzoek systematisch wordt verricht bij kinderen met aangeboren afwijkingen, en dus ook bij gastroschisis, dan kunnen casus vergeleken worden en kan er worden gekeken of zeldzame, pathogene of risico CNVs significant vaker voorkomen bij gastroschisis. Dat zou kunnen leiden tot de identificatie van potentiële kandidaat genen voor gastroschisis. Dit is in het verleden al succesvol gebleken bij andere geïsoleerde congenitale afwijkingen (van o.a. het hart, gelaat en de nieren) nadat enkele honderden, soms duizenden patienten geanalyseerd waren.[32,43]

Drie kinderen in ons studiecohort hadden een neurologische aandoening, waarbij twee ernstig mentaal en motorisch geretardeerd waren. Het belang van genetisch onderzoek bij onverklaarbare retardatie is eerder onderzocht, waarbij array onderzoek in 15-20% van de gevallen leidde tot een diagnose[46] en "whole exome sequency" (WES) in zelfs 33% van de gevallen.[47] Met behulp van WES vonden wij in onze studie in een casus een *de novo MECP2* gen mutatie die de mentale en motorische regressie bij deze patiënt kon verklaren.[48] Bij de tweede casus werd een enkele nucleotide variant in het *KCNQ2* gen gevonden. *De novo* mutaties in dit gen kunnen een epileptische encefalopathie met een slechte ontwikkelingsuitkomst veroorzaken, wat past bij het fenotype van deze casus.[49] De overerving wordt op dit moment bij deze patiënt nader onderzocht.
Een, en waarschijnlijk twee, monogene aandoeningen in een cohort van slechts 21 patiënten suggereert dat monogene afwijkingen vaker een rol spelen in gastroschisis dan gedacht. De meeste pathologische mutaties bij aangeboren afwijkingen zijn *de novo*. Dit is ook een mogelijkheid bij gastroschisis, wat zijn sporadische frequentie kan verklaren. Monogene aandoeningen zijn mogelijk kwetsbaarder voor een 'second hit' en om die reden komen additionele afwijkingen hierbij vaker voor.[45] Studies waarin gastroschisis patiënten met een monogene aandoening worden beschreven zijn schaars en ook lastig te vinden omdat de gastroschisis dan wordt geoormerkt als een toevalsbevinding bij de monogene aandoening.[50,51]
Omdat genetische diagnoses vaak later in het leven worden gesteld en de toepassing van WES daarbij slechts sinds 5 jaar klinisch beschikbaar is, is een onderrapportage van monogene afwijkingen in grote populatie cohortstudies naar gastroschisis zeer waarschijnlijk.

Het feit dat een niet geassocieerde additionele afwijking bij minimaal één op de zes gastroschisis patiënten wordt gevonden[7,30,52,53] rechtvaardigt systematische klinische screening van alle gastroschisis patiënten en, zeker in geval van additionele afwijkingen/dysmorfieën of een vertraagde ontwikkeling, aanvullend genetisch onderzoek.

DEEL II

Prenatale echografische markers om uitkomst te voorspellen

In deel twee van dit proefschrift hebben we potentiële antenatale echografische markers onderzocht om congenitale darmafwijkingen te identificeren, om zo de counselling van ouders te verbeteren en om casus te identificeren die mogelijk profijt hebben van aangepaste obstetrische interventies. Als de aanwezigheid van darmatresie voor de geboorte zou kunnen worden voorspeld, dan zou dit de kinderchirurg aanzienlijk helpen bij het vroegtijdig diagnosticeren van een atresie en bij het plannen van een operatie na de geboorte. Bij gastroschisis wordt tot dusverre een atresie in 40% van de gevallen bij de eerste operatie gemist.[54-56]

In geval van gastroschisis zijn meerdere studies verricht om antenatale echografische bevindingen te correleren met de neonatale uitkomst. De resultaten van deze studies waren vaak tegenstrijdig, wat waarschijnlijk het gevolg is van de kleine studie-populaties, het retrospectieve karakter van de studies, de korte follow up van de casus en het ontbreken van gestandaardiseerde echometingen.[57,58] Een recente meta-analyse, voornamelijk gebaseerd op retrospectieve studies, heeft laten zien dat bij gastroschisis intra-abdominale darmdilatatie en polyhydramnion (te veel vruchtwater) de meest veelbelovende markers voor darmatresie zijn. De afkapwaarden voor de diameter(s) van de darmen werden hierbij niet genoemd of varieerden sterk (tussen de 6-18 mm) en de duur van de zwangerschap ten tijde van de echografie was vaak niet vermeld.[58] Hierdoor zijn de studies niet goed klinisch toepasbaar en de auteurs van de systematische review pleiten dan ook terecht voor gestandaardiseerde prospectieve studies.

Normale referentie curves van de foetale darm diameter

Om een pathologisch verwijde darm te kunnen identificeren, is kennis vereist van de fysiologische ontwikkeling en toename van de darmdiameter gedurende de zwangerschap bij de gezonde foetus. Tot op heden was er geen gestandaardiseerde methode om de foetale darmdiameter te meten. Verder zijn er slechts beperkte data gepubliceerd over referentiewaardes voor metingen van

de darmen. Geen van deze studies heeft longitudinale gegevens gebruikt[59-61] en sommige studies zijn gebaseerd op metingen na overlijden van de foetus.[62,63] In **hoofdstuk 5** ontwikkelden we referentiecurves voor diameters van de normale foetale dunne darm en colon. Deze zijn gebaseerd op longitudinale echografische metingen tussen de 20 en 41 weken zwangerschap, met intervallen van vier weken, bij 39 laag-risico foetussen. Daarnaast hebben we de klinische toepasbaarheid van deze referentiecurves onderzocht in een retrospectieve cohort van 28 foetussen waarbij een dilatatie van de darm werd vermoed.
De diameter van de darmen werd gemeten via een standaard protocol; de grootste lis van de dunne darm en het colon werden geïdentificeerd in een coronaal vlak en de kortste as van het lumen van de darm werd gemeten (van binnenkant tot binnenkant van de darmwand). In totaal werden 198 echografische onderzoeken uitgevoerd bij 39 ongecompliceerde zwangerschappen. De ontwikkeling van de dunne darm en colondiameters kon het beste worden beschreven met respectievelijk een lineair model en een kwadratisch model. De intra-observer en inter-observer coëfficiënt voor dunne darm en colon waren ≥ 0,94. De gemiddelde diameter van het colon was 14,5 mm, met een maximum van 19,4 mm bij 40 weken zwangerschapsduur. Voor de dunne darm was de gemiddelde diameter 5,1 mm, met een maximum van 7,6 mm bij 40 weken.
In de casus waarbij een gedilateerde darm werd vermoed, werd na de geboorte bij slechts 26% van de kinderen een intestinale afwijking vastgesteld. Onze studie heeft laten zien dat darmdilatatie in de zwangerschap van tijdelijke aard kan zijn; 56% van de foetussen waarbij herhaalde metingen werden verricht lieten een afname van de darmdilatatie zien bij opeenvolgende metingen. Deze afname van de darmdilatatie moet als geruststellend worden beschouwd, aangezien bij geen van deze casus na de geboorte een pathologie van de darmen werd vastgesteld. In alle gevallen waarbij progressieve dunne darmdilatatie werd gezien was ook daadwerkelijk sprake van een congenitale darmafwijking postpartum. Een grote diameter van de dunne darm (Z-score >8) na een zwangerschapsduur van 25 weken kon ook geassocieerd worden met pathologie van de dunne darm. Het soort darmafwijkingen varieerde, maar in alle gevallen was chirurgisch ingrijpen nodig. Dit bevestigt het belang van antenatale diagnose van darmpathologie om er zeker van te zijn dat de juiste zorg na de geboorte zo spoedig mogelijk kan worden geleverd.

Hernia van de complete lever bij gastroschisis

In **hoofdstuk 6** beschrijven we een gastroschisis casus met een hoogst ongebruikelijke echografische bevinding: herniatie van de complete lever in de amnionholte, gediagnosticeerd bij een zwangerschapsduur van 12 weken. Bij een zwangerschapsduur van 27 weken werd een sectio verricht op verdenking van foetale nood. Postpartum overleed het kind direct omdat beademing niet mogelijk bleek. Om te onderzoeken of deze afwijking altijd letaal is, hebben we een literatuuronderzoek verricht naar gastroschisis gevallen met een complete herniatie van de lever en casus geïdentificeerd met een antenataal geruptureerde omphalocele (waarbij de lever niet omringd werd door een vlies)

met een compleet gehernieerde lever. Casus met additionele structurele of chromosomale afwijkingen werden niet meegenomen omdat dit de prognose zou kunnen beïnvloeden. Er zijn 16 casus in de literatuur beschreven: 14 hiervan overleden in de neonatale periode en de andere 2 overleden na respectievelijk 3 maanden en 1 jaar. Beide waren volledig afhankelijk van mechanische beademing gedurende hun korte leven. Dit suggereert dus dat deze conditie letaal is (geen overleving uit 16 casus, (95%-BI voor overleving 0 - 19%), waarbij de meeste pasgeborenen overleden aan pulmonale problemen.

Antenatale echografische markers om de prognose van geïsoleerde gastroschisis te voorspellen

Als laatste presenteren we in **hoofdstuk 7** de eerste resultaten van de "Fetal Abdominal Markers Identified by Ultrasound to Predict Neonatal Gastroschisis Outcome" (FLAMINGO) studie. Het betreft een prospectieve, longitudinale, nationale multicenter studie met gestandaardiseerd antenataal echografisch onderzoek en antenaal beleid om zo potentiële antenatale echografische markers te identificeren die de uitkomst van geïsoleerde gastroschisis voorspellen. De primaire uitkomst was simpele of complexe gastroschisis en de secundaire uitkomsten waren sterfte, TFEF en LOS.

Dit onderzoek is uitgevoerd in alle zeven academische centra waar gastroschisis kinderen worden behandeld. Bij een zwangerschapsduur van 18-22 weken werd een geavanceerd echografisch onderzoek verricht om extra intestinale afwijkingen uit te sluiten. Vervolgens werd bij 24, 28, 30, 32, 34, 35 en 36 weken zwangerschapsduur een gestandaardiseerd echografisch onderzoek verricht. Tijdens elk onderzoek zijn de foetale biometrie, Amniotic Fluid Index (AFI) (maat voor hoeveelheid vruchtwater), pulsatility index (PI) (maat voor de bloedstroomsnelheid) van de a. umbilicalis (navelstreng slagader) en a. mesenterica superior (bloedvat dat het grootste deel van de darm voorziet van zuurstofrijk bloed) en de darmdiameters beoordeeld. Het lumen (de holte) van het meest gedilateerde darmsegment, zowel intra- als extra -abdominaal, werd gemeten langs de korte as (van binnenwand tot binnenwand van de darm). De PI van de a. mesenterica superior intra-abdominaal werd gemeten bij de plaats van aftakking uit de aorta, net boven de a. renalis. Het extra-abdominaal gelegen deel van de a. mesenterica superior werd gemeten direct distaal van het buikwanddefect. Deze metingen werden vergeleken met referentiewaarden van ongecompliceerde zwangerschappen.[64]

De partus werd ingeleid vanaf een zwangerschapsduur van 37 weken in een van de deelnemende centra. Een keizersnede werd alleen verricht op basis van gebruikelijke obstetrische indicaties. Het defect werd direct gesloten als dit mogelijk werd geacht door de kinderchirurg, de anesthesist en de neonatoloog. Als dit niet mogelijk bleek werd een silo (kunststof omhulling) geplaatst en werd het defect in tweede instantie gesloten.

Tussen april 2010 en augustus 2014 zijn 101 casus met geïsoleerde gastroschisis geïncludeerd. Er waren 3 intra-uteriene sterftes bij 22, 32 en 33 weken zwangerschapsduur. In één geval was een

chorioamnionitis (ontsteking in de baarmoeder) de waarschijnlijke doodsoorzaak, in de andere gevallen kon er geen evidente doodsoorzaak worden gevonden. Negenenzeventig (80,6%) levendgeborenen werden geclassificeerd als simpele en negentien (19,4%) als complexe gastroschisis. Er waren 3 sterftes na de geboorte: één in de simpele groep (3.8%) en twee in de complexe groep (10.5%) (P = 0.10). De tijd tot TFEF en duur van het verblijf in het ziekenhuis waren gemiddeld en significant drie keer langer in de complexe groep vergeleken met de simpele groep. De complexe groep had ook vaker herhaaldelijke chirurgische ingrepen nodig (P <0.001). Een dunne darm atresie werd gevonden in 18 (94.5%) van de 19 complexe gastroschisis casus.

De foetale buikomtrek (AC) en het foetaal geschatte gewicht waren significant lager in de gastroschisis gevallen ten opzichte van de normaal curves, maar er werd geen significant verschil gevonden tussen de simpele en complexe casus. De PI van de a. umbilicalis was in beide groepen normaal. Polyhydramnion was gerelateerd aan neonatale mortaliteit maar was niet verschillend tussen beide groepen.

De intra-abdominale dunne darm diameters in de simpele gastroschisis groep waren gemiddeld hetzelfde als in de controlegroep, maar waren boven het 97.7^{ste} percentiel in 50% van de complexe casus. De extra-abdominale diameters waren verhoogd in beide groepen ten opzichte van de normaalwaarden, met het grootste verschil in de complexe groep. Echter, differentiatie tussen de simpele en complexe gevallen, gebaseerd op deze waarden, bleek lastig gezien de fluctuaties binnen een individu in het verloop van de tijd. Alleen met behulp van hoge afkapwaarden van de intra-abdominale diameter, variërend van 10mm bij 20 weken tot 30mm bij 40 weken, was het mogelijk om 8 van de 19 complexe casussen te identificeren. Intra abdominale diameters ≥15mm bij de laatste echometing waren gerelateerd aan neonatale morbiditeit (TFEF en LOS).

De laatste variabele die werd onderzocht is de PI in de a. mesenterica superior. Deze was significant lager in de gastroschisis patiënten ten opzichte van normaalwaarden. Er werden echter geen significante verschillen gevonden tussen de simpele en complexe casus. Gedurende de zwangerschap nam de bloedweerstand af, met name in het extra-abdominale deel van de a. mesenterica superior. In een ander longitudinaal onderzoek bij 25 gastroschisis casussen zijn vergelijkbare waarden van de bloedweerstand in de a. mesenterica superior gevonden.[65] Waarschijnlijk kan deze verminderde vasculaire resistentie worden verklaard door vasodilatatie als gevolg van progressieve chronische ontsteking van de darmen. Lagere serum eiwitconcentratie door albumine lekkage, uiteindelijk leidend tot hypovolemie en vervolgens hypoperfusie, kan daarbij ook een rol spelen.[66] Onze resultaten ondersteunen niet de theorie die suggereert dat vasculaire compressie ter hoogte van het buikwanddefect zorgt voor intestinale schade.[67,68]

Beide intra-uteriene sterftes in het derde trimester van de zwangerschap hadden een zeer lage bloedweerstand in het intra-abdominaal gelegen deel van de a. mesenterica superior, wat zou kunnen passen bij een ernstige inflammatoire reactie. Dit is echter zeer speculatief gelet op het lage aantal betrokken casus.

Intra-abdominale darm dilatatie (≥15mm diameter) was wel geassocieerd met complexe gastroschisis en een langere TFEF en LOS, maar helaas was de sensitiviteit van deze marker niet hoog, waardoor niet alle complexe gastroschisis gevallen antenataal kunnen worden gediagnostiseerd.

KLINISCH RELEVANTE STUDIERESULTATEN

Deel I

- De resultaten van **hoofdstuk 2** kunnen gebruikt worden bij de counselling van ouders die een kind met geïsoleerde gastroschisis verwachten. Kwantificering van de prognose van levend geboren kinderen met geïsoleerde gastroschisis zijn beschreven met betrekking tot de duur van TPN, ziekenhuis opname en de kans op sterfte. Dit onderzoek bevestigt dat het bestaan van complexe gastroschisis de uitkomst negatief beïnvloedt.
- In **hoofdstuk 3** hebben we aangetoond dat de neuropsychologische ontwikkeling van schoolgaande kinderen, geboren met gastroschisis, vaker gestoord is dan bij hun leeftijdsgenoten. Dit verschil blijft bestaan als wordt gecorrigeerd voor vroeggeboorte, geboortegewicht en sociaaleconomische status. Doubleren kwam vaker voor bij kinderen met gastroschisis dan bij hun leeftijdsgenoten. Om die reden raden wij aan dat kinderen met gastroschisis tot en met de schoolgaande leeftijd worden gevolgd door een multidisciplinair team om zo ontwikkelingsproblemen eerder te signaleren en te begeleiden.
- In **hoofdstuk 4** toonden we aan dat niet alleen externe factoren, zoals gebeurtenissen vroeg in het leven, de ontwikkeling van het kind met gastroschisis beïnvloeden, maar dat ook (*de novo*-) genetische factoren een rol kunnen spelen. De resultaten van dit onderzoek rechtvaardigen klinisch genetische screening bij alle kinderen met gastroschisis. Aanvullend genetisch onderzoek zou moet worden verricht wanneer additionele dysmorfieën of een ontwikkelingsachterstand worden gezien.

Deel II

- In **hoofdstuk 5** beschreven we een gestandaardiseerde methode om de foetale darmdiameter te meten. Ook stelden we referentie-curves op van de dunne darm en het colon in een gezonde populatie. Deze curves kunnen gebruikt worden om een gedilateerde foetale darm op te sporen.
- We hebben laten zien dat het herhaaldelijk meten van de darm gedurende de zwangerschap van belang is om een pathologische dilatatie te identificeren (**Hoofdstuk 5**).

- Gebaseerd op een case-report en additioneel literatuuronderzoek concluderen we dat de ongebruikelijke verschijning van een complete hernia van de lever bij gastroschisis zeer waarschijnlijk fataal is. Dit gegeven kan gebruikt worden bij het begeleiden en obstetrisch beleid van deze zeldzame casus (**Hoofdstuk 6**).
- Onze prospectieve longitudinale FLAMINGO-studie heeft laten zien dat gastroschisis geassocieerd is met een lagere weerstand in de bloedvaten, in zowel het intra- als extra-abdominale deel van de a. mesenterica superior. Dit kan gerelateerd worden aan een ontsteking van de darmen (**hoofdstuk 7**).
- De enige variabele die enigszins differentieert tussen simpele en complexe gastroschisis was de diameter van de intra-abdominale darm. Hierbij zijn zeer hoge afkapwaarden van 10 mm bij 20 weken tot 30 mm bij 40 weken nodig om een simpele gastroschisis uit te sluiten.

Aanbevelingen voor de toekomst

- Nauwkeurig volgen van kinderen met gastroschisis tijdens (voor-) schoolse leeftijd en een regelmatige evaluatie van zijn/haar ontwikkeling kan helpen om problemen in een vroeg stadium te ontdekken en zo nodig te behandelen. Of vroege interventies ook tot betere resultaten leiden moet nog worden vastgesteld.
- Het genetisch testen met array en WES bij kinderen met gastroschisis kan verder inzicht geven in de rol van genetica in de etiologie van deze aandoening.
- Het bewaken van de foetale conditie met behulp van hartactieregistratie (cardiotocografie) is in de FLAMINGO-studie verricht vanaf 34 weken zwangerschapsduur. Of met een dergelijke bewaking plotselinge intra-uteriene sterfte voorspeld en voorkomen kan worden moet nog worden onderzocht.
- Helaas was de nauwkeurigheid van de onderzochte echografische markers in hoofdstuk 7 niet hoog genoeg om complexe gastroschisis antenataal te kunnen diagnosticeren. Andere markers die nog bekeken zouden kunnen worden zijn: a) maagdilatatie; dit zou een prognostische marker kunnen zijn voor neonatale sterfte[8], b) afwezigheid van een lumen in de extra-abdominale darm, wat een teken zou kunnen zijn van complexe (en mogelijk closing-) gastroschisis (waarbij het defect relatief zeer klein blijft), c) beoordeling van de foetale darm op basis van 3D echografie, wat mogelijk een betere indicatie van het volume van darmlissen en de maag maar ook het gehele extra-abdominale darmpakket kan geven.
- Als antenatale markers met een hoge sensitiviteit en specificiteit voor complexe gastroschisis casus worden gevonden, dan moet de timing van de bevalling van complexe gastroschisis gevallen nader worden onderzocht. Voor zowel complexe als simpele gastroschisis, lijkt een inleiding bij 37 weken zwangerschap de kans op pre- en postnatale sterfte te verkleinen ten opzichte van een expectatief beleid.[69] Een bevalling <37 weken kan mogelijk de darm beschermen

tegen ernstige schade als gevolg van blootstelling aan vruchtwater en compressie. Morbiditeit als gevolg van intra-uteriene darmschade moet zwaarder wegen dan morbiditeit als gevolg van vroeggeboorte. Omdat slechts 19% van de gastroschisis patiënten geboren worden met ernstige darmschade (complexe gastroschisis), zou het prematuur geboren laten worden van alle gastroschisis casus mogelijk onnodige morbiditeit veroorzaken als gevolg prematuriteit. Complexe gastroschisis gevallen zouden kunnen profiteren van een ander obstetrisch beleid met intensieve foetale bewaking en mogelijk ook een voortijdige bevalling om de darm te beschermen tegen ernstige schade als gevolg van veneuze compressie, (gedeeltelijke) ischemie en chronische ontsteking.[70,71]

REFERENTIES

1. Garne E, Loane M, Dolk H, De Vigan C, Scarano G, Tucker D, Stoll C, Gener B, Pierini A, Nelen V, Rosch C, Gillerot Y, Feijoo M, Tincheva R, Queisser-Luft A, Addor MC, Mosquera C, Gatt M, Barisic I. Prenatal diagnosis of severe structural congenital malformations in Europe. *Ultrasound Obstet Gynecol*. 2005;25(1):6-11. 10.1002/uog.1784.
2. Martillotti G, Boucoiran I, Damphousse A, Grignon A, Dube E, Moussa A, Bouchard S, Morin L. Predicting perinatal outcome from prenatal ultrasound characteristics in pregnancies complicated by gastroschisis. *Fetal Diagn Ther*. 2016;39(4):279-286. 10.1159/000440699 [doi].
3. Vachharajani AJ, Dillon PA, Mathur AM. Outcomes in neonatal gastroschisis: An institutional experience. *Am J Perinatol*. 2007;24(8):461-465.
4. Bradnock TJ, Marven S, Owen A, Johnson P, Kurinczuk JJ, Spark P, Draper ES, Knight M. Gastroschisis: One year outcomes from national cohort study. *BMJ*. 2011;343(7832):1036.
5. South AP, Stutey KM, Meinzen-Derr J. Meta-analysis of the prevalence of intrauterine fetal demise in gastroschisis. *Am J Obstet Gynecol*. 2013;2(209):114e1--13. 10.1016/j.ajog.2013.04.032; 10.1016/j.ajog.2013.04.032.
6. Cowan KN, Puligandla PS, Laberge JM, Skarsgard ED, Bouchard S, Yanchar N, Kim P, Lee S, McMillan D, von Dadelszen P, Canadian Pediatric Surgery Network. The gastroschisis prognostic score: Reliable outcome prediction in gastroschisis. *J Pediatr Surg*. 2012;47(6):1111-1117. 10.1016/j.jpedsurg.2012.03.010; 10.1016/j.jpedsurg.2012.03.010.
7. Molik KA, Gingalewski CA, West KW, Rescorla FJ, Scherer LR, Engum SA, Grosfeld JL. Gastroschisis: A plea for risk categorization. *J Pediatr Surg*. 2001;36(1):51-55. 10.1053/jpsu.2001.20004.
8. Bergholz R, Boettcher M, Reinshagen K, Wenke K. Complex gastroschisis is a different entity to simple gastroschisis affecting morbidity and mortality-a systematic review and meta-analysis. *J Pediatr Surg*. 2014;49(10):1527-1532. 10.1016/j.jpedsurg.2014.08.001 [doi].
9. Arnold MA, Chang DC, Nabaweesi R, Colombani PM, Bathurst MA, Mon KS, Hosmane S, Abdullah F. Risk stratification of 4344 patients with gastroschisis into simple and complex categories. *J Pediatr Surg*. 2007;42(9):1520-1525. 10.1016/j.jpedsurg.2007.04.032.
10. Logghe HL, Mason GC, Thornton JG, Stringer MD. A randomized controlled trial of elective preterm delivery of fetuses with gastroschisis. *J Pediatr Surg*. 2005;40(11):1726-1731. 10.1016/j.jpedsurg.2005.07.047.
11. Segel SY, Marder SJ, Parry S, Macones GA. Fetal abdominal wall defects and mode of delivery: A systematic review. *Obstet Gynecol*. 2001;98(5 Pt 1):867-873.
12. Abdel-Latif ME, Bolisetty S, Abeywardana S, Lui K, Australian and New Zealand Neonatal Network. Mode of delivery and neonatal survival of infants with gastroschisis in Australia and New Zealand. *J Pediatr Surg*. 2008;43(9):1685-1690. 10.1016/j.jpedsurg.2008.03.053.
13. Ross AR, Eaton S, Zani A, Ade-Ajayi N, Pierro A, Hall NJ. The role of preformed silos in the management of infants with gastroschisis: A systematic review and meta-analysis. *Pediatr Surg Int.* 2015;31(5):473-483. 10.1007/s00383-015-3691-2 [doi].
14. Payne NR, Gilmore L, Svobodny S, Perdue NR, Hoekstra RE, Olsen S, Moore JR. A cross-sectional, case-control follow-up of infants with gastroschisis. *J Neonatal-Perinat Med.* 2010;3(3):207-215.
15. South AP, Marshall DD, Bose CL, Laughon MM. Growth and neurodevelopment at 16 to 24 months of age for infants born with gastroschisis. *J Perinatol.* 2008;28(10):702-706. 10.1038/jp.2008.71.
16. Gorra AS, Needelman H, Azarow KS, Roberts HJ, Jackson BJ, Cusick RA. Long-term neurodevelopmental outcomes in children born with gastroschisis: The tiebreaker. *J Pediatr Surg*. 2012;47(1):125-129. 10.1016/j.jpedsurg.2011.10.028.

17. Minutillo C, Rao SC, Pirie S, McMichael J, Dickinson JE. Growth and developmental outcomes of infants with gastroschisis at one year of age: A retrospective study. *J Pediatr Surg*. 2013;48(8):1688-1696. 10.1016/j.jpedsurg.2012.11.046; 10.1016/j.jpedsurg.2012.11.046.

18. van Manen M, Hendson L, Wiley M, Evans M, Taghaddos S, Dinu I. Early childhood outcomes of infants born with gastroschisis. *J Pediatr Surg*. 2013;48(8):1682-1687. 10.1016/j.jpedsurg.2013.01.021; 10.1016/j.jpedsurg.2013.01.021.

19. Harris EL, Hart SJ, Minutillo C, Ravikumara M, Warner TM, Williams Y, Nathan EA, Dickinson JE. The long-term neurodevelopmental and psychological outcomes of gastroschisis: A cohort study. *J Pediatr Surg*. 2016;51(4):549-553. 10.1016/j.jpedsurg.2015.08.062 [doi].

20. Giudici L, Bokser VS, Maricic MA, Golombek SG, Ferrario CC. Babies born with gastroschisis and followed up to the age of six years faced long-term morbidity and impairments. *Acta Paediatr*. 2016;105(6):e275-80. 10.1111/apa.13374 [doi].

21. Lejarraga H, Menendez AM, Menzano E, Guerra L, Biancato S, Pianelli P, Fattore MJ, De Raco P, Schejter V, Contreras MM, Glomba C, Bellusci C, Lusnig A, Rautenstrauch C, Paris V, Galeana A, Feinsilber V, Garay ML, Alves L, Del Pino M, Andrews M, Pagano A, Larigoitia D. PRUNAPE: Screening for psychomotor development problems at primary care level. *Arch Argent Pediatr*. 2008;106(2):119-125. 10.1590/S0325-00752008000200005 [doi].

22. Wechsler D, ed. *Wechsler Intelligence Scale for Children*. Fourth Edition Australin Standerdised Edition (WISC-IV Australian) ed. Pearson; 2005.

23. Wechsler D, ed. *Wechsler Preschool & Primary Scale of Intelleigence- Australian Standardised Edition (WPPSI-III Australian)*. Third Edition ed. Pearson; 2004.

24. YouthinMind: Strengths and difficulties questionnaire. .

25. Drongowski RA, Smith RK,Jr, Coran AG, Klein MD. Contribution of demographic and environmental factors to the etiology of gastroschisis: A hypothesis. *Fetal Diagn Ther*. 1991;6(1-2):14-27.

26. Torfs CP, Velie EM, Oechsli FW, Bateson TF, Curry CJ. A population-based study of gastroschisis: Demographic, pregnancy, and lifestyle risk factors. *Teratology*. 1994;50(1):44-53. 10.1002/tera.1420500107.

27. Haddow JE, Palomaki GE, Holman MS. Young maternal age and smoking during pregnancy as risk factors for gastroschisis. *Teratology*. 1993;47(3):225-228. 10.1002/tera.1420470306.

28. Lubinsky M. Hypothesis: Estrogen related thrombosis explains the pathogenesis and epidemiology of gastroschisis. *Am J Med Genet A*. 2012;158A(4):808-811. 10.1002/ajmg.a.35203; 10.1002/ajmg.a.35203.

29. Kohl M, Wiesel A, Schier F. Familial recurrence of gastroschisis: Literature review and data from the population-based birth registry "mainz model". *J Pediatr Surg*. 2010;45(9):1907-1912. 10.1016/j.jpedsurg.2010.05.003.

30. Mastroiacovo P, Lisi A, Castilla EE, Martinez-Frias ML, Bermejo E, Marengo L, Kucik J, Siffel C, Halliday J, Gatt M, Anneren G, Bianchi F, Canessa MA, Danderfer R, de Walle H, Harris J, Li Z, Lowry RB, McDonell R, Merlob P, Metneki J, Mutchinick O, Robert-Gnansia E, Scarano G, Sipek A, Potzsch S, Szabova E, Yevtushok L. Gastroschisis and associated defects: An international study. *Am J Med Genet A*. 2007;143(7):660-671. 10.1002/ajmg.a.31607.

31. Hwang PJ, Kousseff BG. Omphalocele and gastroschisis: An 18-year review study. *Genet Med*. 2004;6(4):232-236.

32. Southard AE, Edelmann LJ, Gelb BD. Role of copy number variants in structural birth defects. *Pediatrics*. 2012;129(4):755-763. 10.1542/peds.2011-2337 [doi].

33. Chen X, Shen Y, Gao Y, Zhao H, Sheng X, Zou J, Lip V, Xie H, Guo J, Shao H, Bao Y, Shen J, Niu B, Gusella JF, Wu BL, Zhang T. Detection of copy number variants reveals association of cilia genes with neural tube defects. *PLoS One*. 2013;8(1):e54492. 10.1371/journal.pone.0054492 [doi].

34. Rankin J, Dillon E, Wright C. Congenital anterior abdominal wall defects in the north of England, 1986-1996: Occurrence and outcome. *Prenat Diagn*. 1999;19(7):662-668.

35. Stoll C, Alembik Y, Dott B, Roth MP. Omphalocele and gastroschisis and associated malformations. *Am J Med Genet A*. 2008;146A(10):1280-1285. 10.1002/ajmg.a.32297.

36. Merks JH, Ozgen HM, Koster J, Zwinderman AH, Caron HN, Hennekam RC. Prevalence and patterns of morphological abnormalities in patients with childhood cancer. *JAMA*. 2008;299(1):61-69. 10.1001/jama.2007.66; 10.1001/jama.2007.66.

37. Ozgen H, Hellemann GS, Stellato RK, Lahuis B, van Daalen E, Staal WG, Rozendal M, Hennekam RC, Beemer FA, van Engeland H. Morphological features in children with autism spectrum disorders: A matched case-control study. *J Autism Dev Disord*. 2011;41(1):23-31. 10.1007/s10803-010-1018-7; 10.1007/s10803-010-1018-7.

38. Gorlin R, Cohen M, Hennekam R. *Syndromes of the Head and Neck*. 4th ed. Oxford England: Oxford University Press; 2001.

39. Marden PM, Smith DW, Mcdonald MJ. Congenital anomalies in the newborn infant, including minor variations. a study of 4,412 babies by surface examination for anomalies and buccal smear for sex chromatin. *J Pediatr*. 1964;64:357-371.

40. Hoyme HE, Jones MC, Jones KL. Gastroschisis: Abdominal wall disruption secondary to early gestational interruption of the omphalomesenteric artery. *Semin Perinato*l. 1983;7(4):294-298.

41. Lubinsky MS. Association of prenatal vascular disruptions with decreased maternal age. *Am J Med Gene*t. 1997;69(3):237-239.

42. Hanemaaijer NM, Sikkema-Raddatz B, van der Vries G, Dijkhuizen T, Hordijk R, van Essen AJ, Veenstra-Knol HE, Kerstjens-Frederikse WS, Herkert JC, Gerkes EH, Leegte LK, Kok K, Sinke RJ, van Ravenswaaij-Arts CM. Practical guidelines for interpreting copy number gains detected by high-resolution array in routine diagnostics. *Eur J Hum Genet*. 2012;20(2):161-165. 10.1038/ejhg.2011.174 [doi].

43. Bianco AM, Girardelli M, Tommasini A. Genetics of inflammatory bowel disease from multifactorial to monogenic forms. *World J Gastroenterol*. 2015;21(43):12296-12310. 10.3748/wjg.v21.i43.12296 [doi].

44. Jarick I, Volckmar AL, Putter C, Pechlivanis S, Nguyen TT, Dauvermann MR, Beck S, Albayrak O, Scherag S, Gilsbach S, Cichon S, Hoffmann P, Degenhardt F, Nothen MM, Schreiber S, Wichmann HE, Jockel KH, Heinrich J, Tiesler CM, Faraone SV, Walitza S, Sinzig J, Freitag C, Meyer J, Herpertz-Dahlmann B, Lehmkuhl G, Renner TJ, Warnke A, Romanos M, Lesch KP, Reif A, Schimmelmann BG, Hebebrand J, Scherag A, Hinney A. Genome-wide analysis of rare copy number variations reveals PARK2 as a candidate gene for attention-deficit/hyperactivity disorder. *Mol Psychiatry*. 2014;19(1):115-121. 10.1038/mp.2012.161 [doi].

45. Girirajan S, Rosenfeld JA, Cooper GM, Antonacci F, Siswara P, Itsara A, Vives L, Walsh T, McCarthy SE, Baker C, Mefford HC, Kidd JM, Browning SR, Browning BL, Dickel DE, Levy DL, Ballif BC, Platky K, Farber DM, Gowans GC, Wetherbee JJ, Asamoah A, Weaver DD, Mark PR, Dickerson J, Garg BP, Ellingwood SA, Smith R, Banks VC, Smith W, McDonald MT, Hoo JJ, French BN, Hudson C, Johnson JP, Ozmore JR, Moeschler JB, Surti U, Escobar LF, El-Khechen D, Gorski JL, Kussmann J, Salbert B, Lacassie Y, Biser A, McDonald-McGinn DM, Zackai EH, Deardorff MA, Shaikh TH, Haan E, Friend KL, Fichera M, Romano C, Gecz J, DeLisi LE, Sebat J, King MC, Shaffer LG, Eichler EE. A recurrent 16p12.1 microdeletion supports a two-hit model for severe developmental delay. *Nat Genet*. 2010;42(3):203-209. 10.1038/ng.534 [doi].

46. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA, Feuk L, Friedman JM, Hamosh A, Jackson L, Kaminsky EB, Kok K, Krantz ID, Kuhn RM, Lee C, Ostell JM, Rosenberg C, Scherer SW, Spinner NB, Stavropoulos DJ, Tepperberg JH, Thorland EC, Vermeesch JR, Waggoner DJ, Watson MS, Martin CL, Ledbetter DH. Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet*. 2010;86(5):749-764. 10.1016/j.ajhg.2010.04.006 [doi].

47. Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, Braxton A, Beuten J, Xia F, Niu Z, Hardison M, Person R, Bekheirnia MR, Leduc MS, Kirby A, Pham P, Scull J, Wang M, Ding Y, Plon SE, Lupski JR, Beaudet AL, Gibbs RA, Eng CM. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. *N Engl J Med*. 2013;369(16):1502-1511. 10.1056/NEJMoa1306555 [doi].

48. Grozeva D, Carss K, Spasic-Boskovic O, Tejada MI, Gecz J, Shaw M, Corbett M, Haan E, Thompson E, Friend K, Hussain Z, Hackett A, Field M, Renieri A, Stevenson R, Schwartz C, Floyd JA, Bentham J, Cosgrove C, Keavney B, Bhattacharya S, Italian X-linked Mental Retardation Project, UK10K Consortium, GOLD Consortium, Hurles M, Raymond FL. Targeted next-generation sequencing analysis of 1,000 individuals with intellectual disability. *Hum Mutat*. 2015;36(12):1197-1204. 10.1002/humu.22901 [doi].

49. Kato M, Yamagata T, Kubota M, Arai H, Yamashita S, Nakagawa T, Fujii T, Sugai K, Imai K, Uster T, Chitayat D, Weiss S, Kashii H, Kusano R, Matsumoto A, Nakamura K, Oyazato Y, Maeno M, Nishiyama K, Kodera H, Nakashima M, Tsurusaki Y, Miyake N, Saito K, Hayasaka K, Matsumoto N, Saitsu H. Clinical spectrum of early onset epileptic encephalopathies caused by KCNQ2 mutation. *Epilepsia*. 2013;54(7):1282-1287. 10.1111/epi.12200 [doi].

50. Quelin C, Loget P, Verloes A, Bazin A, Bessieres B, Laquerriere A, Patrier S, Grigorescu R, Encha-Razavi F, Delahaye S, Jouannic JM, Carbonne B, D'Herve D, Aubry MC, Mace G, Harvey T, Ville Y, Viot G, Joye N, Odent S, Attie-Bitach T, Wolf C, Chevy F, Benlian P, Gonzales M. Phenotypic spectrum of fetal smith-lemli-opitz syndrome. *Eur J Med Genet*. 2012;55(2):81-90. 10.1016/j.ejmg.2011.12.002; 10.1016/j.ejmg.2011.12.002.

51. Dy ME, Sims KB, Friedman J. TPP1 deficiency: Rare cause of isolated childhood-onset progressive ataxia. *Neurology*. 2015;85(14):1259-1261. 10.1212/WNL.0000000000001876 [doi].

52. Feldkamp ML, Botto LD, Byrne JL, Krikov S, Carey JC. Clinical presentation and survival in a population-based cohort of infants with gastroschisis in utah, 1997-2011. *Am J Med Genet A*. 2016;170A(2):306-315. 10.1002/ajmg.a.37437 [doi].

53. Stoll C, Alembik Y, Dott B, Roth MP. Risk factors in congenital abdominal wall defects (omphalocele and gastroschisi): A study in a series of 265,858 consecutive births. *Ann Genet*. 2001;44(4):201-208.

54. Snyder CL, Miller KA, Sharp RJ, Murphy JP, Andrews WA, Holcomb GW,3rd, Gittes GK, Ashcraft KW. Management of intestinal atresia in patients with gastroschisis. *J Pediatr Surg*. 2001;36(10):1542-1545. 10.1053/jpsu.2001.27040.

55. Phillips JD, Raval MV, Redden C, Weiner TM. Gastroschisis, atresia, dysmotility: Surgical treatment strategies for a distinct clinical entity. *J Pediatr Surg*. 2008;43(12):2208-2212. 10.1016/j.jpedsurg.2008.08.065.

56. Kronfli R, Bradnock TJ, Sabharwal A. Intestinal atresia in association with gastroschisis: A 26-year review. *Pediatr Surg Int*. 2010;26(9):891-894. 10.1007/s00383-010-2676-4.

57. Page R, Ferraro ZM, Moretti F, Fung KF. Gastroschisis: Antenatal sonographic predictors of adverse neonatal outcome. *J Pregnancy*. 2014;2014:239406. 10.1155/2014/239406 [doi].

58. D'Antonio F, Virgone C, Rizzo G, Khalil A, Baud D, Cohen-Overbeek TE, Kuleva M, Salomon LJ, Flacco ME, Manzoli L, Giuliani S. Prenatal risk factors and outcomes in gastroschisis: A meta-analysis. *Pediatrics*. 2015;136(1):e159-69. 10.1542/peds.2015-0017 [doi].

59. Nyberg DA, Mack LA, Patten RM, Cyr DR. Fetal bowel. normal sonographic findings. *J Ultrasound Med*. 1987;6(1):3-6.

60. Parulekar SG. Sonography of normal fetal bowel. *J Ultrasound Med*. 1991;10(4):211-220.

61. Zalel Y, Perlitz Y, Gamzu R, Peleg D, Ben-Ami M. In-utero development of the fetal colon and rectum: Sonographic evaluation. *Ultrasound Obstet Gynecol*. 2003;21(2):161-164. 10.1002/uog.26 [doi].

62. Malas MA, Aslankoc R, Ungor B, Sulak O, Candir O. The development of jejunum and ileum during the fetal period. *Early Hum Dev*. 2003;74(2):109-124. S0378378203000859 [pii].

63. Malas MA, Aslankoc R, Ungor B, Sulak O, Candir O. The development of large intestine during the fetal period. *Early Hum Dev*. 2004;78(1):1-13. 10.1016/j.earlhumdev.2004.03.001 [doi].

64. Ebbing C, Rasmussen S, Godfrey KM, Hanson MA, Kiserud T. Fetal superior mesenteric artery: Longitudinal reference ranges and evidence of regulatory link to portal liver circulation. *Early Hum Dev*. 2009;85(4):207-213. 10.1016/j.earlhumdev.2008.09.412 [doi].

65. Abuhamad AZ, Mari G, Cortina RM, Croitoru DP, Evans AT. Superior mesenteric artery doppler velocimetry and ultrasonographic assessment of fetal bowel in gastroschisis: A prospective longitudinal study. *Am J Obstet Gynecol*. 1997;176(5):985-990.

66. Carroll SG, Kuo PY, Kyle PM, Soothill PW. Fetal protein loss in gastroschisis as an explanation of associated morbidity. *Am J Obstet Gynecol*. 2001;184(6):1297-1301. 10.1067/mob.2001.114031.

67. Langer JC, Bell JG, Castillo RO, Crombleholme TM, Longaker MT, Duncan BW, Bradley SM, Finkbeiner WE, Verrier ED, Harrison MR. Etiology of intestinal damage in gastroschisis, II. timing and reversibility of histological changes, mucosal function, and contractility. *J Pediatr Surg*. 1990;25(11):1122-1126.

68. Langer JC, Longaker MT, Crombleholme TM, Bond SJ, Finkbeiner WE, Rudolph CA, Verrier ED, Harrison MR. Etiology of intestinal damage in gastroschisis. I: Effects of amniotic fluid exposure and bowel constriction in a fetal lamb model. *J Pediatr Surg*. 1989;24(10):992-997.

69. Sparks TN, Shaffer BL, Page J, Caughey AB. Gastroschisis: Mortality risks with each additional week of expectant management. *Am J Obstet Gynecol*. 2016. S0002-9378(16)30648-2 [pii].

70. Moir CR, Ramsey PS, Ogburn PL, Johnson RV, Ramin KD. A prospective trial of elective preterm delivery for fetal gastroschisis. *Am J Perinatol*. 2004;21(5):289-294. 10.1055/s-2004-829864.

71. Gelas T, Gorduza D, Devonec S, Gaucherand P, Downham E, Claris O, Dubois R. Scheduled preterm delivery for gastroschisis improves postoperative outcome. *Pediatr Surg Int*. 2008;24(9):1023-1029. 10.1007/s00383-008-2204-y.

Chapter

10

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Lap CCMM, Kramer WLM, Nikkels PG, Pistorius LR, van Vugt JM, Visser GHA, Manten GTR. Isolated abdominal wall defect with complete liver herniation without a covering or remnant membrane: An ominous sign: Case report and review of literature. *J Matern Fetal Neonatal Med*. 2013;26(9):946-948. 10.3109/14767058.2013.765852 [doi].

Lap CCMM, Pistorius LR, Kramer WLM, Visser GHA, Manten GTR. Gastroschisis; de stand van zaken. *NTOG* 2012;127(3):112-117.

Manten GTR, **Lap CCMM**. Gastroschisis; kunnen we de uitkomst verbeteren? *Reproductieve geneeskunde, gynaecologie en obstetrie* anno 2011;288-294.

Bolhuis SW and **Lap CCMM**, van Braeckel KNJA, Reijneveld SA, Manten GTR, Bos AF, Hulscher JBF. Functional outcome at school age of children born with gastroschisis. *Submitted October 2016.*

Lap CCMM, Manten GTR, van Binsbergen E, Kramer WLM, Visser GHA, Knoers NVAM, Pistorius LR, Lichtenbelt KD. The value of genetic testing and morphological examination in children with gastroschisis. *Submitted November 2016*

Lap CCMM, Voskuilen CS, Pistorius LR, Mulder EJH, Visser GHA, Manten GTR.
Reference curves for the normal fetal small bowel and colon diameters; their usefulness in fetuses with suspected dilated bowel. *Submitted October 2016*

CURRICULUM VITAE – OVER DE AUTEUR

Claar Lap, alias Chiara en Claartje, werd op 24 november 1982 geboren op 'Lapland' te Sint-Oedenrode. In 2001 behaalde zijn haar VWO diploma aan het Lorentz Casimir Lyceum te Eindhoven. Na een jaar Work & Travel door Australië, Nieuw-Zeeland en Azië startte ze met de studie Geneeskunde aan de Universiteit Utrecht. Tijdens haar studie had zij verschillende wetenschappelijke en klinische bijbanen binnen het Universitair Medisch Centrum Utrecht (UMCU). Haar voorliefde voor de gynaecologie begon tijdens een co-schap in Malawi, Afrika, en werd bevestigd tijdens een keuzestage perinatologie in het Wilhelmina Kinderziekenhuis (WKZ/UMCU) en haar algemene semi arts stage (ASAS) bij de Verloskunde en Gynaecologie in het Meander Medisch Centrum te Amersfoort. In het laatste jaar van haar studie heeft zij een wetenschappelijke stage uitgevoerd naar de antenatale foetale darmafwijkingen onder leiding van dr. G.T.R. Manten en dr. L.R. Pistorius. Na negen maanden als arts-niet-in-opleiding in het St. Antonius Ziekenhuis te Nieuwegein (opleider dr. J.H Schagen van Leeuwen) kreeg zij de gelegenheid om, onder begeleiding van promotor prof. dr. G.H.A. Visser en co-promotoren dr. G.T.R. Manten en dr. L.R. Pistorius, het onderzoek voort te zetten in een promotie-traject met als aandachtsgebied gastroschisis. Tijdens deze periode werkte zij als arts-onderzoeker en echoscopist in het WKZ/UMCU en kreeg ze de mogelijkheid om zich verder te scholen in het structureel en geavanceerd echoscopisch onderzoek. In oktober 2013 begon zij met haar opleiding tot gynaecoloog in het Meander Medisch Centrum te Amersfoort (opleider dr. J.M. Duk). Vanaf januari 2016 volgt zij het academische deel van de opleiding in het WKZ/UMCU (opleider prof. dr. A. Franx).

Claar is getrouwd met Michiel. Zij hebben een zoontje Philip en verwachten in januari 2017 hun tweede zoontje.

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