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The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-951-29-8116-8 (PRINT)
ISBN 978-951-29-8117-5 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama Oy, Turku, Finland 2020

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Paediatric Surgery
ARIMATIAS RAITIO: Congenital Abdominal Wall Defects in Finland 1993–2014: Epidemiology and Risk Factors
Doctoral Dissertation, 102 pp.
Doctoral Programme in Clinical Research
June 2020

ABSTRACT

Congenital abdominal wall defects are a group of malformations among which gastroschisis and omphalocele are the most common. In omphalocele, abdominal organs are herniated through an open umbilical ring and the defect is covered by membranes. Omphalocele is often associated with other severe anomalies and reasonably high mortality. Gastroschisis, on the other hand, is an open abdominal wall defect lateral to the umbilical cord. Contrary to omphalocele, it carries a far better prognosis. For unknown reasons, the prevalence of gastroschisis has increased dramatically worldwide over the last decades.

The first aim of this study was to assess the national prevalence, mortality, and pregnancy termination rates of both gastroschisis and omphalocele, and to identify associated anomalies. In the second phase, the aim was to identify potential maternal risk factors for both abovementioned anomalies. The analysis is based on several national registries, the majority of which are upheld by the Finnish Institute for Health and Welfare.

The prevalence and mortality rates of both gastroschisis and omphalocele in Finland were comparable with previous worldwide reports. However, the pregnancy termination rate for gastroschisis was significantly higher than previously reported and it was speculated to be due to insufficient antenatal counselling. Young maternal age was a risk factor for gastroschisis. Obesity and diabetes increased the risk of omphalocele, while maternal obesity was protective for gastroschisis. In general, maternal prescription drug exposures during early pregnancy appeared safe, and extended spectrum penicillins significantly reduced the risk of omphalocele.

In conclusion, survival for congenital abdominal wall defects in Finland is high and comparable with other high-income countries. Novel association between extended spectrum penicillins and the risk of omphalocele warrants further studies.

KEYWORDS: abortion, congenital abdominal wall defect, exomphalos, gastroschisis, infant mortality, omphalocele, prevalence, risk factor

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Lastenkirurgia
ARIMATIAS RAITIO: Synnynnäiset vatsanpeitepuutokset Suomessa 1993–2014: Epidemiologia ja riskitekijät
Väitöskirja, 102 s.
Kliininen tohtoriohjelma
Kesäkuu 2020

TIIVISTELMÄ

Synnynnäiset vatsanpeitepuutokset ovat ryhmä malformaatioita, joista gastroskiisi ja omfaloseele ovat yleisimpiä. Omfaloseelessä vatsaontelon elimet hernioituvat avoimen naparenkaan läpi ja defekti on napanuoran kalvojen peittämä. Omfaloseeleen liittyy usein muita vakavia anomalioita ja myös suhteellisen suuri kuolleisuus. Gastroskiisi puolestaan on avoin vatsanpeitepuutos napanuoran oikealla puolen, jossa ennuste, toisin kuin omfaloseelessa, on useimmin erittäin hyvä. Gastroskiisi on useimmiten isoloitu anomalia. Tuntemattomista syistä gastroskiisin prevalenssi on ollut maailmanlaajuisesti kasvussa viimeisten vuosikymmenten ajan.

Tutkimuksen ensimmäinen tavoite oli selvittää sekä omfaloseelen että gastroskiisin kansallinen prevalenssi, mortaliteetti, raskaudenkeskeytyksen yleisyys ja näihin liittyvät liittännäisanomaliat. Toisessa vaiheessa tavoitteena oli etsiä yllämainittujen anomalioiden mahdollisia äitiin liittyviä riskitekijöitä. Tutkimus perustuu useiden kansallisten rekisterien aineistoon, jotka suurelta osin ovat Terveyden ja Hyvinvoinnin laitoksen ylläpitämiä.

Sekä gastroskiisin että omfaloseelen prevalenssi ja kuolleisuus Suomessa olivat yhteneviä aiempien julkaistujen tulosten kanssa. Gastroskiisin abortointi sen sijaan oli merkittävästi yleisempää kuin aiemmissa julkaisuissa, ja tämä saattaa johtua perheiden riittämättömästä informoinnista/ohjauksesta. Äidin nuori ikä oli riskitekijä gastroskiisille. Ylipaino ja diabetes sen sijaan altistivat omfaloseelelle, mutta toisaalta äidin ylipaino suojeli gastroskiisilta. Raskauden alkuvaiheessa käytetty lääkitys ei lisännyt vatsanpeitepuutosten riskiä. Tupakointi lisäsi gastroskiisin riskiä, mutta ei tilastollisesti merkittävästi. Laajakirjoisilla penisilliineillä alkuraskauden aikana todettiin omfaloseelen suhteen suojaavia vaikutuksia.

Vatsanpeitepuutosten osalta kuolleisuus Suomessa on samaa tasoa kuin muissa korkean tuloluokan maissa. Penisilliinien vaikutus omfaloseelen riskiin on uusi löydös ja vaatii lisätutkimuksia tulosten varmistamiseksi.

AVAINSANAT: abortti, gastroskiisi, imeväiskuolleisuus, napanuoratyrä, omfaloseele, prevalenssi, raskaudenkeskeytys, riskitekijä, synnynnäinen vatsanpeitepuutos, vatsahalkio

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Abbreviations

aOR	adjusted Odds Ratio
ASD	Atrial septal defect
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
BWS	Beckwith-Wiedemann Syndrome
CI	Confidence Interval
CNS	Central Nervous System
ICD	International Classification of Diseases
EXIT	Ex Utero Intrapartum Treatment
Kela	Finnish Social Insurance Institution
NEC	Necrotizing enterocolitis
NG	Nasogastric
PDA	Patent Ductus Arteriosus
PN	Parenteral nutrition
OEIS	Omphalocele, bladder Exstrophy, Imperforate anus, and Spinal defects
OR	Odds Ratio
SSRI	Selective serotonin reuptake inhibitors
VSD	Ventricular septal defect
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Raitio A, Lahtinen A, Syvänen J, Kemppainen T, Löyttyniemi E, Gissler M, Hyvärinen A, Helenius I. Gastroschisis in Finland 1993 to 2014–Increasing Prevalence, High Rates of Abortion and Survival: A population-based Study. *European Journal of Pediatric Surgery*, 2019; Dec 31 Epub.

II Raitio A, Tauriainen A, Syvänen J, Kemppainen T, Löyttyniemi E, Sankilampi U, Vanamo K, Gissler M, Hyvärinen A, Helenius I. Omphalocele in Finland from 1993 to 2014: Trends, Prevalence, Mortality and Associated Malformations–A population-based Study. *European Journal of Pediatric Surgery*, 2020; Mar 4 Epub.

III Raitio A, Tauriainen A, Leinonen MK, Syvänen J, Kemppainen T, Löyttyniemi E, Sankilampi U, Gissler M, Hyvärinen A, Helenius I. Maternal risk factors for gastroschisis: A population-based case-control study. *Birth Defects Research,* 2020; May 14 Epub.

IV Raitio A, Tauriainen A, Leinonen MK, Syvänen J, Kemppainen T, Löyttyniemi E, Sankilampi U, Gissler M, Hyvärinen A, Helenius I. Extended Spectrum Penicillins During the First Trimester of Pregnancy Reduce the Risk of Omphalocele – A population-based case-control study. *Manuscript*

1 Introduction

Abdominal wall defects are a group of severe congenital anomalies. Even though this group includes several different diagnoses, all these malformations can be characterized by defective abdominal wall structures causing herniation of abdominal contents. This study concentrates on the two most common abdominal wall defects – namely gastroschisis and omphalocele.

Gastroschisis is an open defect lateral to the umbilical cord. Known risk factors for gastroschisis include young maternal age, maternal smoking, recreational drugs, poor socioeconomic status, and malnutrition (Loane et al. 2007, Draper et al. 2008, Hackshaw et al. 2011, Friedman et al. 2016). However, there are only a few studies on the association of maternal prescription drugs in early pregnancy and the risk of gastroschisis (Werler et al. 2002, Ahrens et al. 2013, Given et al. 2017, Anderson, K. N. et al. 2020). In most cases, gastroschisis is an isolated anomaly and survival in high income countries exceed 90% (Lao et al. 2010, Owen et al. 2010, Cowan et al. 2012, Bhatt et al. 2018, Anderson, J. E. et al. 2018). For unclear reasons, the worldwide prevalence has been increasing (Bhatt et al. 2018, Anderson, J. E. et al. 2018). However, most of these studies have lacked total prevalence.

Omphalocele, or exomphalos, is also an abdominal wall defect involving herniation of bowel and occasionally other abdominal organs. Contrary to gastroschisis, the defect in omphalocele is covered with membranes of the abdominal wall and the umbilical cord (Khan et al. 2019). Omphalocele is often associated with other congenital anomalies, including cardiac defects and chromosomal abnormalities, and hence associated with high morbidity and even mortality (Yazbeck et al. 1986, Byron-Scott et al. 1998, Stoll et al. 2001, Deng et al. 2014). There are a number of recognized risk factors for omphalocele, including advanced or very young maternal age (Salihu et al. 2003, Frolov et al. 2010), alcohol consumption during pregnancy (Bird et al. 2009), smoking (Bird et al. 2009, Feldkamp et al. 2014), maternal obesity (Waller et al. 2007), inflammatory bowel disease (Auger et al. 2020), disorders of glycaemic control (Waller et al. 2001), and male gender (Goldkrand et al. 2004). Regardless, the possible association of maternal use of prescription medicine during early pregnancy has only been

addressed in a handful of studies (Stoll et al. 2001, Alwan et al. 2007, Lin et al. 2012, Kapapa et al. 2019).

The national register data in Finland is upheld by the Finnish Institute of National Health and Welfare. The quality and coverage of the registers has been validated in multiple national and international investigations (Gissler et al. 1995, Pakkasjärvi et al. 2006, Leoncini et al. 2010, Artama et al. 2011). The aforementioned data was combined with the data on maternal prescription medicine use from the Register on Reimbursed Drug Purchases by the Finnish Social Insurance Institution (Kela). As foetal structures and organs are most susceptible to teratogenic effects at 3–8 weeks after conception (Moore & Persaud 2003), we limited this data to a time window of one month prior conception and the first trimester of pregnancy.

The first aim of this thesis was to assess the prevalence, mortality, and the rates of termination of pregnancy of gastroschisis and omphalocele in the Finnish population between 1993 and 2014, and to identify possible long-term changes in trends and the most commonly associated malformations. As very little is known about the associations of maternal prescription drugs and the risk of abdominal wall defects, we sought to address this question in the second part of this study.

2 Review of the Literature

Gastroschisis and omphalocele were first described as early as the 16th century (Mayer et al. 1980). First survivors were described as early as 1802 for omphalocele (Hey 1802) and 1878 for gastroschisis (Fear 1878). Skin flap coverage for congenital abdominal wall defects was first introduced in 1887 (Olshausen 1887). Staged reduction and repair was introduced in 1967 as an alternative treatment modality for large congenital abdominal wall defects (Schuster 1967). For a long time gastroschisis was thought to be a 'ruptured omphalocele'. Until 1953, they were described as separate entities (Moore, T. C. & Stokes 1953), and in 1963, Duhamel emphasized their distinct pathogenesis and clinical presentation (Duhamel 1963). For this thesis, a PubMed search with relevant keywords for epidemiology and risk factors of omphalocele and gastroschisis was performed concentrating on most recent publications. A summary of these studies published in the last 20 years is presented in **Tables 2 & 4**.

2.1 Embryology

The development of both defects is essentially related to the embryology of the abdominal wall, and therefore it is helpful to understand the normal development of the ventral body wall. During the second week of gestation, the embryo is a 2 layered flat disk, which is then converted into three layers (ectoderm, mesoderm and endoderm) during the third week of foetal development in a process called gastrulation (Sadler 2010). The dorsally located ectoderm will later form the central nervous system, skin, and sensory organs. Mesoderm in the middle will make skeletal and connective tissues, the cardiovascular system, and the urogenital system. The ventral layer is endoderm and gives rise to the gut, liver, pancreas, and gall bladder. At this stage, the circumference of the flat embryo represents the eventual umbilical ring (Khan et al. 2019). A combination of parietal mesoderm and ectoderm comprises the body wall and forms lateral body folds, which eventually fuse in the midline to close the ventral body wall (Sadler 2010). Leaving only umbilical vessels in the region of the umbilical ring, this process is finalized by the tenth week of

gestation (Moore, K. L. et al. 2011). Coordinated cell death and deposition is responsible for the decrease in the size of the umbilical ring (Khan et al. 2019).

2.2 Gastroschisis

Gastroschisis is an open abdominal wall defect, almost always on the right to the umbilical cord **(Figure 1).** *Gastroschisis* derives from two Greek words: *gastro* (stomach or belly) and *schisis* (cleft or to split). Herniated bowel loops are in direct contact with amniotic fluid, causing a chemical peritonitis. In high-income countries, over 90% of the cases are detected in antenatal ultrasound screening (Rossi & Prefumo 2013, Fleurke-Rozema et al. 2017). These infants tend to be born slightly prematurely, on 36 weeks of gestation on average (Brindle et al. 2012, Overcash et al. 2014). Caesarean section is often the choice of delivery method, even though evidence does not associate mode of delivery with mortality (Brebner et al. 2018, Lopez et al. 2019). Usually only bowel loops are herniated through the defect but sometimes also stomach, urinary bladder, or liver. Herniated bowels can appear relatively normal (**Figure 1**) but may also show evidence of matting and bowel damage in some cases (Christison-Lagay et al. 2011). Both males and females are affected equally (Anderson, J. E. et al. 2018, Bhatt et al. 2018).

2.2.1 Embryology

The pathogenesis of gastroschisis is largely unknown. The closure of body walls occurs in early weeks of pregnancy and failure in this process leads to a defect (Sadler, T. W. & Feldkamp 2008). Neural tube defects occur with dorsal wall failure and ventral wall failures cause various defects, including gastroschisis, ectopia cordis and bladder and cloacal exstrophy. However, it has also been hypothesised that gastroschisis might be a result of disruption or thrombosis of umbilical vasculature in early pregnancy (Raveenthiran 2012). The most recent evidence suggests, however, that gastroschisis is a primary midline malformation of the umbilical ring (Rittler, Monica et al. 2013, Bargy & Beaudoin 2014, Opitz et al. 2019), possibly resulting from the rupture of the physiological hernia (Beaudoin 2018). Regardless, it seems clear that the clinical window of susceptibility for teratogenic exposures occurs early, in the first trimester of pregnancy (Feldkamp & Botto 2008).

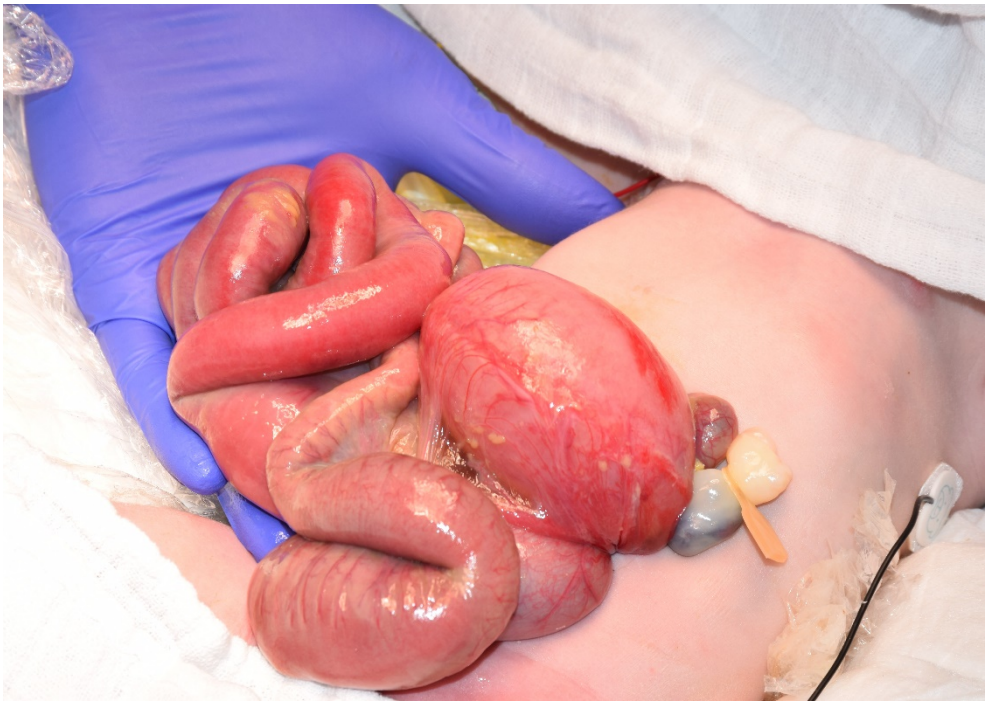

Figure 1. A newborn with a typical case of gastroschisis. Stomach and most of the small bowel herniated through the defect lateral to the umbilical cord.

2.2.2 Prevalence

Gastroschisis occurs in western countries in 2.1 to 5.3 per 10,000 live births (Bhatt et al. 2018, Fleurke-Rozema et al. 2017, Anderson, J. E. et al. 2018, Castilla et al. 2008). Latest reported prevalence in Finland was 2.7 per 10,000 births by the Finnish Institute of Health and Welfare (Kiuru-Kuhlefelt & Lahesmaa-Korpinen 2017). However, much lower prevalence rates have been reported in Asian countries: Taiwan, Japan, and Singapore all reported prevalence rates around 0.5 per 10,000 live births (Suita et al. 2000, Tan et al. 2008, Chen, M. et al. 2019). On the other hand, Greenland reported very high prevalence (10.7 per 10,000 births) in their population-based study (Bugge, Merete et al. 2017). The rate for termination of pregnancy among antenatally detected cases varies from 0 to 14% (Fleurke-Rozema et al. 2017, Nicholas et al. 2009, Ekin et al. 2015). For unknown reasons, the worldwide prevalence has been steadily rising over the last decades, and a similar trend was observed in Finland as early as the 1970s (Hemminki et al. 1982). This has been reported in the majority of the published and reviewed articles as seen in **Table 2**. China (Xu et al. 2011), Taiwan (Chen, M. et al. 2019) and the US (Clark et al. 2020) appear to be the only exceptions regarding the worldwide increasing trend

in the prevalence of gastroschisis. However, many of these studies have lacked total prevalence (Castilla et al. 2008, Bhatt et al. 2018, Anderson, J. E. et al. 2018). No explanation for this increasing trend has been found, but theories have suggested that this might be due to increased teen pregnancies, increased illicit substance abuse during pregnancy, and more frequent chemical exposures (Winchester et al. 2009, Souther et al. 2017, Short et al. 2019). Interestingly, the prevalence has not only been increasing among young mothers but rather in all age groups (Loane et al. 2007, Vu et al. 2008, Chabra et al. 2011, Robledo-Aceves et al. 2015).

2.2.3 Risk Factors

Even though the pathophysiology behind gastroschisis is not completely clear, there are several well-recognized risk factors for gastroschisis, among which young maternal age is the most consistent (**Table 1**) (Anderson, J. E. et al. 2018, Vu et al. 2008, Chabra et al. 2011, Robledo-Aceves et al. 2015, Kapapa et al. 2019, Stallings et al. 2019, Dewberry et al. 2020). Similarly, smoking, alcohol consumption, and the use of recreational drugs during pregnancy increase the risk of gastroschisis (Bird et al. 2009, Hackshaw et al. 2011, Perry et al. 2019, Hawkins & Baum 2019, Freitas et al. 2020, Baldacci et al. 2020, Draper et al. 2008, Richardson et al. 2011, Dewberry et al. 2020). These exposures are often associated with low socioeconomic status, which is also a known risk factor of gastroschisis (Bronberg et al. 2020). Regional opioid prescription rates in the US appear to have a correlation with the prevalence of gastroschisis (Short et al. 2019). Some environmental factors, especially pesticides, have been associated with the higher risk of gastroschisis (Mattix et al. 2007, Waller, Sarah A. et al. 2010, Souther et al. 2017). As nulliparity and short cohabitation are also significant risk factors, it has been hypothesised that antigenic or immunological factors might be involved in the origin of gastroschisis (Rittler, M. et al. 2007, Duong et al. 2012). An increased risk of gastroschisis has been found with herpes infection and/or antiherpetic medication (Ahrens et al. 2013). Chlamydia and urinary tract infections are also associated with an increased risk of gastroschisis (Dewberry et al. 2020, Freitas et al. 2020). Similarly, limited, and yet consistent, evidence suggest that pseudoephedrine in early pregnancy is associated with an increased risk of gastroschisis (Werler, M. M. et al. 1992, Werler et al. 2002, Torfs et al. 1996). Maternal use of SSRI medication in early pregnancy is also associated with an increased risk of gastroschisis (Anthony Wemakor et al. 2015). Contrary to all these abovementioned factors, maternal obesity has been consistently associated with a significantly decreased risk of gastroschisis even though no explanation for this association has been found (Stothard et al. 2009, Khodr et al. 2013, Jenkins et al. 2014, Baer et al. 2015). Reports on the association of pregestational and gestational diabetes and the risk of gastroschisis remain controversial. A Canadian

study (Skarsgard et al. 2015) found history of gestational or pregestational diabetes to be associated with an increased risk of gastroschisis, while protective influence of diabetes was reported by US (Baer et al. 2015) and European (Given et al. 2017) groups.

Table 1. Influence of different exposures and factors on the risk of gastroschisis.

Increased Risk	Reduced Risk	Controversial
Young maternal age	Maternal obesity	Maternal diabetes
Alcohol		
Smoking		
Substance abuse		
Nulliparity		
Short cohabitation		
Pseudoephedrine		
SSRI		

2.2.4 Treatment

Most often (>90%) these infants have an antenatal diagnosis before delivery, allowing obstetrical, neonatal, surgical, and anaesthetic teams to prepare for initial care (Rossi & Prefumo 2013, Fleurke-Rozema et al. 2017). When the infant is born, vitality of the herniated bowel is confirmed, and the defect is most often covered with cling film to reduce heat and fluid loss. A nasogastric (NG) tube on free drainage and a rectal examination to evacuate meconium aids to decompress the intestines. Also, a minimum of one intravenous cannula is inserted. If the infant is not born in a paediatric surgical centre, transport is organised urgently after initial resuscitation. Subsequently, the infant is taken to operating theatre aiming for reduction of the bowel and primary closure of the defect with or without sutures (**Figure 2**). If primary closure is deemed impossible or too risky due to increased intra-abdominal pressure, a silo is placed or formed. The surgeon can choose between a preformed silastic silo or a custom-made, sutured silo. If a silo is placed, the bowel contents are then gradually reduced within the silo during the following days, and later closed when closure of the defect is deemed possible (Klein, Michael D. 2012). As all these infants will require parenteral nutrition (PN) for days or even weeks, placement of a central venous access should be considered at the time of primary operation, especially in cases with intestinal atresia. (Klein, Michael D. 2012) Enteral feeds can be started as soon as bilious NG tube aspirates cease.

The optimal method of closure is currently under debate, and several recent studies have addressed the advantages and disadvantages between sutureless and sutured abdominal wall closure. Prospective studies on this have not been published to date, but currently a US group is planning to conduct one. (Fraser et al. 2020) In retrospective cohorts and meta-analyses, sutureless closure appears to be associated with less general anaesthetics, antibiotic use, surgical site and deep infections, and decreased ventilator time and requirement for pain medication. (Youssef et al. 2016, Miyake et al. 2019, Grabski et al. 2019, Witt et al. 2019, Fraser et al. 2020) According to Miyake et al., sutureless closure can be considered and may be beneficial even after silo formation. (Miyake et al. 2019) The data on umbilical hernias requiring surgical repair is controversial. Sutureless closure had equivalent or superior outcomes regarding fascial closure according to systematic review and meta-analysis by Youssef et al. (Youssef et al. 2016) A retrospective single-centre cohort, however, had considerably more umbilical hernias requiring surgery with sutureless flap repair. (Witt et al. 2019) Given the concerns of the effects of general anaesthesia on the developing brain, sutureless closure should be considered especially in those cases where general anaesthesia can be avoided. (Grabski et al. 2019)

Gastroschisis is associated with abnormal intestinal motility, and introduction of enteral feeds may often take several weeks. During this period of dysmotility, nasogastric decompression and parenteral nutrition are required. To minimize the risk of oral aversion, it is important to introduce early oral stimulation. Necrotizing enterocolitis (NEC) is a risk even for full-term infants with gastroschisis. (Christison-Lagay et al. 2011) Long-term outcomes are generally excellent, and the majority will achieve normal growth and development after an initial catch-up period in early childhood. (Henrich et al. 2008)

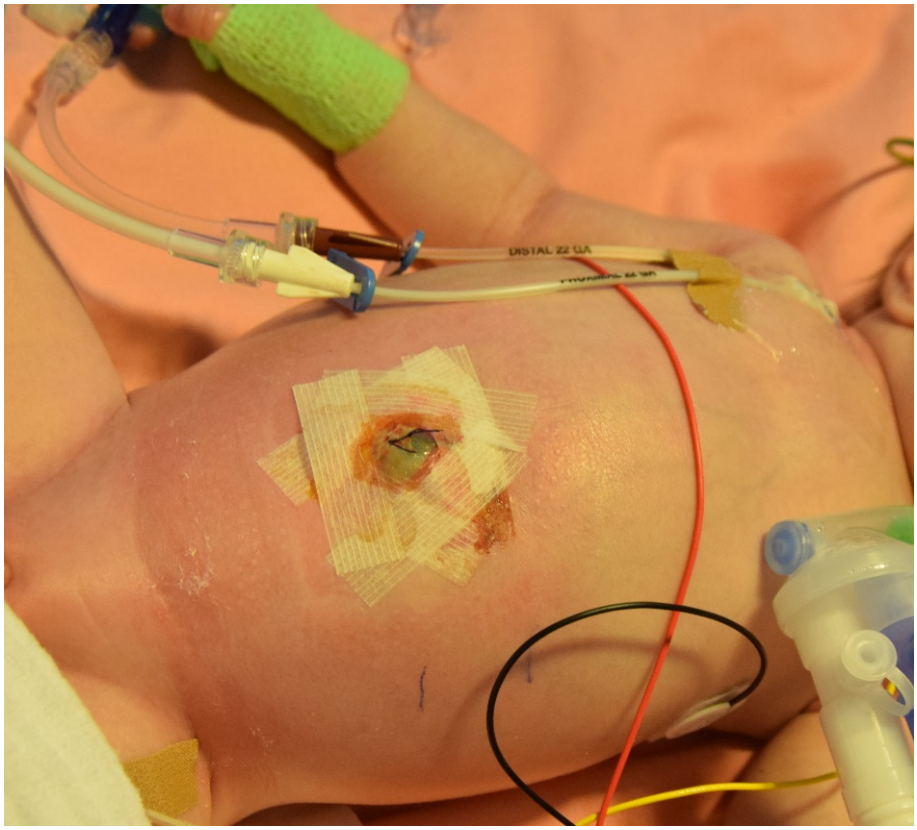

Figure 2. Post-operative situation in operating theatre after bowel reduction and sutureless closure of gastroschisis. Note the central venous line in the right internal jugular vein inserted by the anaesthetist with ultrasound guidance.

2.2.5 Associated Anomalies

In most cases gastroschisis is an isolated anomaly. However, so called complex gastroschisis with bowel atresia, damage, or obstruction occurs in 13 to 21% of the cases. (Bergholz et al. 2014, Mutanen et al. 2018, Bhatt et al. 2018) Up to one third of gastroschisis patients have associated anomalies including cardiac defects in 2 to 15%, among which ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA) are the most common. (Garne et al. 2005, Akhtar et al. 2012, Benjamin, B. & Wilson 2015, Benjamin, Bonna & Wilson 2014) Other associated anomalies in previous reports include central nervous system (2–10%, hydrocephaly, anencephaly, and spina bifida being the most common), musculoskeletal structures (<1–20%, limb reduction defects and arthrogryposis being the most common), genitourinary system (3–24%, hypospadias and renal agenesis being the most common), facial anomalies (1–3%, cleft lip ± palate), and

chromosomal abnormalities (<1–3%, trisomies and other syndromes) (Snyder et al. 2001, Klein, Michael D. 2012, Benjamin, Bonna & Wilson 2014). Due to the possibility of associated malformations, appropriate investigations, i.e. ultrasound of abdomen and spine, are performed during the stay at the neonatal unit, and cardiac echo usually prior to surgery.

2.2.6 Outcome

Pregnancies with gastroschisis are often complicated and at risk for miscarriage or stillbirth. It is estimated that foetal demise occurs in 2.5 to 15% of the pregnancies affected by gastroschisis (Brantberg et al. 2004, Nicholas et al. 2009, Fleurke-Rozema et al. 2017). Once born, however, the overall survival rates exceed 90% given that appropriate obstetric and neonatal care are provided (Lao et al. 2010, Owen et al. 2010, Cowan et al. 2012, Bhatt et al. 2018, Anderson, J. E. et al. 2018). Even mortality rates <5% have been reported with no statistical significance between simple and complex cases of gastroschisis (Bhatt et al. 2018, Anderson, J. E. et al. 2018). The condition of the bowel at the time of surgery is a predictor of a more prolonged hospital stay, morbidity, and mortality (Abdullah et al. 2007).

Table 2. Summary of prevalence rates and risk factors of gastroschisis reported in literature.

Author (data collection years)	**Country** Type of study (n=number of cases)	**Prevalence (per 10,000)**	**Main findings**
Dewberry et al. 2020 (2007 – 2016)	**USA** Retrospective case-control study (n=236)	-	Risk factors: Young maternal age, cigarette exposure, alcohol, and chlamydia infection
Freitas et al. 2020 (2013 – 2015)	**Brazil** Retrospective case-control study (n=57)	-	Risk factors: Alcohol, tobacco, and urinary tract infection
Stallings et al. 2019 (2012 – 2016)	**USA** Retrospective study (n=5,349)	4.3	Young maternal age (<25) underweight/normal weight
Kapapa et al. 2019 (2000 – 2011)	**Germany** Retrospective case-control study (n=36)	13.1 (in hospital)	Risk factors: young maternal age, short cohabitation time, antibiotics, alcohol consumption, and immune diseases
Chen et al. 2019 (1998 – 2013)	**Taiwan** Retrospective study (n=179)	0.50	Low prevalence
Short et al. 2019 (2006 – 2015)	**USA** Retrospective study (n=2,249)	4.2	Higher prevalence in counties with high opioid prescription rates
Wittekindt et al. 2019 (2010 – 2015)	**Germany** Retrospective study (n=55)	1.79	Comparable with previous data
Anderson et al. 2018 (1998 – 2011)	**USA** Retrospective case-control study (n=1,381)	2.7	Risk factors: Young maternal age and unspecified substance exposure
Bhatt et al. 2018 (2010 – 2014)	**USA** Retrospective study (n=8,700)	4.9	Increasing prevalence
Salinas-Torres et al. 2018 (2000 – 2014)	**Mexico** Retrospective study (n=10,287)	4.01	Increasing prevalence

Singh & Kumar 2017 (1992 – 2012)	**Barbados** Retrospective study (n=14)	2.22	High mortality (28.5%)
Bugge et al. 2017 (1989 – 2015)	**Greenland** Retrospective study (n=28)	10.7 (birth prevalence)	Increasing and highest reported prevalence of gastroschisis
Souther et al. 2017 (2008 – 2015)	**USA (Hawaii)** Retrospective study (n=71)	-	Pesticides may contribute to the development of gastroschisis
Given et al. 2017 (1995 – 2012)	**Europe** Retrospective case-control study (n=1,577)	-	Risk factors: antidepressant use, sexually transmitted infections, topical antivirals
Campaña et al. 2017 (1967 – 2013)	**Argentina** Retrospective case-control study (n=864)	-	High risk of gastroschisis related to repeated miscarriages
Kong et al. 2016 (1992 – 2009)	**Australia** Retrospective study (n=336)	3.3	Increasing prevalence
Wemakor et al. 2015 (1995 – 2009)	**Europe** Retrospective case-control study (n=413)	-	SSRI use increased risk
Benjamin & Wilson 2014 (1999 – 2008)	**USA** Retrospective study (n=1,831)	4.8	Large number with associated anomalies (32%)
Ahrens et al. 2013 (1997 – 2007)	**USA** Retrospective case-control study (n=941)	-	Risk factors: antiherpetic medication and/or herpes infection
Richardson et al. 2011 (1997 – 2005)	**USA** Retrospective case-control study (n=720)	-	Periconceptual alcohol consumption increased risk
Xu et al. 2011 (1996 – 2007)	**China** Retrospective study (n=1,601)	2.54	No change in prevalence
Whitehall et al. 2010 (1988 – 2007)	**Australia** Retrospective study (n=59)	3.2	Increasing prevalence
Mac Bird et al. 2009 (1997 – 2003)	**USA** Retrospective case-control study (n=485)	-	Moderate risk factors: tobacco, alcohol, and ibuprofen

Fillingham et al. 2008 (1997 – 2006)	**UK** Retrospective study (n=143)	4.28 (birth)	Increasing prevalence
Stoll et al. 2008 (1979 – 2003)	**France** Retrospective study (n=60)	1.79	Often isolated anomaly
Draper et al. 2008 (2001 – 2003)	**UK** Retrospective case-control study (n=165)	-	Risk factors: Tobacco, aspirin, and recreational drugs
Tan et al. 2008 (1993 – 2002)	**Singapore** Retrospective study (n=21)	0.46	Increasing prevalence
Loane et al. 2007 (1980 – 2002)	**Europe** Retrospective study (n=936)	0.54 → 2.12	Increasing prevalence
Laughon et al. 2003 (1997 – 2000)	**USA** Retrospective study (n=149)	1.96 → 4.49	Increasing prevalence
Salihu et al. 2003 (1992 – 1999)	**USA** Retrospective study (n=308)	1.43	Increasing prevalence
Bugge et al. 2002 (1970 – 1989)	**Denmark** Retrospective study (n=166)	1.33 (births)	Increasing prevalence
Stoll et al. 2001 (1979 – 1998)	**France** Retrospective case-control study (n=47)	1.76	Risk factor: medication during pregnancy
Suita et al. 2000 (1975 – 1997)	**Japan** Retrospective study (n=970)	0.13 – 0.47	Increasing prevalence

2.3 Omphalocele

Omphalocele or exomphalos is a congenital abdominal wall defect where the herniated bowels, and sometimes liver, are covered by a membranous sac consisting of three layers: inner and outer layers being continuation of peritoneum and amnion, respectively, and the middle layer which is called Wharton's jelly (Khan et al. 2019) **(Figure 3).** Both terms derive from Greek: *omphalos* (navel) and *cele* (hernia). Hence, the literal meaning of *exomphalos* is "outside the navel" and *omphalocele* is "hernia of the navel". The vast majority of the cases are picked up in antenatal ultrasound screening and as high as 96% detection rates have been reported (Fleurke-Rozema et al. 2017). In general, infants with omphalocele tend to be born prematurely (Gong et al. 2016), especially those with chromosomal defects (Marshall et al. 2015). The size of the defect and herniation varies markedly, ranging from minor bowel herniation (**Figure 3**) to giant omphaloceles, where the majority of abdominal contents are herniated (**Figure 4**). Males are affected more often by omphalocele than females (Marshall et al. 2015).

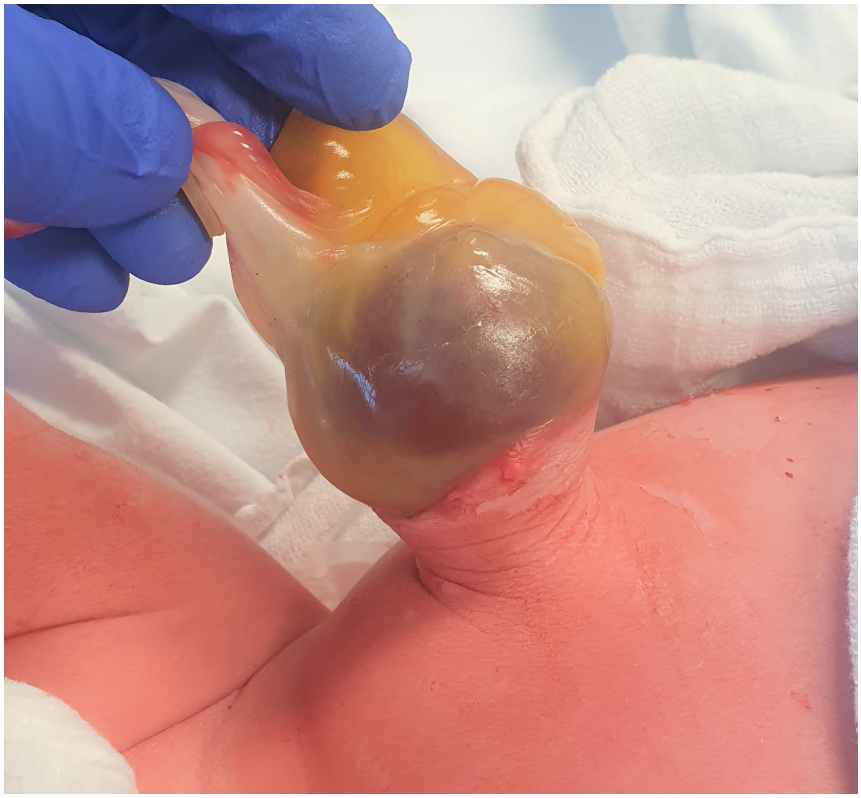

Figure 3. A small omphalocele with minimal herniation of abdominal contents.

2.3.1 Embryology

There are several theories on the embryologic basis of the development of omphalocele. The pathogenesis is thought to be related to the development of ventral body wall, the amnion, and the umbilical ring occurring in early weeks of pregnancy (Khan et al. 2019). Suggested theories include failure of union of the mesodermal septum (Margulies 1945), germinal disc defects (Herva & Karkinen-Jääskeläinen 1984), embryonic dysgenesis due to malformation of ectodermal placodes (Hartwig et al. 1989, Russo et al. 1993), and defective cell-signalling between the lateral and ventral body walls (Brewer & Williams 2004). The most widely accepted theory explaining the development of exomphalos is a malfunction of the ectodermal placodes combined with embryonic dysplasia (Khan et al. 2019).

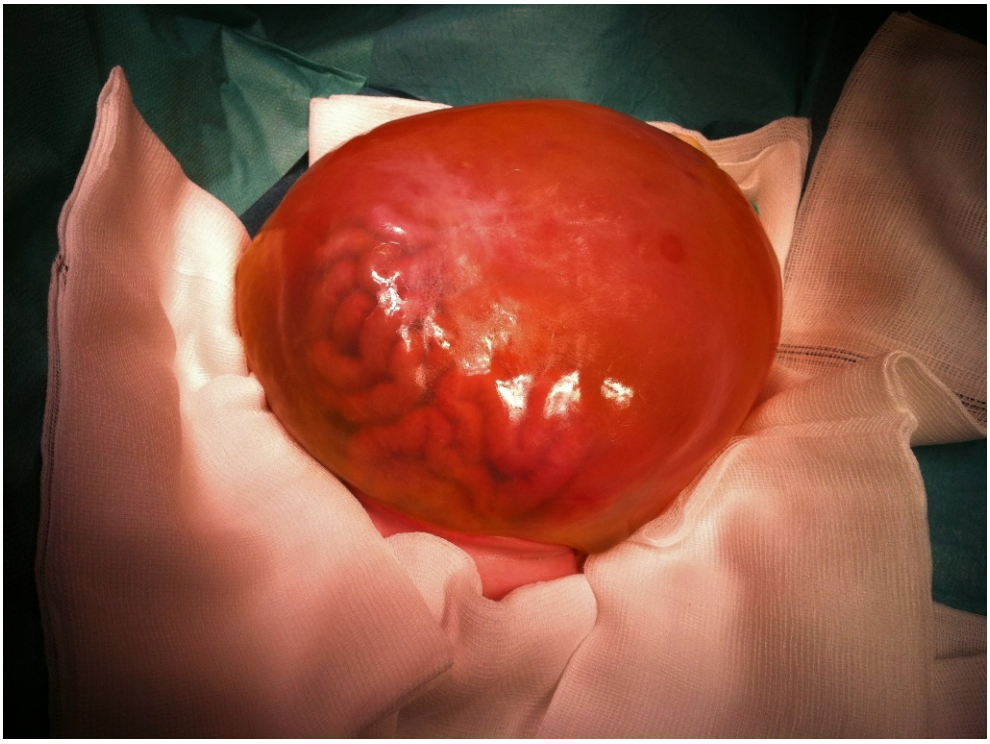

Figure 4. A giant omphalocele with herniated bowels covered by intact membranes.

2.3.2 Prevalence

The reported prevalence of omphalocele varies markedly in literature. Live birth prevalence rates ranging from 0.32 to 5.13 in 10,000 have been reported with no significant long-term trends in general (Gong et al. 2016, ICBDSR Office 2011, Li et al. 2015). A summary of the reported prevalence rates in our literature review can be found in **Table 4**. A recent US study (Mai et al. 2019) and another from Singapore (Tan et al. 2008) reported increasing prevalence in their studies differing from other findings. The incidence of omphalocele seen on ultrasonography at 14–18 weeks of pregnancy is as high as 1 in 1100 (Christison-Lagay et al. 2011). This discrepancy between numbers detected in antenatal screening and reported birth prevalence stems from high rates of foetal demise and terminations of pregnancy (Forrester & Merz 1999). Hence, the significant variations in the prevalence of omphalocele can be explained by differing cultures and practices regarding planned termination of pregnancy due to anomalies.

2.3.3 Risk Factors

Several risk factors for omphalocele have been identified in the literature **(Table 3)**. Both very young and advanced maternal age are known to be associated with an increased risk of omphalocele (Salihu et al. 2003, Frolov et al. 2010, Marshall et al. 2015). Similarly, maternal obesity and disorders of glycaemic control are well-recognized risk factors (Waller, D. K. et al. 2001, Waller, D. Kim et al. 2007). Also, history of miscarriages, as well as nulliparity, have been reported to be significant risk factors (Agopian et al. 2009, Duong et al. 2012, Campaña et al. 2017). Exposure to alcohol and smoking in early pregnancy have also been found to be associated with an increased risk of omphalocele (Bird et al. 2009, Feldkamp et al. 2014). Contrary to gastroschisis, exomphalos does not seem to be associated with low socioeconomic status (Kapapa et al. 2019). There are also some reports on maternal use of prescription drugs in the first trimester of pregnancy, and an increased risk has been associated with exposure to selective serotonin reuptake inhibitors (SSRI) (Alwan et al. 2007, Louik et al. 2007), asthma medication (Lin et al. 2012), and unspecified antibiotics (Kapapa et al. 2019). Occupational exposure to ionizing radiation increases the risk of omphalocele among other major structural birth defects (Lim et al. 2015). Additionally, male sex of the foetus/infant significantly increases the risk (Goldkrand et al. 2004, Bahado-Singh et al. 2011, Marshall et al. 2015). Folate and vitamin B12 are important in DNA methylation process, and variations in genes associated with them are associated with an elevated risk of omphalocele (Mills et al. 2012). As folic acid deficiency is a risk factor for several

birth defects, a US study found that grain fortification with folic acid decreased the risk for omphalocele along with several other anomalies (Canfield et al. 2005).

Table 3. Influence of different exposures and factors on the risk of omphalocele.

Increased Risk	Reduced Risk	Controversial
Young and advanced maternal age	Folic acid	Smoking
Maternal obesity		
Alcohol		
Nulliparity		
History of miscarriages		
SSRI		
Male sex		

2.3.4 Treatment

The optimal treatment of exomphalos depends on the size of the defect and on the presence of associated malformations. Large defects, i.e. giant omphaloceles (**Figure 4**), pose a great challenge and make up to 50–70% of the cases (Bauman et al. 2016). No consensus on the definition of a giant omphalocele has been reached. However, most surgeons define them as a defect larger than 5 cm in diameter (Whitehouse et al. 2010, Bauman et al. 2016). The size of the defect matters, because increased defect size is an independent predictor of mortality (Raymond et al. 2019). Ex Utero Intrapartum Treatment (EXIT) has also been proposed as an alternative treatment option for giant omphalocele and it appears to be effective and safe, yielding results that are comparable with the traditional approach. However, more experience is needed before it can be recommended more widely (Chen, X. et al. 2018).

The goal of the treatment is reduction of the herniated abdominal contents and closure of the defect. Visceroabdominal disproportion is the primary determinant when choosing the method of closure (Bauman et al. 2016). Primary closure generally consists of resection of the omphalocele sac, approximation of umbilical fascial tissue, and closure of the defect. In case of small defects (**Figure 3**), amenable to primary closure, this can often be done easily. However, primary closure should not even be attempted in cases with large tissue defects and massive visceroabdominal disproportion. Complications, such as abdominal compartment syndrome with respiratory compromise, bowel obstruction or ischaemia, or inferior vena cava obstruction, are common if primary repair is attempted with giant

omphalocele (Hatch & Baxter 1987, Lee et al. 2006, Eijck et al. 2008, Ein & Langer 2012). Furthermore, the risk of subsequent herniation is over 50% (Eijck et al. 2011).

Three distinct strategies for managing these cases are nonoperative, delayed closure; staged surgical closure; and serial taping followed by surgical closure. Reported methods of nonoperative closure include topical silver, iodine, manuka honey or aqueous eosin, and negative pressure wound therapy, while staged surgical closure has been performed with Proline silo, Silastic silo, and interposition mesh (Bauman et al. 2016). Complete epithelialization of the sac often takes months, but the resulting hernia can often be closed in a single operation, while staged surgical closure obviously requires several operations (Eijck et al. 2008). Serial taping can be performed bedside at NICU without anaesthesia, and the defect is later closed surgically after the viscera is completely reduced (Kogut & Fiore 2018). Currently it seems that nonoperative management with topical silver and delayed closure of the fascial defect is associated with lower mortality and shorter time to full feeds compared to staged surgical closure (Bauman et al. 2016). Serial taping appears to be a promising treatment modality for giant omphalocele (Kogut & Fiore 2018). However, no large series comparing these treatment methods exist.

After surgery, most patients will require mechanical ventilation postoperatively. Intra-abdominal pressure will decrease gradually when abdominal wall and bowel wall oedema resolves. Enteral feeds can begin when NG aspirates are no longer bilious (Christison-Lagay et al. 2011).

2.3.5 Associated Anomalies

Other organ anomalies and chromosomal abnormalities are often seen with omphalocele; according to previous studies in 27–88% of cases (Stoll et al. 2008, Ionescu et al. 2014, Marshall et al. 2015, Fleurke-Rozema et al. 2017). The most common association is with cardiac anomalies, which are seen in 7–50% (Greenwood et al. 1974, Bianchi 2010, Klein, Michael D. 2012, Marshall et al. 2015). Reported cardiac anomalies include VSD, ASD, ectopia cordis, tricuspid atresia, and coarctation of the aorta (Klein, Michael D. 2012). Association with Down syndrome has been reported, and chromosomal abnormalities can be found in up to 20% (Reddy et al. 1994, Klein, Michael D. 2012, Stoll et al. 2008). Also, musculoskeletal (4–25%, limb reduction deficiencies and club foot most common) and neural tube (4–30%, anencephaly and spina bifida most common) defects are more common (Ardinger et al. 1987, Loder & Guiboux 1993). Other organ systems involved are respiratory (1–4%, hypoplastic lungs), gastrointestinal (3–20%, atresia and duplication most common), genitourinary (6–20%, obstructive genitourinary defects, cloacal and bladder exstrophy most common), and facial (1–14%, clef lip ± palate) (Klein, Michael D. 2012). Pulmonary hypoplasia and/or hypertension is

associated with 9.8% of omphalocele cases according to a literature review, and its co-occurrence is associated with increased mortality (Saxena & Raicevic 2018). Omphalocele can also be associated with syndromes like Beckwith-Wiedemann Syndrome (BWS) and OEIS (Omphalocele, bladder Exstrophy, Imperforate anus, and Spinal defects) complex (Klein, MD 2012). BWS is an overgrowth syndrome with a predisposition for tumour development. Pentalogy of Cantrell is an extremely rare congenital anomaly where omphalocele is accompanied by ectopia cordis, lower sternal defect and heart malformations and diaphragmatic defect (Jnah et al. 2015).

2.3.6 Outcome

It has been estimated, that due to the high rates of planned terminations of pregnancy, an elevated risk of intrauterine foetal demise and high perinatal mortality, less than 10% of the antenatally detected omphaloceles reach the stage of operative repair (Lakasing et al. 2006, Marshall et al. 2015, Fleurke-Rozema et al. 2017). Co-occurring chromosomal abnormalities and organ anomalies are the best predictors of survival (Springett et al. 2014, Marshall et al. 2015). In isolated cases, one-year survival rates exceeding 90% have been reported (Springett et al. 2014, Marshall et al. 2015). Infant mortality (died before age of one year) ranges from 20 to 30% in those born with multiple anomalies, while 27–38% of the cases with chromosomal defects survive the first year (Salihu et al. 2003, Springett et al. 2014, Marshall et al. 2015). As omphalocele is seldom an isolated anomaly, the reported overall survival rates in literature range from 15 to 54% (Yazbeck et al. 1986, Byron-Scott et al. 1998, Stoll et al. 2001, Deng et al. 2014, Marshall et al. 2015). Most children with a small omphalocele recover well and do not have any long-term complaints (Christison-Lagay et al. 2011). However, up to 60% of patients with giant omphalocele suffer from persisting medical problems, including gastroesophageal reflux, feeding difficulties with failure to thrive, and recurrent chest infections (Koivusalo et al. 1999, Biard et al. 2004). We postulate that this may reflect the associated anomalies rather than omphalocele itself.

Table 4. Summary of the reviewed articles on omphalocele. Prevalence rates are given per 10,000 live births if not otherwise mentioned.

Author (data collection years)	**Country** Type of study (n=number of cases)	**Prevalence (per 10,000)**	**Main findings**
Stallings et al. 2019 (2012 – 2016)	**USA** Retrospective study (n=2,601)	2.1	Older (>40) and obese (BMI >30) mothers have higher risk
Mai et al. 2019 (2010 – 2014)	**USA** Retrospective study (n=1,270)	1.27	Increasing prevalence compared to previous periods
Kapapa et al 2019 (2000 – 2011)	**Germany** Retrospective case-control study (n=18)	6.6 (in hospital prevalence)	Hormonal treatment increased the risk
Wittekindt et al. 2019 (2010 – 2015)	Germany Retrospective study (n=47)	1.60	Trisomy 13 and 18, heart defects and prematurity increased early mortality
Saxena & Raicevic 2018	**UK** Review of literature (n=396)	-	Pulmonary hypertension, respiratory failure and ruptured sac increased mortality
Singh & Kumar 2017 (1992 – 2012)	**Barbados** Retrospective study (n=16)	2.53	Low mortality (12.5%)
Bugge et al. 2017 (1989 – 2015)	**Greenland** Retrospective study (n=4)	1.5	No trend
Campaña et al. 2017 (1967 – 2013)	**Argentina** Retrospective case-control study (n=438)	-	Previous repeated miscarriages increased the risk
Kong et al. 2016 (1992 – 2009)	**Australia** Retrospective study (n=166)	1.7	No change in prevalence
Marshall et al. 2015 (1995 – 2005)	**USA** Retrospective study (n=2,308)	1.92	Young (<20) and advanced (>35) maternal age, multiple gestation and male sex increased the risk
Reefhuis et al. 2015 (1997 – 2009)	**USA** Retrospective case-control study	-	SSRI increased the risk

Li et al. 2015 (1996 – 2010)	**China** Retrospective study (n=1,322)	1.50	No long-term trends, seasonality in rural areas
Lim et al. 2015 (1997 – 2009)	**USA** Retrospective case-control study (n=264)	-	Ionizing radiation increased risk
Springett et al. 2014 (2005 – 2011)	**UK** Retrospective study (n=671)	3.8 (per 10,000 births)	High prevalence
Benjamin & Wilson 2014 (1999 – 2008)	**USA** Retrospective study (814)	2.1	Large proportion had associated anomalies (80%)
Feldkamp et al. 2014 (1997 – 2007)	**USA** Retrospective case-control study (n=301)	-	Active smoking was not associated with increased risk, but second-hand smoke exposure increased the risk
Lin et al. 2012 (1997 – 2005)	**USA** Retrospective case-control study (n=154)	-	Asthma medication increased the risk
Mills et al. 2012 (1998 – 2005)	**USA** Retrospective case-control study (n=169)		Variations in folate and vitamin B12-related genes increased the risk
Agopian et al. 2009 (1999 – 2004)	**USA** Retrospective study (n=325)	2.16	Advanced maternal age and nulliparity as risk factors
Blomberg et al. 2009 (1995 – 2007)	**Sweden** Retrospective study (n=103)	-	Obesity (BMI >30) increased the risk
Mac Bird et al. 2009 (1997 – 2003)	**USA** Retrospective case-control study (168)		Modestly elevated risk among women who used alcohol and among women who were heavy smokers
Stoll et al. 2008 (1979 – 2003)	**France** Retrospective study (86)	2.57	Often associated with other malformations
Tan et al. 2008 (1993 – 2002)	**Singapore** Retrospective study (n=100)	2.17	Increasing trend

Waller et al. 2007 (1997 – 2002)	**USA** Retrospective study (n=177)	-	Obesity (BMI>30) increased risk
Alwan et al. 2007 (1997 – 2002)	**Canada** Retrospective case-control study (n=181)	-	SSRI increased risk
Louik et al. 2007 (1993 – 2004)	**USA** Retrospective case-control study (n=127)	-	SSRI increased risk
Canfield et al. 2005 (1995 – 2000)	**USA** Retrospective study (n=455)	-	Grain fortification with folic acid has reduced birth prevalence
Salihu et al. 2003 (1992 – 1999)	**USA** Retrospective study (287)	1.33	Decreasing trend
Watkins et al. 2003 (1993 – 1997)	**USA** Retrospective study (n=18)	-	Obesity (BMI>30) increased risk
Botto et al. 2002 (1968 – 1980)	**USA** Retrospective case-control study (n=41)	-	Maternal febrile illness in early pregnancy increased risk
Bugge et al. 2002 (1970 – 1989)	**Denmark** Retrospective study (258)	2.07 (per 10,000 births)	No trend
Stoll et al. 2001 (1979 – 1998)	**France** Retrospective case-control study (58)	2.18	Medication use more common among omphalocele mothers
Suita et al. 2000 (1975 – 1997)	**Japan** Retrospective study (970)	0.32 – 0.74	High number of associated anomalies (56%)

3 Aims

The aim of this thesis was to investigate epidemiology and risk factors of abdominal wall defects in Finland.

The thesis consisted of four separate studies, and their specific aims were:

I To assess the prevalence, mortality, associated anomalies, rates of planned termination of pregnancy, and to identify possible long-term trends of gastroschisis in Finland from 1993 to 2014.

II To assess the prevalence, mortality, associated anomalies, rates of planned termination of pregnancy, and to identify possible long-term trends of omphalocele in Finland from 1993 to 2014.

III To assess and identify potential maternal risk factors of gastroschisis, and especially to assess the safety and effects of the medications used during the first trimester of pregnancy in Finnish population.

IV To assess and identify potential maternal risk factors of omphalocele, and especially to assess the safety and effects of the medications used during the first trimester of pregnancy in Finnish population.

4 Materials and Methods

4.1 Methods

This thesis is a register study based on several national registers upheld by the Finnish Institute of Health and Welfare: the Finnish Register of Congenital Malformations, the Medical Birth Register, the Register of Induced Abortions, the Care Register for Health Care, and the Register of Visual Impairment and National Hospital Discharge Register complemented by the Cause of Death statistics collected by Statistics Finland. The data on maternal prescription medicine use was obtained from the Register on Reimbursed Drug Purchases upheld by the Finnish Social Insurance Institution (Kela). These registers receive information based on a legally compulsory announcement request on all health personnel in our country. These registers contain information on all terminated and born cases with congenital anomalies in Finland. Regarding stillbirths and other mortalities, the diagnoses are entered in the register according to the autopsy report if a postmortem examination has been performed; in other instances, a death certificate is utilized. As antenatally detected cases are not reported, we were not able to assess the detection rate of antenatal screening for abdominal wall defects.

After the concept of the thesis was agreed on with all members of the study group, we applied for study permits with the Finnish Institute for Health and Welfare and locally at Turku University Hospital. The data collection was done by the Finnish Institute for Health and Welfare, as only employees are allowed access to the register data. After the anonymised data was acquired, it was analysed with the help of two statisticians (Löyttyniemi and Kemppainen) under supervision of principal investigators (Raitio and Helenius). The first author (Raitio) drafted all the manuscripts included in this thesis and handled the submission processes and revisions as requested by the journals. Before being submitted to journals, the manuscripts were critically revised and accepted by all authors.

4.1.1 Antenatal Screening and Legislation

Every pregnant woman in Finland is entitled to two ultrasound scans during pregnancy. The first of these scans is done 10 to 14 weeks after conception. The second scan to screen for foetal anomalies takes place at 18 to 21 weeks (Klemetti & Hakulinen-Viitanen 2013). According to Finnish legislation, termination of pregnancy due to social circumstances can only be done before the 12th week of pregnancy. However, termination of pregnancy due to significant foetal anomaly(s) is permitted until the end of 24th week of gestation (Suomen laki). This procedure always requires authorization by the National Supervisory Authority for Welfare and Health (Valvira).

4.1.2 Epidemiology

The first two studies are mostly based on the Finnish Register of Congenital Malformations data. This registry has been maintained by the National Institute for Health and Welfare since 1963. As the "Declaration of Malformation" forms are received from the maternity and paediatric hospitals, the list of diagnosis is obtained and confirmed with the previously mentioned registries, and additional information (patient records, radiographs, photographs, specialist consultation, etc.) is requested if deemed necessary before entering the data to the register. All recorded diagnoses are evaluated, classified, coded, and double-checked by a medical geneticist, and the coverage and data quality of the register have been considered good in several studies (Greenlees et al. 2011, Artama et al. 2011, Syvänen et al. 2014).

The diagnoses in the register are coded according to the International Classification of Diseases and Health Related Problems (ICD) by the World Health Organization – both ninth and tenth revisions (ICD-9 and ICD-10) were used during our study period from January 1, 1993 to December 31, 2014. For our analysis, we searched the register for all the cases with codes 756.73 and 756.72 (ICD-9), or Q79.3 and Q79.2 (ICD-10) for gastroschisis and omphalocele, respectively, and included them in the study. The acquired data contained all live births, stillbirths, and planned terminations of pregnancy. However, the first three years of our study period contained information only on the live births, as the data on stillbirths and terminations of pregnancy only became available in 1997. The data on the Finnish Register of Congenital Malformations was then complemented with the data on the above-mentioned registers. Birth prevalence and total prevalence are given per 10,000 births, and live birth prevalence is given per 10,000 live births as defined by EUROCAT (EUROCAT Working Group 2019).

4.1.3 Case-control Studies

For our case-control studies, we included cases from January 1, 2004 to December 31, 2014, as the data on maternal Body Mass Index (BMI) only became available in the beginning of 2004. As maternal BMI is significantly associated with the risk of gastroschisis (Stothard et al. 2009, Khodr et al. 2013, Jenkins et al. 2014, Baer et al. 2015) and omphalocele (Waller, D. K. et al. 2001, Waller, D. Kim et al. 2007), it was important to include that data on our multivariable analysis on the risk factors of abdominal wall defects.

We selected all previously identified gastroschisis and omphalocele cases born between January 1, 2004 and December 31, 2014 for our case-control cohort. Five healthy controls matched for maternal age (±1 year), residency, and time of conception (±1 month) were randomly selected for each case from the Medical Birth Register. For the aborted foetuses, live-born, healthy controls were selected. All maternal risk factors in the register were analysed, including BMI, parity, smoking, illnesses and history of miscarriages.

The data on maternal prescription medicine use was obtained from the Register on Reimbursed Drug Purchases upheld by the Finnish Social Insurance Institution (Kela). The data on maternal drug purchases was limited to a time window of one month before conception and the first trimester of pregnancy. The initial analysis on maternal medication was done at the 4th level of the Anatomical Therapeutic Chemical (ATC) Classification System by WHO. Subsequently, we identified and selected those ATC groups with higher frequency of events among cases for further analysis.

4.2 Statistical Analysis

All risk factors were evaluated with chi-square test or Fisher's exact test. The average age of mothers who had a child with an abdominal wall defect was compared with the average age of all mothers who have given birth in Finland with one sample t-test. The change in live birth prevalence during our study period was evaluated with linear regression. Continuous variables were summarised with mean and standard deviation (SD). Categorical variables were summarised with counts (n) and percentages (%). For mortality, odds ratios (with 95% confidence interval) were calculated where possible.

For the case-control study, conditional logistic regression was used to evaluate different risk factors based on literature and data availability. First, univariate models were programmed, and finally multivariable models were created. All significant risk factors in univariate models along with risk factors reported in previous studies were included in multivariable models. Odds ratios (OR) along with adjusted odds

ratios (aOR) with 95% confidence intervals (CI) were calculated. Also, Fisher's exact test was executed to search potential risk factors. All statistical tests were performed as two-sided, with a significance level set at $p<0.05$. The analyses were performed using the SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

4.3 Ethical Aspects

As required by the Finnish national legislation, the use of the data was authorised by the National Institute of Health and Welfare after consulting the data protection authority. The approval of the Institutional Review board at Turku University Hospital, Turku, Finland, was also obtained before conducting this study. As no patients were contacted during these studies, no informed consent was required. All data was obtained and stored anonymously.

5 Results

5.1 Epidemiology

5.1.1 Gastroschisis

In our review, we identified 320 gastroschisis cases from 1993 to 2014 in Finland, including 235 (73.4%) live births, 16 (6.4%) stillbirths, and 69 (21.6%) planned terminations of pregnancy. Total prevalence of gastroschisis was 2.57 per 10,000 births. Birth prevalence (live births and stillbirths) was 1.85/10,000 and live birth prevalence was 1.73 per 10,000 live births. During our study period, the live birth prevalence of gastroschisis increased significantly, even though the number of stillbirths and abortions remained constant. (p=0.0018) – **Figure 5**. Gastroschisis was rarely associated with other birth defects, and almost 95% of cases were classified as 'simple gastroschisis'.

The majority of infants with gastroschisis were born slightly preterm, on 36th week on average. Caesarean section (N=146, 58%) was more common than vaginal delivery (N=105, 42%). Gastroschisis was significantly associated with lower than average maternal age (mean 24.3 [SD 4.6] years vs 30.0 years, p<0.001).

Infant mortality of gastroschisis was low, 7.7% (18/235). Simple gastroschisis had slightly lower mortality, 7.2% (16/222), while complex cases with bowel compromise and/or atresia had higher mortality (15%, 2/13). The mode of delivery, maternal obesity, diabetes and smoking had no impact on mortality. Interestingly, mothers who opted for termination of pregnancy were significantly older than those who decided to continue their pregnancy (mean age 28.8 [SD 6.4] years vs 24.3 [SD 4.6] years, p<0.001).

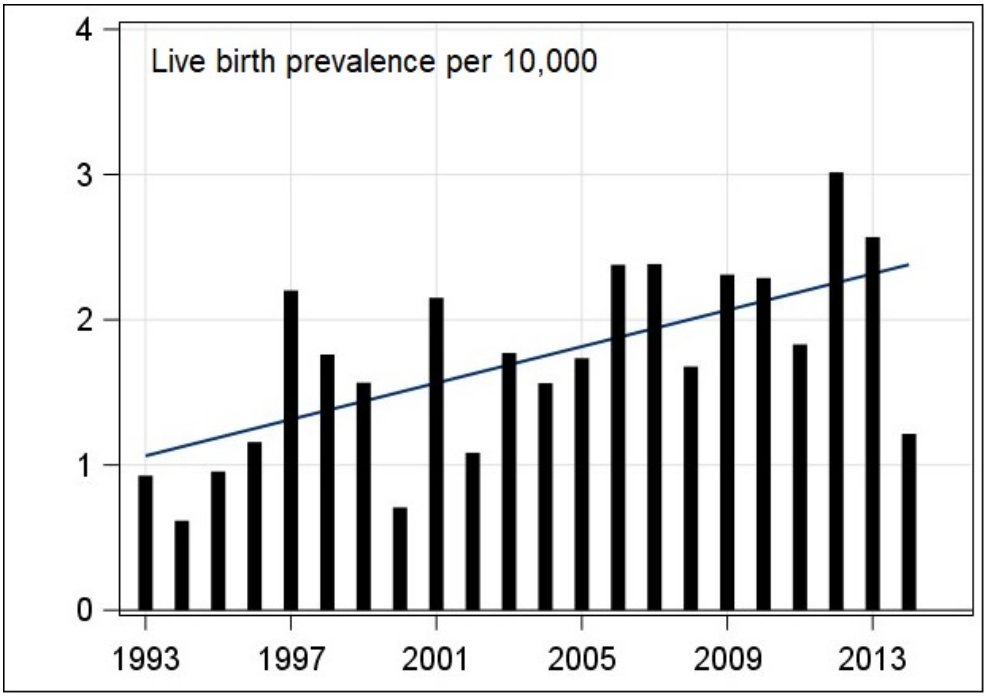

Figure 5. Increasing trend in live birth prevalence of gastroschisis in Finland.

5.1.2 Omphalocele

Our register search identified 600 cases with omphalocele: 332 (55%) abortions and 268 (45%) births, of which 229 (38%) were live births and 39 (6.5%) stillbirths. Total prevalence of omphalocele in Finland was 4.71 per 10,000 births with no consistent trend over time. Birth prevalence and live birth prevalence were much lower; 1.96 and 1.69 in 10,000 respectively (**Figure 6**). No changes in abortion rates were observed during our study period. However, termination of pregnancy was significantly more common in the southern parts of Finland, as presented in **Table 5**. Also, the maternal age was significantly higher in those who opted for termination than in those who continued with pregnancy (mean age 32.0 [SD 6.4] years vs 30.0 [SD 6.0] years, $p<0.001$).

On average, infants with omphalocele tend to be born prematurely (average 36.4 weeks of gestation), and in total, there were 135 (50%) premature babies in our cohort (<38 gestational weeks). Vaginal delivery was favoured in most cases (152 vaginal births vs 116 caesarean sections). Omphalocele is often associated with other major anomalies, as summarised in **Table 6**. Most common co-occurring anomalies were chromosomal abnormalities (trisomy 18, trisomy 13, and trisomy 21 being the most common), heart defects (VSD and ASD being the most common) and

central nervous system (hydrocephaly, anencephaly, and spina bifida being the most common) and gastrointestinal anomalies (intestinal atresia and cloacal anomalies being the most common). Interestingly, only 8 infants (3.0%) had Beckwith-Wiedemann syndrome. Congenital diaphragmatic hernia was found in total of 6 infants/foetuses (1.0%).

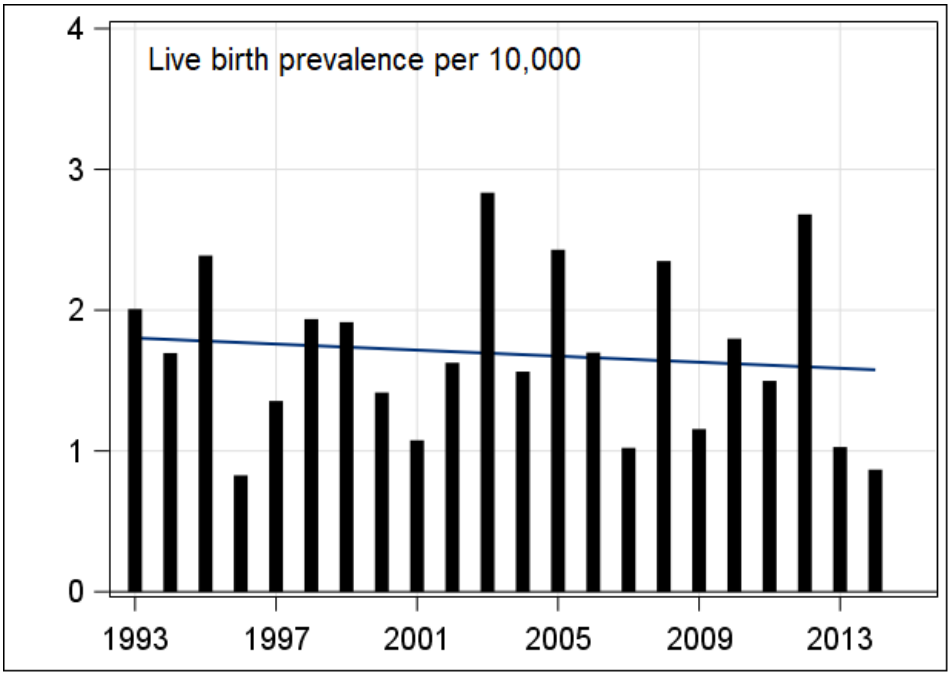

Figure 6. Live birth prevalence of omphalocele in Finland.

At the age of one year, 179 (78%) patients were alive. Hence, the overall infant mortality of omphalocele was 22%. Mortality was highest among those with chromosomal abnormalities. No differences between tertiary centres were detected (**Table 5**). However, there was a significant decline in the mortality rate during our study period after the first five years (p=0.03), as demonstrated in **Table 7**. Maternal diabetes (p=0.45), obesity (OR: 0.93, 95% CI 0.28 to 3.12), smoking (OR: 0.78, 95% CI 0.38 to 1.68), hypertension (p=0.59), and mode of delivery (OR for caesarean: 0.65, 95% CI 0.34 to 1.22) had no impact on the infant mortality.

Table 5. Case distribution of omphalocele cases in Finland from 1993 to 2014. No differences were found in survival. However, termination of pregnancy was significantly more common in the south coast of Finland (Helsinki and Turku) compared with the rest of the country (p=0.03).

Tertiary Centre	Number of live births	Infant mortality (%)	Abortion rate (%)
Helsinki	72	26.4	68.9
Turku	21	19.1	66.7
Tampere	21	25.5	48.5
Kuopio	40	17.5	51.1
Oulu	33	21.2	53.0

Table 6. The most common anomalies associated with omphalocele.

	Chromosomal	Heart	CNS*	Gastrointestinal	Urogenital	Skeletal
Born (n=268	12 (4.5%)	17 (6.3%)	4 (1.5%)	8 (3.0%)	8 (3.0%)	8 (3.0%)
Aborted (n=332	44 (13%)	4 (1.2%)	14 (4.2%)	4 (1.2%)	4 (1.2%)	4 (1.2%)
All (n=600)	56 (9.3%)	21 (6.3%)	18 (3.0%)	12 (2.0%)	12 (2.0%)	12 (2.0%)

* CNS: Central nervous system

Table 7. Survival and infant mortality of omphalocele in Finland 1993 – 2014.

	Number of cases	Infant mortality (%)
Isolated omphalocele	176	19.9
Multiple anomalies	41	12.2
Chromosomal abnormalities	12	83.3
Total	229	21.8
1995 – 1999	43	34.9
2000 – 2004	54	11.1
2005 – 2009	48	18.8
2010 – 2014	45	17.8

5.2 Risk factors

5.2.1 Gastroschisis

For the case-control study, we identified 188 cases of gastroschisis and compared them with 910 matched controls (see paragraph 4.1.2). In univariate analysis, nulliparity was a significant risk factor for gastroschisis, OR 1.65 (95% CI 1.14 – 2.39). Similarly, smoking appeared to increase the risk for gastroschisis, however not significantly: OR 1.35 (95% CI 0.92 – 1.99). Also, the use of oral pseudoephedrine (World Health Organization's ATC code R01BA) during the first trimester of pregnancy suggested an elevated risk of gastroschisis, OR 10.0 (95% CI 0.91 – 110). In Finland, pseudoephedrine is only available with a prescription and as a combination drug with different antihistamines (desloratadine, acrivastine or cetirizine) (Pharmaca Fennica 2019).

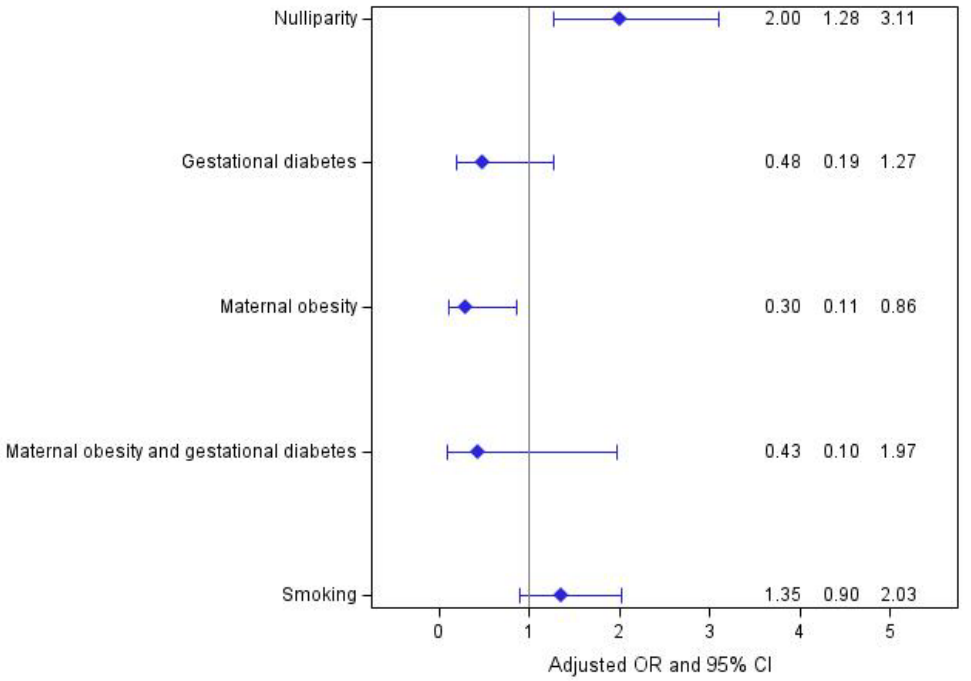

Figure 7. Adjusted odds ratios for maternal risk factors of gastroschisis. Significant association was observed with nulliparity and maternal obesity.

Maternal obesity was associated with a significantly lower risk of gastroschisis, OR 0.39 (95% CI 0.16 – 0.91) and maternal age for gastroschisis cases was significantly lower than mean maternal age in the Finnish population (mean 24.3 [SD 4.6] years vs 30.0 years, p<0.001). Also, gestational diabetes moderately decreased the risk of gastroschisis, OR 0.49 (95% CI 0.22– 1.09). As a strong interaction was observed between maternal BMI and gestational diabetes (p<0.001), we created new combination variables for multivariable models.

The associations were similar in our multivariable analysis: nulliparity, aOR 2.00 (95% CI 1.29 – 3.11), smoking, aOR: 1.32 (95% CI 0.88 – 1.97), and pseudoephedrine, aOR 5.45 (95% CI 0.49 – 60.8) increasing the risk, while obesity was protective, aOR 0.35 (95% CI 0.15, 0.83) – **(Figure 7)**. Analysing obesity and gestational diabetes separately revealed the risk to be associated with obesity rather than hyperglycaemia. All analysed maternal risk factors are summarised in **Table 8** and prescription drugs in **Table 9**. The number of previous miscarriages, maternal diabetes, the sex of the newborn/foetus, and other maternal medications in early pregnancy did not affect the risk of gastroschisis.

Table 8. Univariate analysis of the maternal risk factors for gastroschisis in Finland 1993 –2014.

	Number of Events		Odds ratio (95% CI)
	Cases (n=147–188)	Controls (n=880–910)	
Maternal Obesity (BMI >30)	7147 (4.8%)	93/880 (10.6%)	0.39 (0.16 – 0.91)
Maternal low body weight (BMI <18.5)	10/147 (6.8%)	59/880 (6.7%)	0.89 (0.43 – 1.85)
Nulliparity	129/188 (68.6%)	536/910 (58.9%)	1.65 (1.14 – 2.39)
Smoking	52/150 (34.7%)	248/891 (27.8%)	1.35 (0.92 – 1.99)
Previous miscarriage(s)	35/187 (18.7%)	137/910 (15.1%)	1.22 (0.79 – 1.89)
Pregestational diabetes	3 /154 (2.0%)	17/910 (1.9%)	1.09 (0.22 – 3.98)
Gestational diabetes	7/154 (4.6%)	86/910 (9.5%)	0.49 (0.22 – 1.09)
Male sex	86/153 (56.2%)	454/910 (49.9%)	1.39 (0.94 – 1.92)

Table 9. Univariate analysis of all analysed prescription drugs used in early pregnancy and their association with the risk of gastroschisis in Finland 1993 – 2014.

	Number of Events		Odds ratio (95% CI)
	Cases (n=172)	Controls (n=838)	
Penicillin	20 (11.6%)	104 (12.4%)	0.97 (0.58 – 1.62)
Non-steroidal anti-inflammatory drugs	12 (7.0%)	75 (9.0%)	0.72 (0.38 – 1.39)
Inhaled steroids	10 (5.8%)	36 (4.3%)	1.44 (0.70 – 2.95)
Hormonal drugs for infertility	2 (1.2%)	15 (1.8%)	0.70 (0.16 – 3.19)
Antihistamines	8 (4.7%)	24 (2.9%)	1.65 (0.70 – 3.89)
Pseudoephedrine	2 (1.2%)	1 (0.1%)	10.0 (0.91 – 110)

5.2.2 Omphalocele

Between January 1, 2004 and December 31, 2014, we found 359 cases of omphalocele and compared them with 1738 matched controls (see paragraph 4.1.2). In univariate analysis, nulliparity was a significant risk factor for omphalocele, OR: 1.46 (95% CI 1.15 – 1.86). There were 226 obese mothers (BMI ≥30) in our cohort (12.7%) and obesity was associated with a higher risk of omphalocele, OR 2.03 (95% CI 1.21 – 3.42). Similarly, maternal low body weight (BMI <18.5) was associated with the risk for omphalocele, OR 1.63 (95% CI 0.66 – 4.04). In addition, newborns/foetuses with omphalocele were more likely to be male, although it did not reach statistical significance, OR 1.27 (95% CI 0.87 – 1.87).

Table 10. Univariate analysis of all analysed maternal risk factors for omphalocele in Finland 1993 – 2014.

	Number of Events		Odds ratio (95% CI)
	Cases (n=122–359)	Controls (n=1662–1738)	
Maternal BMI ≥30	26/122 (21.3%)	200/1662 (12.0%)	2.03 (1.21 – 3.42)
Maternal BMI <18.5	8/122 (6.6%)	58/1662 (3.5%)	1.63 (0.66 – 4.04)
Nulliparity	167/359 (46.5%)	638/1738 (36.7%)	1.46 (1.15 – 1.86)
Smoking	17/128 (13.6%)	243/1703 (14.3%)	0.92 (0.50 – 1.70)
Previous miscarriage (1)	65/344 (18.9%)	304/1738 (17.5%)	1.14 (0.83 – 1.57)
Previous miscarriages (≥2)	35/344 (10.2%)	129/1738 (7.4%)	1.52 (1.00 – 2.31)
Pregestational diabetes	6/130 (4.6%)	39/1738 (2.2%)	1.35 (0.67 – 2.74)
Gestational diabetes	22/130 (16.9%)	200/1738 (11.5%)	1.35 (0.67 – 2.74)
Male sex	76/129 (58.9%)	866/1738 (49.8%)	1.27 (0.87 – 1.87)

Note: Missing values due to fewer data stored in the Register of Induced Abortions.

Oral use of extended spectrum penicillins (WHO's ATC Code J01CA: amoxicillin or pivmecillinam) during the first trimester of pregnancy had a protective influence on the risk of omphalocele, OR 0.44 (95% CI 0.25 – 0.77). The number of previous miscarriages, maternal diabetes, and smoking had no influence on the risk. Furthermore, no significant changes in risk were observed with the use of non-steroidal anti-inflammatory drugs (M01AB, M01AE), antihistamines (R06AE, R06AX), inhaled steroids (R01AD, R03BA), or the hormonal drugs used to treat infertility (G03DA, G03GA, H01CA, H01CC, L02AE). A summary of the analysed maternal risk factors can be found in **Table 10** and analysed prescription drugs in **Table 11**.

Table 11. Univariate analysis of all analysed prescription drug exposures in early pregnancy.

	Number of Events		Odds ratio (95% CI)
	Cases (n=328)	Controls (n=1656)	
Extended spectrum Penicillins	15 (4.6%)	151 (9.1%)	0.44 (0.25 – 0.77)
Non-steroidal anti-inflammatory drugs	23 (7.0%)	134 (8.1%)	0.87 (0.54 – 1.41)
Inhaled steroids	17 (5.2%)	95 (5.7%)	0.87 (0.50 – 1.52)
Hormonal drugs for infertility	14 (4.3%)	66 (4.0%)	1.10 (0.60 – 2.01)
Antihistamines	14 (4.3%)	77 (4.7%)	0.94 (0.52 – 1.70)

The protective effects of extended spectrum penicillins were confirmed in our multivariable analysis, aOR 0.15, (0.04 – 0.64), whereas nulliparity was not significantly associated with an increased risk (aOR 1.25, 0.80 – 1.95). Even though previous miscarriages were not associated with an increased risk in univariate analysis, history of two or more miscarriages was a statistically significant risk factor in the multivariable model (2.39, 1.10 – 5.18). Due to strong interaction ($p<0.0001$), a combination variable was created to analyse maternal obesity and both pregestational and gestational diabetes. An elevated risk was observed with both types of diabetes and maternal obesity and the risk accumulated further with co-occurrence of these two risk factors. **(Figure 8)**

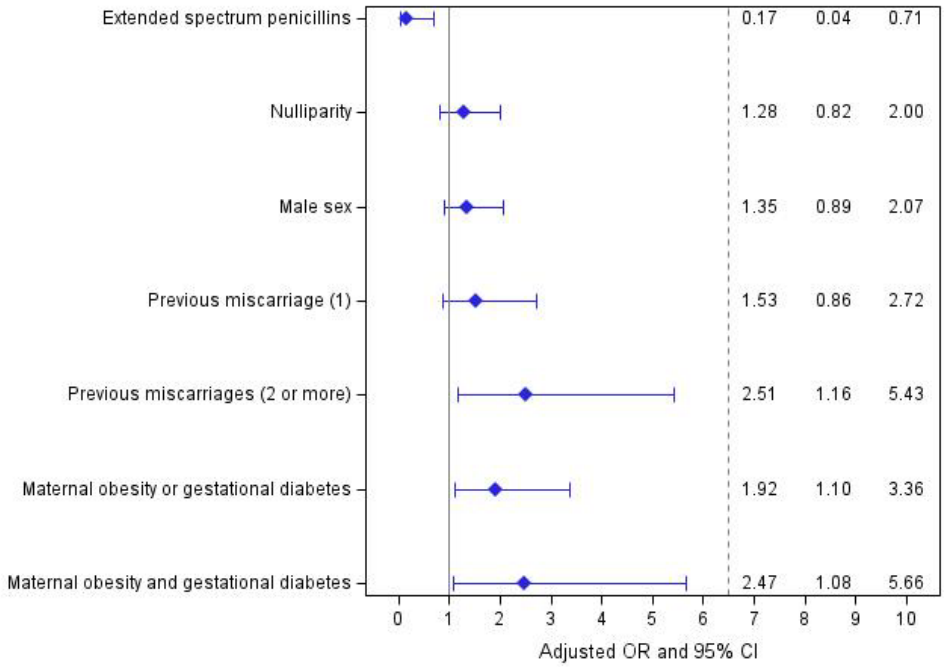

Figure 8. Adjusted odds ratios for maternal risk factors of omphalocele. Significant associations were observed with extended spectrum penicillins, multiple miscarriages, maternal obesity, and gestational diabetes.

6 Discussion

6.1 Gastroschisis

Our main findings on gastroschisis cohort were increasing prevalence, high rate of abortions, and low rates of associated anomalies and mortality. A higher risk of gastroschisis was associated with young maternal age, nulliparity, maternal smoking and pseudoephedrine use in early pregnancy. Maternal obesity significantly mitigated the risk of gastroschisis.

Increasing prevalence of gastroschisis is a well-recognised and worldwide phenomenon (Castilla et al. 2008, Jones et al. 2016, Brebner et al. 2018, Bhatt et al. 2018). Our study confirms these observations, as we also found a significantly increasing trend in live birth prevalence of gastroschisis in Finland from 1993 to 2014, while no significant trend was observed in the number of induced abortions. In addition, the prevalence has increased significantly from the reported numbers from the 1970s by Hemminki et al. (Hemminki et al. 1982). Even though all reports have been consistent on the increasing prevalence worldwide, no clear explanation has been found. However, the use of recreational drugs, a known risk factor for gastroschisis (Draper et al. 2008), has increased in Finland since 1992 (Alcohol and Drug Statistics 2018). Additionally, there has been a marked increase in the number of blended families in Finland since the 1990s (Väisänen & Helamaa 2014), and short length of sexual cohabitation appears to be associated with an elevated risk (Rittler et al. 2007). Furthermore, there has been a marked increase in genital herpes infections since the 1970s (Vuorenmaa et al. 2012), and the infection itself and/or the antiherpetic drugs have been found to be associated with a higher risk of gastroschisis (Ahrens et al. 2013). Similarly, chlamydia infections predispose to an increased risk of gastroschisis (Dewberry et al. 2020) and chlamydia infections have also become more common from 1995 to 2010 (Vuorenmaa et al. 2012). We speculate that altered exposure to certain risk factors could be associated with the increasing prevalence in Finland.

Infant mortality for gastroschisis in Finland was in keeping with previous reports, 7.7% (Lao et al. 2010, Owen et al. 2010, Cowan et al. 2012, Brindle et al. 2012, Overcash et al. 2014, Brebner et al. 2018). For obvious reasons, those with

complex gastroschisis had higher mortality, but due to a rather small number of patients, it did not reach statistical significance (p=0.26). Even though maternal obesity, smoking and diabetes have been identified risk factors for infant mortality in gastroschisis, their impact on mortality was no significant in our series. The proportion of stillbirths was in range with other studies, 6% (Brantberg et al. 2004, Nicholas et al. 2009, South et al. 2013).

Gastroschisis was an isolated anomaly in most cases and our data were concordant with previous studies (Nicholas et al. 2009, Bhatt et al. 2018, Brebner et al. 2018). However, we only had 5% of complex cases with bowel necrosis, atresia, or volvulus, while it is usually seen in 13 – 20% of cases according to literature (Bergholz et al. 2014, Bhatt et al. 2018, Mutanen et al. 2018). We believe it is possible, that co-occurring conditions and associated anomalies may not be reported as accurately as the main diagnosis in the registers.

There is a clear trend towards Caesarean delivery with pregnancies affected by gastroschisis, also in our series (Brebner et al. 2018, Lopez et al. 2019). As most cases are detected antenatally, this allows planning and selecting optimal mode and time of delivery. However, there is no evidence of the benefits of Caesarean section on clinical outcomes including mortality, sepsis, primary repair, duration of parenteral nutrition, and hospital stay (Nicholas et al. 2009, Kirollos & Abdel-Latif 2018, Lopez et al. 2019). We would encourage a practise where neonatal and surgical teams could take part in planning the optimal time and mode of delivery, as obstetricians may not have sufficient knowledge of the condition of the foetus/neonate and the treatment required after birth. Personal communication with colleagues verifies that this type of practise is currently provided in many of the university hospitals in our country.

Rates of abortion for any reason vary markedly due to regional practises related to culture, religion, and legislation. Generally, termination rates for gastroschisis vary from 5 to 14% (Nicholas et al. 2009, Ekin et al. 2015, Fleurke-Rozema et al. 2017). Our study revealed that Finland has, to the best of our knowledge, the highest rate of planned termination of pregnancy due to gastroschisis. In our series, 22% of cases were terminated. If those not detected in prenatal screening had been excluded, the proportion of families opting for abortion would have been even higher. We found this high abortion rate controversial, as gastroschisis was often an isolated anomaly in our series, and mortality rates were also low. We hypothesise that this might be due to insufficient antenatal counselling provided for the families when they how pregnancy is complicated by gastroschisis. We believe that it would be beneficial for all the families with a pregnancy affected by gastroschisis to meet both neonatal and paediatric surgical teams to discuss the risks and required treatment associated with this condition.

Young maternal age was a significant risk factor for gastroschisis, and several previous reports support this finding (Loane et al. 2007, Vu et al. 2008, Chabra et al. 2011, Robledo-Aceves et al. 2015). Consistent with previous reports, we also found nulliparity to be a significant risk factor (Rittler et al. 2007, Duong et al. 2012). However, as Rittler et al. compared epidemiologic variables between primiparae and multiparae, and between those who had and had not changed partners, only length of cohabitation showed significant risk (Rittler et al. 2007). They found no significant risk associated with nulliparity or change of paternity alone, and speculated that some antigenic or immunologic factors could be involved in the origin of gastroschisis.

Smoking is one of the most commonly agreed upon risk factors of gastroschisis (Draper et al. 2008, Hackshaw et al. 2011, Perry et al. 2019, Hawkins & Baum 2019) known to alter the mechanical and functional properties of placental arteries, which may compromise the foetal placental blood flow (Clausen et al. 1999). In our series, the risk associated with smoking did not reach statistical significance, possibly due to limited number of exposures. It seems evident, however, that smoking is associated with an increased risk of gastroschisis. A recent US study also found that tobacco tax increases reduced the prevalence of gastroschisis among other birth defects (Hawkins & Baum 2019).

Even though we had a small number of exposures in the pseudoephedrine group, our results support earlier findings regarding the association between an elevated risk of gastroschisis and pseudoephedrine (Werler et al. 1992, Torfs et al. 1996, Werler et al. 2002). Pseudoephedrine is a vasoconstrictive decongestant (Brunton et al. 2017), available in Finland only with a prescription and combined with antihistamines (Pharmaca Fennica 2020). As the risk did not increase with exposure to antihistamines alone, we believe that the influence is associated with the vasoconstrictive characteristics of pseudoephedrine. Both smoking and pseudoephedrine have vasoactive influence. Having both as risk factors supports the theory of disruption of umbilical vasculature in early pregnancy being the origin of gastroschisis.

Protective influence of maternal obesity on the risk of gastroschisis has been established in several studies (Stothard et al. 2009, Khodr et al. 2013, Jenkins et al. 2014, Baer et al. 2015). Due to direct correlation between maternal age and weight, a systematic review published in JAMA speculated that the decreased risk of gastroschisis in obese mother would be caused by the inverse correlation of risk of gastroschisis and maternal age. However, we also found maternal obesity to be protective despite having age-matched controls. Hence, maternal obesity appears to be an independent protective factor for gastroschisis regardless of maternal age as reported by Baer et al. (Baer et al. 2015) Previous studies have associated maternal diabetes with both an increased (Skarsgard et al. 2015) and a decreased (Baer et al.

2015, Given et al. 2017) risk of gastroschisis. According to our results, it appears that protective influence could be associated with obesity rather than diabetes. Regardless, hyperglycaemia does not seem to be associated with an increased risk.

6.2 Omphalocele

The main findings on our omphalocele cohort were high mortality among those with chromosomal defects, but relatively good outcome without. We also found that isolated cases were more common in Finland than previously reported. Regardless, omphalocele is often associated with other anomalies, and therefore abortion is often chosen. Maternal obesity and history of previous miscarriages increase the risk for omphalocele. We found the use of extended spectrum penicillins during the first trimester of pregnancy to be associated with a significantly lower risk of omphalocele.

Live birth prevalence of omphalocele is strongly dependant on the abortion rates. However, the prevalence in Finland remained constant during our study period, and similar static trends have been also reported earlier (ICBDSR Office 2011, Li et al. 2015, Marshall et al. 2015, Gong et al. 2016). Our prevalence trend in Finland was decreasing, but not statistically significantly. A similar observation was also made in two US studies previously (Salihu et al. 2003, Marshall et al. 2015). This might be at least partially explained by improved antenatal detection rates, as abortion rates nearly doubled in the Netherlands after their prenatal screening program was introduced (Fleurke-Rozema et al. 2017). Another possible explanation could be that in western countries the influences of folic acid and/or vitamin B12 deficiencies are currently only seen among those with variances in genes related to them (Canfield et al. 2005, Mills et al. 2012). The proportion of planned terminations was also high in our cohort, 55%. However, this is keeping with other reports in western countries (Brantberg et al. 2005, Nicholas et al. 2009, Fleurke-Rozema et al. 2017).

Interestingly, maternal age for those who opted for termination of pregnancy was significantly higher than the maternal age of those who decided to continue with the pregnancy. In our series, this trend was seen in pregnancies with both gastroschisis and omphalocele. It has been speculated that older women may have greater concerns with potential offspring health (Virgo & Sear 1997). They may also feel more pressured to undergo the antenatal examination and act according to the findings (Kelhä 2009).

To our surprise, only 23% of our omphalocele cases had associated anomalies, while previous studies have reported other anomalies among 27–88% of the cases (Stoll et al. 2008, Ionescu et al. 2014, Marshall et al. 2015, Fleurke-Rozema et al. 2017). Similarly, we also had a lower number of abnormal karyotypes in both aborted foetuses (13%) and born infants (5%) comparing with 17–49% aneuploidy

rates in other reports (Brantberg et al. 2005, Marshall et al. 2015, Fleurke-Rozema et al. 2017). Even though our register data quality has been validated to be accurate and to have high coverage, we speculate that there might be some reporting bias especially among stillbirths, as those were all classified as isolated cases of exomphalos. Alternatively, it is possible that death certificates have been created in these instances according to the apparent diagnoses without requesting a postmortem examination.

The mortality related to omphalocele is best predicted by the presence of co-occurring chromosomal abnormalities and organ anomalies (Springett et al. 2014, Marshall et al. 2015). Our overall mortality of 22% is at the lower range of mortality rates reported in previous studies (15–54%) (Yazbeck et al. 1986, Byron-Scott et al. 1998, Stoll et al. 2001, Deng et al. 2014, Marshall et al. 2015). Infant mortality among cases with chromosomal abnormalities ranges from 27 to 38%, while in our cohort only 17% survived the first year. On the other hand, cases with multiple anomalies in our cohort had infant mortality of only 12%. Both may be affected by a reasonably low number of cases in these two groups. Isolated cases in our cohort had a 20% infant mortality. However, as previously mentioned, there may be some degree of reporting bias involved.

The reports on the association between maternal medication and omphalocele have been contradictory (Alwan et al. 2007, Källén & Olausson 2007). There is limited evidence on the elevated risk associated with maternal asthma medication (Lin et al. 2012) and unspecified antibiotics (Kapapa et al. 2019). In our series, maternal use of inhaled steroids was not associated with an elevated risk of omphalocele, and the use of oral extended spectrum penicillins significantly mitigated the risk both in univariate and multivariable analysis. Previously, maternal febrile illness has been found to be a risk factor for omphalocele (Botto et al. 2002). As half of omphalocele cases are born prematurely (Raitio et al. 2020) and chorioamniotic microorganisms are also more likely to be found from women with preterm labour (Hillier et al. 1988), it is possible that chorioamnionitis could be associated with both prematurity and omphalocele. Additionally, one dose of amoxicillin given at birth has been found to significantly reduce the prevalence of umbilical hernias in a case-control study on newborn piglets (Yun et al. 2017). We speculate that microbiological factors may play a role in the pathogenesis explaining the protective role of penicillins.

Maternal obesity is a well-established risk factor for omphalocele and several other birth defects, including spina bifida, hypospadias, heart defects, anorectal malformations, limb reductions, and congenital diaphragmatic hernia (Watkins et al. 2003, Waller, D. Kim et al. 2007, Blomberg & Källén 2010, Auger et al. 2020). The mechanism remains unclear. However, there is substantial evidence provided by both human and animal studies that disorders of glycaemic control are responsible

for an increased risk of structural birth defects (Becerra et al. 1990, Eriksson et al. 2003). Therefore, it has been speculated that similar mechanisms may be responsible for the elevated risk of birth defects in obese mothers (Waller, D. Kim et al. 2007). According to our results, both obesity and diabetes are associated with an increased risk, and co-occurrence of these risk factors accumulates the risk.

There is also limited evidence that maternal smoking is a risk factor for omphalocele. According to previous reports, an elevated risk has been associated with heavy smoking (Bird et al. 2009) and second-hand smoke exposure (Feldkamp et al. 2014). Paradoxically, Feldkamp et al. (2014) found no risk to be associated with active smoking, and no dose-response relationship was observed. In keeping with this and the results of a German group (Kapapa et al. 2019), maternal smoking was not significantly associated with an increased risk of omphalocele in our study. Even though male sex is a known risk factor for omphalocele (Goldkrand et al. 2004, Bahado-Singh et al. 2011, Marshall et al. 2015), the association was not significant in our series.

6.3 Limitations

The main limitation in all the studies in this thesis is their retrospective design. Furthermore, they all rely on the accuracy of the national registers. On the other hand, as already mentioned earlier, the data quality and coverage of these registers have been considered good in several national and international studies (Gissler et al. 1995, Pakkasjärvi et al. 2006, Leoncini et al. 2010, Greenlees et al. 2011, Artama et al. 2011, Syvänen et al. 2014, Kela 2019). As gastroschisis and omphalocele are both apparent congenital anomalies with little risk of misdiagnosis, we believe that the cases are recorded in an accurate manner. However, there may be some bias regarding the co-occurring anomalies, especially among stillbirths and those who died in early days of life. We speculated on this possibility after noticing that all stillbirths with omphalocele were reported as “isolated omphalocele”, which is unlikely to be the case. This could be explained by doctors creating death certificates without requesting a postmortem examination. Similarly, there was a disproportionate amount of mortalities among cases reported as isolated omphaloceles, while cases with reported multiple anomalies had higher infant mortality. These factors were the main limitations and the source of possible bias in the first two studies (I & II) of this thesis.

Studies III and IV aimed to assess and identify risk factors for abdominal wall defects. Hence, the possible underreporting of associated anomalies did not influence these results. However, we had to limit these studies to cover years 2004 – 2014, even though the data on maternal medication was available for the whole study period from January 1993. Maternal BMI is significantly associated with the risk of

both gastroschisis and omphalocele, and became available in the register only in January 2004. Hence, to be able to create reliable multivariable models, we had to, unfortunately, limit the data on risk factors for the last ten years of our study period. An additional limitation regarding our data on maternal prescription drugs is that even though the data itself is accurate and limited to the critical time window of one month before conception and the first trimester of pregnancy, we had no means of confirming if the mothers actually used the drugs they purchased. The other limitation of our risk factor analysis was the lacking data on socioeconomic status and alcohol consumption, both of which are recognized as risk factors for abdominal wall defects (Bird et al. 2009, Richardson et al. 2011, Bronberg et al. 2020, Freitas et al. 2020, Baldacci et al. 2020).

Regarding statistical analysis, we believe that the biggest risk of bias comes from analysing several different potential risk factors, which unavoidably increases the risk of coincidence, rather than true association, explaining the statistically significant findings. However, our results were in keeping with previous reports for the most part regarding the risk factors for both gastroschisis and omphalocele.

6.4 Future considerations

Several studies have aimed to explain the worldwide increasing trend in prevalence of gastroschisis. Our findings did confirm the increasing prevalence but failed, however, to provide an explanation. According to our findings, maternal use of prescription drugs does not appear to significantly increase the risk of gastroschisis. Hence, we feel that an explanation for this trend should be sought elsewhere.

Further studies are warranted to confirm our novel findings regarding the association of extended spectrum penicillins and the risk of omphalocele. If our results are confirmed, microbiological factors should be considered as a potential etiological explanation behind the failure of closure of the umbilical ring and development of omphalocele.

6.5 Prevention strategies

To minimize the risk of abdominal wall defects, the prevention strategies should be aimed at those risk factors that can be influenced. Smoking increases the risk for gastroschisis, and a US study has already shown that cigarette tax increases effectively reduced the number of birth defects (Hawkins & Baum 2019). Folic acid deficiency, a risk factor for several birth defects (Canfield et al. 2005), is already taken into account in our prenatal clinics. Maternal obesity is a significant risk factor for several birth defects with gastroschisis as an exception. Gestational diabetes also

increases the risk of birth defects, and these two risk factors have a strong interaction, as our results have shown. Similarly, alcohol consumption is a known risk factor for both gastroschisis and omphalocele. According to our results and previous studies, the majority of prescription drugs are safe regarding the risk of abdominal wall defects. However, certain drugs should be used cautiously, if at all, by women trying to conceive. Special consideration should be given to the use and necessity of SSRI drugs and pseudoephedrine during early pregnancy. Also, attention should be paid to sexual health and sexually transmitted diseases, as both chlamydia and herpes infections increase the risk of gastroschisis, and their rates are rising in Finland.

In conclusion, several risk factors for abdominal wall defects have been identified, but the majority of them are challenging to influence, as they are related to a western lifestyle and diet. However, cigarette tax increases could provide a method to reduce the risk of several birth defects. The potential role of extended spectrum penicillins in the pathogenesis of omphalocele suggests an interesting topic for future research. Similarly, the mechanism behind the association of maternal obesity and reduced risk of gastroschisis needs to be further explored.

7 Summary/Conclusions

The prevalence and mortality rates of both gastroschisis and omphalocele in Finland are comparable with those reported in other high-income countries. Hence, we conclude that the quality of care in Finland for these anomalies is good.

The following conclusions have been drawn based on the results of our studies:

1. The prevalence of gastroschisis is increasing in Finland, and despite low mortality rate, a high number of pregnancies are terminated.
2. Survival rates of omphalocele in Finland are high, and isolated cases are more common than previously reported. Termination of pregnancy is more commonly chosen in Southern Finland compared with the rest of the country.
3. Young maternal age and nulliparity are significant risk factors for gastroschisis, while maternal obesity mitigates the risk. No significant risk was observed with any maternal prescription drug exposures.
4. Maternal obesity and history of repeated miscarriages increase the risk of omphalocele. Extended spectrum penicillins significantly reduced the risk of omphalocele, and this novel association warrants further studies.

Acknowledgements

Friday June 3rd, 2016 was a sunny summer day that also marked the beginning of this project as we drove to Helsinki with my supervisor, professor Ilkka Helenius, to meet with our collaborators at the Finnish Institute for Health and Welfare (THL). A lot has happened since that day, and there are several people without whom this project would never have been possible.

First, I want to express my gratitude to my supervisor, professor Ilkka Helenius. You have provided everything that a PhD student can dream of from excellent supervision to financial support. My impatient personality has especially enjoyed that no email or text has gone unanswered for more than 24 hours, no matter the circumstances. You have my utmost respect both in clinical and academic fields, and it has been a great pleasure to work and to continue working with you.

The data collection was done exclusively by THL employees, with irreplaceable contributions from professor Mika Gissler and Dr Maarit Leinonen. I am most pleased to have been able to work with them. I also want to thank Dr Anna Hyvärinen for her co-operation in this project, especially for her input in obtaining study permits and data acquisition.

From the beginning of 2019, I have had the pleasure to work with the crucial members of our statistical team, Eliisa Löyttyniemi and Teemu Kemppainen. Their exceptional efforts with data analyses has made it possible for me to concentrate on my academic and clinical work simultaneously. The expertise of Dr Johanna Syvänen has been invaluable allowing us to avoid several pitfalls with the register data. I also want to thank all my other co-authors Asta Tauriainen, Ulla Sankilampi, and Kari Vanamo.

This study would never have been possible without funding. Financial support from the Clinical Research Institute HUCH facilitated the data analyses mainly done by Teemu Kemppainen. Personally, grants from Clinical Research Institute HUCH, Emil Aaltonen Foundation, and Turku University Foundation made my study leaves possible allocating time for research.

I am grateful for my understanding and supporting boss, adjunct professor Olli Pajulo, who has been very flexible with my leaves related to research particularly. I also feel very blessed to share my working days with all my colleagues. I want to

thank Marianna Nikoskelainen especially for taking the sole responsibility of our patients in my absence.

I want to express my gratitude to the encouraging members of my follow-up committee, professor Liisa Lehtonen and professor Ville Peltola. Also, I thank my pre-examiners, adjunct professor Annika Mutanen and adjunct professor Satu-Liisa Pauniaho, for their thorough advice and revisions, and their help in finalising this thesis.

Last but also most importantly, I want to thank my family. My parents, Eija and Matti Raitio – you have provided us a home, a safe and loving environment to grow up in. I have had the privilege to share my childhood with three amazing siblings, Tuomo, Tuovi, and Jenni. I am extremely proud of all of you and looking forward to sharing the coming years with you.

Barösund, Midsummer Day, June 20, 2020
Arimatias Raitio

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UNIVERSITY OF TURKU

Painosalama Oy, Turku, Finland 2020

ISBN 978-951-29-8116-8 (PRINT)
ISBN 978-951-29-8117-5 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)