A RETROSPECTIVE REVIEW OF THE OUTCOMES OF GASTROSCHISIS AT A TERTIARY HOSPITAL IN CAPE TOWN.

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Thesis presented in fulfillment of the requirements for the degree of Masters in Medicine (MMed) in the Faculty of Medicine and Health sciences at Stellenbosch University

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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the owner of the copyright thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Date: December 2017

I, the undersigned, hereby declare that the work contained in this assignment is my original work and that I have not previously, in its entirety or in part, submitted it any other university for a degree.

Date: December 2017

Signature: Andrew Van Eck

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ABSTRACT

Background

The incidence of gastroschisis (GS) is rising and the outcomes in low to middle income countries are believed to be poor. Many studies from developed countries have evaluated prognostic factors and outcomes of GS, however there is little data from the developing world.

Aim

To determine the outcome of neonates treated for GS in a tertiary neonatal service in South Africa.

Methods

A retrospective case series of neonates admitted from January 2004 to July 2015 to the neonatal intensive care unit (NICU) at Tygerberg Children's Hospital, Western Cape was conducted. Of the 39 cases, full clinical data was available for 31. All had surgery (primary closure or silo placement with delayed closure) and initial total parenteral nutrition (TPN). Main outcomes assessed were mortality rate, sepsis rate, time to full enteral feeding, occurrence of bowel related complications and the development of parenteral nutrition associated cholestasis (PNAC).

Results

Of the 31 neonates with GS, five (16%) cases were complex GS. Two (6.4%) neonates died. The culture proven sepsis rate was 46% and overwhelming infection was the most common cause of death. Seventy-one percent had no bowel related complications and the majority (67%) achieved full enteral feeding by 21 days. Six (24%) developed PNAC.

Conclusion

The outcome of GS in a single center tertiary hospital is comparable to that in high-income countries. The mortality and bowel complication rate is low, however there is a high rate of sepsis. To reduce mortality, strict infection prevention control is mandatory.

OPSOMMING

Agtergrond

Die insidensie van gastroskese styg en die uitkomste in lae to middle inkomste lande is swak. Baie studies vanaf ontwikkelde lande het die prognostiese faktore en uitkomste van gastroskese ge-evalueer maar daar is min data op hierdie gebied.

Doel

Om die uitkomste van neonate met gastroskese te evalueer in n tersiere neonatale diens in Suid Afrika.

Metodiek

n Retrospektiewe gevalle studie van neonate toegelaat vanaf Januarie 2004 tot Julie 2015 tot die neonatale intensiewe eenheid by Tygerberg Kinder Hospitaal, Wes Kaap is onderneem. Nege-en-dertig gevalle is geindentifiseer waarvan 31 gevalle volledige kliniese rekords gehad het. Alle babas het chirurgie ondergaan (primere sluiting of 'silo' plasing met vertraagde sluiting) en binneaarse voeding. Hoofuitkomste beoordeel was sterftesyfer, infeksiekoers, tyd tot volle enterale voeding, voorkoms van derm verwante komplikasies en die ontwikkeling van binneaarse voedings verwante cholestase.

Resultate

Van 31 neonate met gastroskese, was daar 5 (16%) met gekompliseerde gastroskese. Twee neonate het gesterf. Die kultuur positiewe infeksie insidensie was 46% en oorweldigende infeksie was die mees algemeenste oorsaak van sterfte. Ee-en-sewentig present (71%) het geen derm verwante komplikasies ontwikkel nie en die meerderheid (67%) het volle enterale voedings teen 21 dae bereik. Ses (23%) het binneaarse voedings verwante cholestase ontwikkel.

Gevolgtrekking

Die uitkomste van gastroskese in n enkel tersiere hospitaal in Suid Afrika is vergelykbaar met die van hoe-inkomste lande. Die sterftesyfer en buik-verwante komplikasie syfer is laag, maar daar is n hoe infeksie insidensie. Om die sterftesyfer te verminder, is streng infeksiebekamping verpligtend.

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List of Abbreviations

BMI – Body mass index

CRP - C-reactive protein

EXO - Exomphalos

GS - Gastroschisis (GS)

HREC - Health Research Ethics Committee

IUGR - Intrauterine Growth Restriction

IUFD - Intrauterine Fetal Death

NICU - Neonatal Intensive Care Unit

NEC - Necrotising Enterocolitis

PN - Parenteral Nutrition

PNAC - Parenteral Nutrition Associated Cholestasis

SGA - Small for Gestational Age

SMOF – Soybean oil, Medium-chain triglycerides, Olive oil, Fish oil

TEF - Time To Total Enteral Feeding

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Chapter 1: INTRODUCTION

Gastroschisis (GS) is a serious congenital anomaly involving the full thickness of the anterior abdominal wall. In this neonatal anomaly, the small intestine, and occasionally the stomach, colon, liver and spleen are outside of the body without a membranous protective sac[1].

Simple GS occurs as an isolated defect, whereas complex GS is associated with other gastrointestinal anomalies such as intestinal atresia, perforation, necrosis or volvulus[2]. Urgent treatment is required to minimize abdominal fluid losses, decrease the risk of infection, and prevent additional damage to the exposed bowel.

GS remains a challenging surgical emergency in neonates. The management protocols have gradually evolved and improved over the years, but the principles of safe bowel reduction, cosmetically acceptable closure of the abdominal wall defect and proper nutritional support; remain the same.[3]
Complexities in the care of infants with GS in the developing world relate to factors such as prematurity, late referral to capable tertiary centers, surgical challenges with respect to the type of defect closure, lack of modern supportive facilities and sepsis.[3]

The impact of GS on patients, families, and the health care system in general is enormous. There is a need, especially in developing countries, to evaluate maternal factors such as maternal age, substance abuse, socioeconomic status, as well as neonatal factors such as gestational age at delivery, medical and surgical management and complications, which may affect the outcome of neonates with GS. Knowledge of these factors in the context of a developing country will assist in optimising the perinatal management of neonates with GS.

Chapter 2: LITERATURE REVIEW

Gastroschisis occurs in approximately 1 in 4000 live births and is the most common abdominal wall abnormality in the neonatal period, with significant morbidity and even mortality in some settings[1, 2].

Over the past 20 years, the prevalence of gastroschisis has increased internationally[4,5,6,7,8]. In Western Europe and North America the incidence increased from one in 2000 to one in 4000 births [9, 10]. Kirby et al[11] found that the incidence of gastroschisis increased since the mid-nineties from 3.6 per 10 000 live births to 4.9 per 10 000 live births in the period 2006 to 2012.

In South Africa, a retrospective analysis conducted at Pretoria Academic Hospital and Kalafong Hospital in Pretoria, from March 1981 to December 2001, showed that the admission rate of GS had risen dramatically at these two hospitals and in fact rose above that of exomphalos (EXO) [12].

Improved antenatal detection has allowed for more definitive neonatal and surgical management at centers capable of handling the delivery of these neonates[13]. While short-term survival rates have been reported as being greater than 90%, the morbidity in terms of short- and long-term adverse outcomes is still significant [2, 14 15].

Environmental factors such as teratogens, poor antenatal care, maternal infections and a younger maternal age have been associated with the increased incidence of gastroschisis[1]. It has been shown that a maternal age below 20 years is a major risk factor for gastroschisis [6, 7] with an incidence of around 11,45% per 10 000 live births [16]. Primigravida status, low socioeconomic status, poor maternal nutritional status with low body mass index (BMI), smoking and substance abuse have been identified as other notable risk factors [16].

The pathogenesis of GS is poorly understood. In 2012, Lubinsky proposed a dual pathogenesis based on a structural vascular predisposition and oestrogen-related thrombophilia as possible contributors to the risk of GS. He suggested that the normal involution of the right umbilical artery creates a localized predilection to a

thrombotic event, leading to weakening of the umbilical ring and creating an area of possible herniation. Oestrogen-related thrombophilia is implicated in the pathogenesis given that oestrogen levels in early pregnancy are shown to be higher in women who are younger, nulliparous or have a lower BMI [17].

Phytoestrogens is a class of nutrients potentially associated with the aetiology of GS. They are structurally similar to oestrogens, thus produce oestrogenic effects and are found in diets high in soy products, some types of seeds and nuts.

Wadhwa et al found a modest association of maternal phytoestrogen intake with the risk of GS, and thus provides some support to the hypothesis by Lubinsky, that maternal oestrogenic exposures may increase GS risk [18]. (Wadhwa et al 2016)

A retrospective review conducted by Overcash et al[19] on factors associated with the outcomes of gastroschisis, demonstrated that prenatal predictors such as intrauterine growth restriction (IUGR) oligohydramnios, and bowel dilatation on ultrasonography were not found to be predictors of adverse neonatal outcomes. Other variables such as the presence of meconium stained liquor, small for gestational age (SGA), 5 minute Apgar score and other fetal anomalies were also not predictors of adverse outcomes. However, gestational age, prematurity and maternal smoking were associated with adverse neonatal outcomes. In Zimbabwe, the GS-related mortality was 84% in 2013 and was associated with well-known perinatal risk factors, such as low birth weight, preterm birth and teenage mothers [20].

Diagnosis

Fetal ultrasound is a highly sensitive investigation to identify abdominal wall defects. The EUROCAT study reported a 90% sensitivity for gastroschisis detection across Europe (Garne et al., 2005). The typical sonographic feature of gastroschisis is multiple loops of bowel floating freely in the amniotic fluid.

Antenatal predictors of outcome

Little evidence exists regarding the optimal antenatal surveillance and monitoring strategies once the diagnosis of gastroschisis is made and current practices, such as regular ultrasound surveillance, are variable. Ultrasound monitoring of growth,

umbilical artery Doppler and bowel diameter measurements may assist in the early detection of complications and possibly reduce mortality [21]. Tower et al[22] conducted a systematic review of the prognosis of isolated gastroschisis with antenatal bowel dilatation and found that there was no difference in perinatal outcome compared to those infants without bowel dilatation.

Timing of Delivery

There is no consensus with regard to the appropriate timing and mode of delivery for the neonate with gastroschisis.

It has been shown in animal models that amniotic fluid exposure in utero is quite damaging to the bowel. This intestinal damage may result in diminished motility and absorptive capacity of the bowel; consequently affected neonates may require prolonged parenteral nutrition after birth [23].

Those who advocate for early delivery believe that prolonged bowel exposure to amniotic fluid increases the risk of complications and therefore recommend elective preterm delivery[24, 25]. Baud et al[26] found that induction of labour at 37 weeks of gestation was associated with lower rates of sepsis, bowel damage, and neonatal death compared with pregnancies managed expectantly beyond 37 weeks of gestation.

Overcash et al[19] found that neonates born preterm had a higher rate of parenteral nutrition (PN) related cholestasis, and those born before 35 weeks of gestation were most at risk for adverse outcomes such as neonatal death, bowel related complications [intestinal stricture, atresia or ischaemia and necrotising enterocolitis (NEC)]. Furthermore, those neonates with adverse outcomes invariably had longer hospitalisation, prolonged ventilation and delayed initiation of feeds.
However, in a randomized controlled trial of elective preterm delivery of fetuses with gastroschisis, Logghe et al[27] showed no difference in outcome between elective delivery at 36 weeks of gestation compared with cases where spontaneous delivery took place.

Gestation

As with other studies, Overcash et al[19] demonstrated a higher rate of preterm births with about 60% of neonates with gastrochisis being delivered before 37 weeks gestation in that study. The majority of these preterm births (47%) were due to spontaneous preterm labour, followed by caesarian section for abnormal fetal heart tracing (19%). It was also shown that there were fewer adverse outcomes in neonates delivered at 37 weeks gestation or beyond and the majority of adverse events occurred in neonates delivered at less than 35 weeks gestation[19].

In a meta-analysis of 54 studies describing the rate of intrauterine fetal death (IUFD) in gastroschisis, the overall rate of IUFD was 4,48 per 100,while the rate of IUFD for pregnancies beyond 36 weeks of gestation was1.28 per 100 [28].

Surgical management

In an attempt to improve outcome many studies have tried to identify modifiable factors that influence outcome. Over the last 20 years, it has become apparent that the presence of 1 or more intestinal complications, such as atresia, volvulus, perforation or necrosis, places the patient in a high-risk category and is associated with a worse outcome [2, 29].

The surgical management is influenced by whether the GS is simple or complex. As previously mentioned, simple GS is an isolated defect where the bowel is considered to be in a good condition and amenable to primary surgical closure or the application of a preformed spring loaded silo. The standard management of GS used to be immediate primary closure; however, this practice has now largely been replaced by the placement of a preformed, spring-loaded silastic silo followed by the gradual reduction of the abdominal organs and delayed closure of the primary abdominal wall defect [30].

Primary repair has the advantage of allowing for more immediate closure, reduced length of hospital stay as well as intensive care stay and less time to achieve full feeds. On the other hand, a staged closure using a preformed silo has the advantage of

decreasing the risk of abdominal compartment syndrome, which in turn shortens the duration of ventilation, reduces bowel ischaemia and decreases the incidence of necrotizing enterocolitis [30].

An electronic survey conducted amongst second year residents in North American and Canadian paediatric surgery training programs, found that primary closure was the treatment of choice in more than 70% centres, while routine silo placement was in 24% of centres. In this survey, the most common silo-related complications were dislodgement, the inability to achieve primary fascial closure and intestinal injury [31].

Complex GS refers to GS in which the bowel is either inflamed, adherent with peel, dilated, perforated, atretic, ischaemic or necrotic. In these cases, primary closure may not be achieved in up to 50% of cases and these patients generally require a more staged management with silo application. This allows for bowel recovery and then further staged bowel surgery in the form of a stoma formation, bowel resection and finally bowel anastomosis to re-establish gastrointestinal continuity [32].

In a study by Hashish and Elhalaby in Egypt, of the 52 neonates with GS that were treated over a 12-year period, primary closure was possible in 56% of patients, with the remainder undergoing a staged reduction with delayed closure. More patients required ventilation post primary closure but the time to initiation of enteral feeding and achievement of full feeding was earlier in this group. The duration of hospital stay was significantly longer for patients who had a staged reduction [3].

Due to transient gut dysmotility, enteral feeding is delayed. Therefore, for all types of GS, central venous access is essential to achieve parenteral nutrition (PN). The use of PN alone or in combination with enteral nutrition in neonates is effective in providing sufficient nutrients to maintain growth in the ill newborn infant. Many studies have noted that the timely initiation of enteral nutrition is pivotal to outcome optimization in gastroschisis. The best outcomes are observed when feeds are started within 7 days post-closure [33]. Cholestasis is a frequent complication of TPN and the etiology of the liver disease is unknown and likely multifactorial [34, 35].

Outcomes

In Europe and North America mortality is low, postnatal survival rates up to one year are as high as 96% in the USA [32]. In Africa, the reported mortality for infants with GS is 40 – 60% in contemporary series [12]. Studies in Zimbabwe and Nigeria have reported overall mortality rates of 84% and 60% respectively [20, 36].

In complex GS, the mean duration of hospital stay is 105 days, double that of simple GS; and the survival after complex GS is approximately 89%. The majority of patients achieve full oral feeding by 2 years in the US [32].
In an observational study conducted by Van Manen et al[37] over a period of 3 years, other complications noted on follow up included sepsis (37%), NEC (10%), parenteral nutrition related cholestasis (PNAC) (25%), and short bowel syndrome (13%). The management of short bowel syndrome in the context of complex GS is very difficult and the overall survival rate depends on the length of the remaining bowel post operatively [38].
In contrast to this, where sub-Saharan Africa data is available, the mortality has been shown to be high (33% - 100%) [39]. GS presenting to Pretoria Academic Hospital had a mortality rate of 38,7 % [11]. Durfee et al[40] found that only about 16% of GS patients had an uncomplicated post-operative course, with a mean hospital stay around 53 days. Bowel related complications followed by infectious complications were the most frequent problems encountered.

Chapter 3: RESEARCH JUSTIFICATION

There is a paucity of literature and research evaluating the outcomes of GS in the developing world and particularly in South Africa.

Although there are many studies that have evaluated the prognostic factors affecting the outcome of GS, these results have not been applied to the South African population.

The World Health Organization has indicated, that as infectious diseases and malnutrition are brought under control in developing countries, congenital malformations will assume a greater importance as a cause of mortality and morbidity among infants and children, as has been the case in the developed world. Therefore, there is the need to determine the outcome of children treated for their congenital abnormalities and investigate which reversible complications occur that can be prevented to improve these neonates' outcome. It has been proposed that GS can be used as a bellwether on the standard of neonatal surgery enabling neonatal surgical services in different regions of the world to be compared [41].

The patient demographic profile at Tygerberg Children's Hospital differs from that evaluated in other international studies. Poor socio-economic circumstances, including high rates of illicit drug use, and the heavy burden of teenage pregnancy, may in fact influence the long-term outcomes of GS in this population.

The outcomes of this study were compared to those outcomes described internationally. By understanding the factors that contribute to the morbidity and mortality of GS in our setting, we will be able to improve treatment in an environment with limited resources.

Chapter 4: RESEARCH DESIGN AND METHODOLOGY.

A. Aim

The outcome of neonates treated for GS in a tertiary hospital in a middle-income country will be similar to those experienced in a high-income country.

The aim of the study was to determine the outcome of neonates treated for GS in a tertiary care neonatal service situated in the Western Cape, South Africa and the factors contributing to outcome.

B. Outcomes and Objectives

Primary outcome of the study:
The primary aim of the study was to determine the mortality rate of neonates treated for GS in a tertiary neonatal service in the Western Cape and ascertain the risk factors linked with mortality.

Secondary outcomes:
The secondary aim was to establish the factors which are associated with prolonged need for total parenteral nutrition (TPN), prolonged hospital stay and sepsis and whether there was any difference in outcomes (death, prolonged TPN, cholestasis, sepsis) in silo treatment with delayed closure compared to primary closure.

The objectives of the study:
1. Determine the GS admission rates to the neonatal intensive care unit, and by using the annual reports, to calculate the incidence of gastroschisis at Tygerberg Children's Hospital.
2. Calculate the GS survival rate/ mortality rate at Tygerberg Children's Hospital.
3. Describe the demographic features of the study population such as gestational age, gender, maternal age and drug use, associated congenital anomalies.
4. Describe the neonatal outcomes such as postoperative bowel complications; development of sepsis and total parenteral nutrition (TPN) related complications.

5. Document the factors contributing to adverse outcomes, such as the duration of hospital stay, the number of ventilator days, duration and complications of TPN, and the initiation and attainment of full feeds.

C. Study Setting

This was a retrospective, descriptive, hospital based case series of all neonates referred to or diagnosed with gastroschisis at Tygerberg hospital, from 1st January 2004 till 31st July 2015.

Tygerberg Children's Hospital is the tertiary referral hospital for approximately half of the Western Cape Province. In the hospital 50 000 neonates are delivered per annum (2014) of which 2629 are admitted to the neonatal wards for care. In addition, approximately 400 neonates are referred to the hospital for tertiary neonatal care (2014 Annual Report).

All neonates (up to the age of 10 days) born with gastroschisis in Tygerberg Hospital or referred from other hospitals with GS and admitted to the Neonatal Intensive Care Unit (NICU) were included in the study. These patients were identified form the NICU admissions register. The time frame of the study was from 1 January 2004 to 31 July 2015.The study sample was drawn from this population.

D. Study design and Time Frame

This was a retrospective, descriptive, hospital based case series. The study investigated neonates with GS admitted to the neonatal intensive care unit over a 10-year period, from 1st January 2004 till 31st July 2015.

E. Study Population and Sampling

Neonates included in the study

All neonates (up to the age of 10 days) with the diagnosis of GS admitted to the NICU in Tygerberg Children's hospital were included. The patients without clinical data and those with exomphalos were excluded. Neonates who received post-natal surgery outside the hospital, prior to admission to the NICU were also excluded.

F. Data Collection and Analysis

Data capture

Clinical data was extracted from the patient folders, clinical notes and the neonatal intensive care unit admissions register. All collected data was recorded on a case recording form (See Appendix 1) in an Excel spreadsheet, using a specific data scoring sheet (See Appendix 2).

Demographic information (date of birth, gender), maternal age, tobacco and drug abuse; and perinatal variables including gestational age and birth weight at delivery, preterm labour, mode of delivery, and whether the delivery was elective, were collected. Available antenatal sonar reports were evaluated for evidence of intrauterine growth restriction, bowel dilatation and for the presence of other intestinal pathology.

Data pertaining to the surgical intervention were collected which included whether the defect was simple or complicated, the size of the defect, the method of closing the defect (silo method, primary closure of a combination) and complications related to the surgery (bowel related complications, wound sepsis, wound breakdown) and the need for further surgery. The bowel related complications assessed included, abdominal compartment syndrome, bowel perforation, NEC and whether there was adhesive bowel obstruction.

Adverse neonatal outcomes were recorded including: length of NICU stay, duration of mechanical ventilation, days to initiation of enteral feeds, time to full enteral feeds, duration of PN, complications of PN (including PNAC), bouts of presumed sepsis and bouts of proven sepsis.

The bowel related complications assessed included, abdominal compartment syndrome, bowel perforation, wound breakdown, NEC and whether there was adhesive bowel obstruction.

Case Definitions

- Prematurity was defined as a gestational age less than 37 completed weeks and low birth weight as a birth weight less than 2500g.
- IUGR was defined as an estimated fetal weight less than the 10th percentile on antenatal sonar.
- Spontaneous labour defined by the onset of regular uterine contractions without mechanical or pharmacological stimulation.
- Simple and Complex (intestinal atresias, perforation or stricture) gastroschisis were categorized according to the definition of Molik et al [25]. If 1 or more of the following conditions were diagnosed at birth or during the initial hospitalization, intestinal atresia, stenosis, volvulus, perforation or gangrene, the patients were labeled as complex gastroschisis. . If these conditions were not present, patients were labeled as simple gastroschisis
- The silo method of closure was defined as gradual reduction of the herniated abdominal contents with the use of a silo, followed by delayed surgical closure of the abdominal wall defect.
- Primary closure was defined as immediate surgical closure of the defect following reduction of the herniated bowel.
- TEF was defined as receiving the total caloric need of the infant enterally, at a total intake of 150ml/kg/day. The aim in this study was to achieve TEF by 21 days post closure.
- PNAC was defined as a conjugated bilirubin level >34 umol/l in this study.
- Presumed sepsis was defined as a clinical suspicion or a raised C-reactive protein (CRP) without a causative organism isolated.
- Proven sepsis was defined as a positive blood or tissue culture.

Statistical analysis

Statistical analysis was performed using Statistica® version 12 (Statsoft) and a p-value < 0.05 was considered to be statistically significant.

Descriptive statistics

Variables are described using means with standard deviations (for continuous data or ranges where appropriate) or frequencies and percentages (for categorical data).

Inferential statistics

Means of continuous data were compared using the Students t Test. Categorical data was compared with the Chi Square (X_2) test.

G. Ethical Considerations

This study was conducted according to the ethical guidelines and principles of the International Declaration of Helsinki[42], the South African Guidelines for Good Clinical Practice and the South African Medical Research Council Ethical Guidelines for Research. Patient identity remained anonymous throughout and a study number was allocated to each participant.

As this study was a retrospective review of patient folders, a waiver of individual informed consent was requested and obtained from the Health Research Ethics Committee (HREC), University of Stellenbosch. There was minimal risk to the study subjects and the investigator was never in contact with any of the study patients.

The HREC, of the University of Stellenbosch, approved the Study protocol (Ethics Reference number **S15/05/103**) on the 22nd July 2015.

The intention of this study was to gain more insight into the critical outcomes of gastroschisis at Tygerberg hospital and how this may reflect differences between a hospital in the developing world compared to the developed world. Prognostic factors that could improve the management of neonates with gastroschisis were identified. This may guide clinicians when counseling parents regarding the morbidity of these

neonates, in terms of hospital stay, feeding and also follow –up. The findings in this study may not benefit the patients in this study but may be of benefit to future patients with gastroschisis.

Since this was a retrospective study, there were minimal risks to the patients. The risk entailed having access to information that the investigator would not have had otherwise. However, all data captured was kept strictly confidential and securely stored in a password-protected computer.

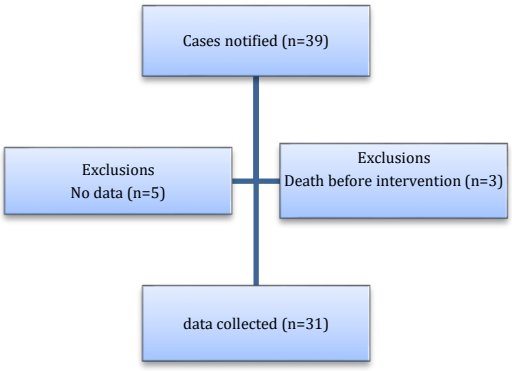
Patient confidentiality was not compromised in any way and the patient information gained in this study was kept in a database identified only by a study number. The data was recorded on a data capture sheet (see addendum A), identified only by the study number. Personal identifying information was only known to the investigator and kept in a separate folder. All the data was anonymous and only the investigator had access to link the folder number to the study number. All data was stored in a secure location in the paediatric department and this was password protected.

Chapter 5: RESULTS

Study Population.

During the study period, 39 neonates with the diagnosis of GS were identified. Of those, we were unable to retrieve the clinical notes of 5 patients and 3 patients died prior to intervention. Of the 3 patients who demised early, 1 patient had necrotic bowel on presentation and died despite resuscitation and the other 2 patients who presented with gastroschisis, died soon after admission, but the cause of death was unknown. These 8 patients were included in the admission rate and mortality calculated but excluded from the descriptive component of the study. (See figure 1)

Figure 1: Flow Diagram depicting patient population



The admission rate of gastroschisis at Tygerberg Hospital was calculated to be 2.7 ± 1.7 cases per year, with an incidence of 0.08 cases/1000 live births. The data of the 31 neonates with complete records were used for further analysis. Of the 31 neonates, 11 (35.5%) were male.

Diagnosis

The diagnosis of gastroschisis was made on prenatal ultrasound in 65% of the cases. Of the 20 patients who had antenatal sonars, only 1 patient had another congenital anomaly, an associated bladder extrophy with a right duplex kidney. On prenatal ultrasound, bowel dilatation was present in 5 fetuses (25%).

Gestation and mode of delivery

Eighteen patients were premature, with the average gestational age at delivery 36.2 ± 2.5 weeks. The average birth weight was 2.324 ± 409.7 grams and 3 (10%) neonates had intrauterine growth restriction (IUGR). Fifteen babies (48.3%) were born outside of Tygerberg hospital and transferred to the NICU for postnatal care. (See table 1) There were 12 (39%) delivered by caesarian section. Nine were emergency caesarian sections for fetal distress with variable decelerations and suspicious cardiotocographs, One pateint was electively delivered at 36 weeks and 2 cases had spontaneous preterm labours. Twenty-two (71%) women went into spontaneous labour.

Maternal variables

The mean maternal age was 21.8 ± 5.2 years and 19 (61%) women were primigravid. More than half of the mothers, 18/31 (58%), smoked tobacco during the pregnancy. Only 27 (87%) women were tested for human immunodeficiency virus infection and 24 (89%) of those tested, were uninfected (Refer Table 1 - page 42).

Description of the defect and surgical management

There were 5 (16%) cases of complex gastroschisis and 10 (32%) cases had a large abdominal wall defect of more than 4cm. Eighteen patients (58%) underwent silo placement with delayed closure, 10 (42%) patients had primary surgical closure and the remaining 3 (10%) patients with small defects of 1cm were closed by manual reduction of bowel and bedside closure. Fifteen patients (49%) were closed on day 1 of life, 4 underwent silo placement and 9 were closed primarily. The average number of days to closure, in both the delayed (silo reduction) and primary surgical closure group, was 3.5 ± 3.3 days. (See Table 2 – page 43)

Non-surgical management

Intensive care

Twenty-eight (90%) patients required ventilator support and the average duration of ventilation was 6.1 ± 6.9 days. The comparison between the simple and complex GS groups in relation to days spent on the ventilator approached statistical significance (p= 0.059); however when comparing the ventilator time in relation to the method of closure [delayed vs. primary closure] there was no statistically significant difference observed (p = 0.8).

The average length of stay in the NICU was 16.8 ±15.7 days. Twelve (39%) patients stayed in hospital for more than 30 days, and of those, 7 (58%) patients stayed in hospital for more than 60 days. The average length of hospital stay was 37.5 ± 27 days. The longest hospital stay was 106 days.

There was no statistically significant difference in the length of ICU stay between the simple and complex GS groups (p = 0.46), and the method of defect closure [delayed vs. primary closure] had no impact on the length of ICU time (p = 0.18).

Nutrition

First feeds on average began on day 7 of life ± 5.7 days in all 31 cases. Full enteral feeds were achieved on average by day 21.1 ±13.2 days of life. All 31 patients received PN and the average duration of PN was 19.4 ± 13.5 days. Those neonates with complex GS, took an average of 12.4 days (range 6 – 30 days) to initiate feeds, compared to the simple GS group where feeds were initiated around 6.24 days (range 1 – 22 days). Three of the 5 cases (60%) of complex GS initiated feeds after 7 days post closure, compared to only 6 of the 26 cases (24%) of the simple GS group. It took longer for those with complex GS to achieve full enteral feeds, average time of 29.2 days (range 15 – 62 days), compared to those with simple GS, in whom full feeds were established by 19.5 days (range 6 – 50 days). There was no statistically significant difference in the average time to full enteral feeding between the premature and term neonates (p = 0.4). In premature neonates the average time to full feeds was 21.2 days (range 8 – 62 days) and for term neonates, it was 21.1 days (range 6 –43 days) (See Table 3 – page 44).

Complications

Surgical

The majority of patients, 22 (71%) patients, had no bowel related complications; and 20 of these patients had simple GS. Of the 9 patients who had bowel related complications, 3 (10%) patients developed bowel obstruction secondary to intra-abdominal adhesions; 2 patients developed necrotizing enterocolitis; 1 patient had a bowel perforation and 2 patients had surgical wound dehiscence. One patient was presumed to have abdominal compartment syndrome on clinical suspicion, but did not require surgical relief. (See Table 5, page 45)

The surgical related complications occurred in 5 (16%) patients. Five patients had repeat surgical exploration and the average day of the repeat surgery was day 13 (range 2 - 34).

The average numbers of repeat surgical procedures were 2.8 (range 1 – 7). At repeat surgery, 2 patients were found to have adhesions, 1 patient had a bowel perforation, 1 patient had full thickness bowel necrosis and 1 patient had NEC.

Readmission to neonatal intensive care unit (NICU)

A total of 9 (29%) patients were readmitted to the NICU. The average day of readmission was day 49 (19 – 84) and the average duration of stay was 3,5 $\pm$1.4 days. The reasons for readmission included central line placement for PN, suspected bowel obstruction, NEC, sepsis and postoperative closure of a stoma.

Infection

Twenty-eight (90%) patients had sepsis. Of those, 13 cases were confirmed by positive blood cultures giving a proven sepsis rate of 46%. The other 15 (54%) cases were suspected based on an elevated CRP but no positive cultures. Early onset sepsis (< 72 hours) developed in 7 (25%) of the patients and 21 patients (75%) developed sepsis after 72 hours (late onset). Of the 28 cases, wound sepsis was the most common type of sepsis, with 8 (53%) cases of presumed wound sepsis. Five of the 8 cases of wound sepsis were in the silo with delayed surgical closure group. Six (46%) patients with proven sepsis, had central line associated infections, 5 patients had septicaemia, 1 patient had intra-abdominal peritonitis and 2 patients developed ventilator associated pneumonia.

Acinetobacter Baumanii was cultured from the surgical wound in 3 patients and cultured in the blood in 2 patients. Enterococcus, Escherichia Coli and Methicillin resistant Staphylococcus Aureus (MRSA) were all cultured in the blood in 3 different patients. MRSA, Klebsiella Pneumonia and Coagulase Negative Staphylococcus were the organisms implicated in the development of central line associated sepsis. All were successfully treated except the one who died from Klebsiella sepsis and the second from Acinetobacter sepsis. There was no statistically significant difference in the proven sepsis rate between the premature and term neonates (p =0.4), with both groups having a proven sepsis rate of 69%. Of those with complex GS, 3/5 (60%) had proven sepsis compared to the simple GS group 12/26 (46%) (p=0.5). (See table 4 – page 45)

Parenteral nutrition associated cholestasis (PNAC)

Only 26 patients had liver biochemistry tests done while on PN and of those, 6 (23%) patients had PNAC. The mean duration of PN in the PNAC group was 34.8 days (range 10 -68) compared to the non-PNAC group (mean 13.4 days; range 10 – 68 days). Of the PNAC group, 5/6 (83%) were on PN for longer than 14 days. In the non-PNAC group, 8/20 (40%) were on PN for longer than 14 days (p = 0.06). In premature neonates, 5/18 (28%) developed PNAC compared to the term neonates (1/13;8%) (p =0.16) (See table 3).

Mortality

Two patients (6.4%) in the study population died and if the 3 patients that died soon after admission were included, then 16% of patients admitted with GS to the NICU died. Both patients included in the study died due to confirmed sepsis. One patient had 7 surgeries and demised due to klebsiella pneumoniae sepsis after a prolonged stay in NICU. The other patient died after 6 days in neonatal ICU due to overwhelming Acinetobacter baumanii sepsis. Both patients had simple GS. The deaths were not related to complex GS (p = 0.5), prematurity (p = 0.2) or being born outside the tertiary hospital (p = 0.15).

Chapter 6: DISCUSSION

GS is a common condition (3 admissions per year) in our setting. In this study, the mortality rate for GS at Tygerberg Children's hospital is low (6.4%). The most common reason for death in this setting was overwhelming sepsis. The majority (71%) of the study population had no bowel related complications and only 5 patients required a repeat surgical exploration. The majority of neonates (67%) achieved full feeds by 21 days and few (23%) developed parenteral nutrition associated cholestasis. The patient and maternal profile in this study is similar to what has been described internationally.

Demographics and Aetiology

A low maternal age is considered a major risk for the development of gastroschisis [6, 7]. Already in 1997, Nichols et al[7] showed that, not only had the incidence of GS risen from 0.48 per 10,000 births in 1980 to 3.16 per 10,000 births in 1993, but that the maternal age group 15-19 years had 10 times the incidence of the age group 25-29 years. The average maternal age in this study was 21.8 + 5.2 years, which supports its importance as a notable risk factor.

In 2010, Frolov et al[16] conducted a systematic review of risk factors for GS and omphalocoele, and reported that there was little evidence for a genetic cause in the development of GS and much evidence supporting the possibility that environmental teratogens (tobacco smoking, substance abuse, low socioeconomic status, poor nutrition) were important contributors to the development of this defect. Primigravid status and tobacco smoking are other risk factors for GS, and in our study population more than half our mothers were primigravid and smokers.

Lubinsky suggested that the cause of GS was heterogeneous. There is a strong maternal age effect and he found that the occurrence of GS correlated with high early pregnancy oestrogen in first time and younger mothers and in those with a low BMI. Furthermore, he proposed that early pregnancy oestrogen induced thrombus formation, which contributes to the pathogenesis of GS [17].

Gestation and Delivery

As demonstrated by Overcash et al[19], we demonstrated a higher rate of preterm births with about 58% of neonates with GS being delivered before 37 weeks gestation in our study. The majority of these preterm births (70%) were due to spontaneous preterm labour, followed by caesarian section (38%) for abnormal fetal heart tracing. Prenatal predictors such as intrauterine growth restriction (IUGR), oligohydramnios and bowel dilatation on ultrasonography were not found to be predictors of adverse neonatal outcomes, but gestational age, prematurity and maternal smoking were associated with adverse neonatal outcomes [19].

Incidence and Mortality

Many studies have emphasized the rising incidence of gastroschisis in the developed world [4, 9, 10, 11]. Both Kilby[9] and Holland et al[10] in their systematic review of the literature, consistently report this rising incidence particularly in the UK and other high-income countries. In South Africa, Arnold[12] showed that the admission rates of gastroschisis presenting to Pretoria Academic Hospital and Khalafong Hospital had risen dramatically relative to the admission rates of exomphalos over the period 1981 to 2001. Though the mortality is low in these high-income settings, the morbidity is still significant [14, 15]. In low and middle-income countries, infants with gastroschisis are reported to have higher mortalities when compared to those born in high-income countries [2, 14, 39].

We speculate in this study that the mortality in our setting, a tertiary hospital in South Africa, was on par with the mortality described in high-income countries. The all-cause mortality in this study was 6.4% compared to the figures presented by Ford et al[41], which reported mortality rates in sub-Saharan Africa ranging from 60%-100%. Even then, a lower mortality rate of 29% was documented in South Africa (Pretoria Academic hospital) compared to countries like Uganda, Malawi and Nigeria, where the reported mortality rates were 100%, 60% and 75% respectively. In the UK, a high-income country, the mortality was reported as 0% [41]. This places our mortality rate closer to that achieved by the high income countries. Had we included the deaths of the 3 patients excluded from the study, the all-cause mortality rate would be 12.8%. This is still lower than the figures reported for the other countries in Sub-Saharan Africa, as reported by Ford et al [41]. The mortality rate in this study most likely reflects

advances in the surgical and NICU care of neonates with gastroschisis at our institution. We speculate that the reasons for the demise of 3 patients before intervention, relate to issues with handling, timeous referral, resuscitation and also the severity of the defect.

Mortality has been associated with prolonged hospitalization, multiple operations, long PN duration and sepsis [33]. Erdogan et al [33] in a retrospective study of 29 neonates over a period of 10 years, reported higher mortality rates associated with very long-term hospitalization (average length of hospitalization was 113 days), sepsis, multiple operations and a long duration of PN with a mean duration of PN 38 days.
These reported associations with mortality were notable in one of our patients, who was in hospital for 60 days, had 7 surgeries, was on PN for more than 21 days and developed Acinetobacter sepsis, followed by Klebsiella sepsis which led to eventual death. However the other patient demised after only 6 days in NICU from overwhelming Acinetobacter sepsis during an Acinetobacter outbreak in the NICU.

Nutrition

There is no consensus regarding the optimal time to initiating and achieving full enteral feeding in gastroschisis. Many studies have noted that the timely initiation of enteral nutrition is pivotal to outcome optimization in gastroschisis. Aljahdali et al[34] found that earlier enteral feeding after closure was associated with better overall outcome. They found that patients who started enteral feeding within 0-7 days after closure had significantly shorter length of hospital stay, fewer number of days on PN, and fewer infectious complications when compared with those that started 21 days after closure. In this study the average time to initiating feeds was 7 days, with most patients starting feeds within 3-4 days post closure.

The time to full tolerance of enteral feeding is an important outcome measure as it determines the duration of parenteral nutrition and hence the risk of complications, including central line sepsis, hepatic dysfunction associated with parenteral nutrition, and liver transplant [35].

A Centers for Disease Control analysis in the United States and a population based study in Canada reported mean duration of parenteral nutrition of 28 and 29 days, respectively [43, 44]. In a study by Bradnock et al[14], 81% and 41% of infants with complex and simple gastroschisis, respectively, required PN for more than 28 days.

The average duration of parenteral nutrition requirement was 19 days in this study, and the majority of patients (67%) achieved full enteral feeds by 21days. This is most likely a reflection of earlier feeding practices and probably relates to earlier surgical closure, as the majority of patients were closed on day 1 of life.

Harris et al[45] demonstrated that earlier closure of gastroschisis after silo placement was associated with earlier feed initiation and shorter time to full feeds. Returning bowel into the abdominal cavity sooner may minimize intestinal inflammation, leading to earlier return of bowel function. Also by intiating early enteral feeding, the incidence of sepsis can be reduced [46].

With regards to the onset of feeds Singh et al[47] in a review of 181 neonates with gastroschisis found that those that were fed within 10 days of operation had a significantly lower incidence of sepsis as compared to those who were fed after 10 days.

Sepsis

Sepsis was the major cause of mortality in our study population. Even though mortality now is quite low, studies report that sepsis still causes over 70% of mortality in gastroschisis [48]. The incidence of sepsis in gastroschisis varies worldwide with reports of up to 47% in complex cases [29]. Ford et al[41] showed that the most common reported causes of death, amongst patients with gastroschisis were septicaemia and hypothermia. What was striking was the relatively high sepsis rate of 46% in our study population. The major sources of sepsis were central lines, blood borne and the surgical wounds. Many studies have associated a longer duration of PN with an increasing development of sepsis due to the lengthy requirement of central lines [49].

Pierro et al[50] found that the inflammatory response to bacterial challenge is impaired in infants on PN compared with enterally fed infants, implicating parenteral nutrition as the cause of sepsis. They suggested that this could be due in part to impaired cytokine response after bacterial invasion in infants on PN.

Resource constraints and a lack of sufficient experience (by all medical personnel) in the aseptic handling of central lines may in part be responsible for the 6 cases of central line associated sepsis found in this study. Sepsis has also been noted to cause an increase in the length of hospital stay and increases the financial costs of treatment [51].

Ford K et al[41] suggested that the high mortality rates in the sub-Saharan countries reflect inadequate resuscitation, sepsis and abdominal compartment syndrome after primary closure. Compounding this is inadequate post-operative support due to limitations in the NICU resources for example ventilation and intravenous access.

Surgical Complications

Seventy-one percent of the study population had no bowel related complications. This contrasts with the findings of Durfee et al[40], who showed that only about 16% of gastroschisis patients had an uncomplicated post-operative course, and that bowel related complications followed by infectious complications were the most frequent problems encountered.

In this this study, there was one case of suspected abdominal compartment syndrome, who later died due to sepsis. This patient had a simple gastroschisis with a large abdominal wall defect and had primary closure on day 1 of life.

The low rate of bowel related complications in our setting might reflect better post-operative support, compared to our neighbouring African countries, in terms of timeous paediatric surgeon involvement and availability of NICU resources.
Only 16% of patients in the study cohort needed repeat surgical exploration. Since the majority of our patients had no bowel related complications, this figure is not surprising.

PNAC

The use of PN is an effective way of nourishing an infant that is unable to receive full enteral feeds. Originally described by Peden et al [52], cholestasis is a frequent complication of parenteral nutrition. The aetiology is unknown and likely to be multifactorial [38]. PNAC was not highly prevalent in our population. However, our figure of 24% is comparable to the incidence of 20% and up to 35% reported by other authors [35].

An intravenous mixed lipid emulsion containing soybean oil, medium-chain triglycerides, olive oil and fish oil (SMOF) has been associated with less cholestasis and morbidity than the currently available parenteral soybean oil therapy [53]. SMOF is not routinely used in our institution as the first choice of parenteral nutrition due to the expense, but it may be a viable alternative to prevent PNAC.

Limitations

There are significant study limitations. This was a retrospective study, with a relatively small sample size. Eight patients were excluded based on missing data. We were reliant on clinical notes made by a variety of different clinicians, and in some cases, the notes were not consistent and easily legible. Regrettably, we had very limited surgical input in interpretation of the notes and data, and this would have been most helpful in addressing more of the surgical outcomes.

While gastroschisis appears to be relatively common in our setting, we need to account for selection bias. The patient population encountered in our setting is mostly classified as high risk, since this is a tertiary referral hospital and one of 3 paediatric surgical hospitals in the Western Cape. While this study shows only a few patients developing PNAC, not all the patients in this study had regular liver biochemistry tests done while on PN. Furthermore, this was a single-center review and findings may not be transferrable to other settings. Other low to middle income countries may not have similar neonatal services at their disposal.

Chapter 7: CONCLUSION AND RECOMMENDATIONS

Gastroschisis is a fairly commonly encountered condition in our setting and the outcomes are not as poor. We have better access to valuable resources for antenatal diagnosis, referral and management than our counterparts. Our mortality rate is low and were are on par with international management strategies with regards to the preferred silo reduction and delayed closure and early feeding practices.

However there is room for improvement, especially with regards to the high rate of sepsis encountered in this condition.

1. The reasons for sepsis in this setting is likely to be multifactorial and larger studies in this setting are needed to assess possible associations with the development of sepsis in these patients.
2. Strict adherence to existing protocols regarding the management of neonates on PN is essential to prevent complications related to parenteral nutrition. Therefore, due to the prolonged need for PN in these cases, every patient on PN should have baseline liver biochemistry, with regular assessment of liver biochemistry if on PN for longer than 14 days.
3. Existing protocols outlining the initial management of GS, including pre-intervention resuscitation and bowel handling, should be adhered to in order to standardize the care of these infants. This may be particularly useful for those infants born outside of a tertiary hospital.
4. The study should be repeated in other tertiary care neonatal settings in Southern Africa to test the external validity of the findings and recommendations.

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List of Tables

Table 1: Maternal and neonatal demographics

Variables	n = 31 (%)	Mean (SD)
Male gender (%)	11 (35.5)	
Gestational age at delivery[1] (weeks)		36.2 (2.5)
Premature (%)	18 (58)	
Birthweight (grams)		2324.6 (409.7)
IUGR (%)	3 (15)	
Maternal age (years)		21.8 (5.2)
Nulliparity (%)	19 (61.2)	
Smoking (%)	18 (58)	
Maternal HIV status Uninfected [2] (%) [n=27]	24 (88.4)	
Born outside of Tygerberg hospital (%)	15 (48.3)	
Caesarian section (%)	12 (38.7)	
Spontaneous labour (%)	22 (70.9)	
Antenatal sonar diagnosis (%)	20 (64.5)	
Bowel dilatation on antenatal sonar (%) [n=20]	5 (25)	
Other congenital abnormalities (%) [n=20]	1 (5)	

[1]Gestational age as the dates recorded in the patient's notes, regardless of whether determined by last menstrual period (LMP), early ultrasound (<20 weeks) or late ultrasound (>20 weeks)
[2] Only 27 mothers were tested for HIV infection

Table 2: Gastroschisis defect description and management

Variable	n=31 (%)
Simple gastroschisis (%)	26 (83.3)
Complex gastroschisis (%)	5 (16.2)
Defect size (> 4cm)* (%)	10 (32.2)
Primary surgical closure (%)	10 (32.2)
Silo placement (%)	18 (58)

Data are n (%) unless otherwise specified.

* Defect size greater than 4 cm is considered to be a large defect

Table 3: Neonatal outcomes

Outcomes	**n=31**
Length of hospital stay (days)	37.5 (27)
Ventilator days	6.1 (6.9)
Days to initiation of feeds	7.2 (5.7)
PNAC* (%) [n=26]	6 (23%)

*6 patients did not have documented bilirubin levels

Table 4: Specific adverse outcomes

Adverse outcomes*	**n=31 (%)**
Confirmed sepsis (%) n=28	13 (46.4)
Bowel complications (%)	9 (29)
Greater than 21days to full feeds (%)	10 (32.2)
Relook surgery (%)	5 (16.1)
Death (%)	2 (6.4)

Data are incidents and % of total study sample unless otherwise specified.
* Some infants had more than one adverse outcome

Table 5: Surgical Complications

Complication	Simple GS	Complex GS
Abdominal Compartment Syndrome	□	
Wound Dehiscence	□	□
Bowel Perforation		□
Necrotizing Enterocolitis	□□	
Bowel Adhesions or Obstruction	□□	□

□ = 1 case with recognized complication. Of the total 9 complications, 6 complications occurred in the group with simple GS.

Appendices

Appendix 1: Case Recording Form

study number		1	2	3	4	5	6	7	8	9
year										
mat age										
nulliparous										
smoking										
drug use										
HIV infected										
admission age										
discharge age										
gestation										
birth weight										
gender										
in/outborn										
preterm(<37)										
delivery mode										
delivery type										
antenatal sonar										
sonar abnormal										
GS type										
defect size										
antenat diag										
defect closure										
day of life closure										
vent days										
length ICU stay										
length hosp stay										
bowel complications										
sepsis										
suspect/confirm										
ealy/late										
sepsis type										
micro/organism										
CVP duration										
TPN duration										
PNAC										
IFALD										
initiation of feeds										
full feeds										
ICU readmission										
day readmission										
length readm										
reason readm										
death										
relook surgery										
day of relook										
number of relook ops										
findings at relook										
no. of sepsis epsisodes										
type										
micro										

Appendix 2: Data Scoring Sheet

Maternal factors

age

nulliparous	yes = 1 no = 2
smoking	yes = 1 no = 2 unknown=9
drug use	methamphetamines =1 other (cocaine, heroin)=2 Unknown=9
HIV status	infected = 1 uninfected = 2 Unknown=3

Neonatal factors

age at admission to ICU

age at discharge from hospital

gestation

brith weight

gender	male = 1 female = 2
Inborn	1
Outborn	2
Preterm (<37 weeks)	yes = 1 no = 2
mode of delivery	caesarian = 1 NVD = 2
type of delivery	elective = 1 emergency = 2 spontaneous = 9
antenatal sonar	yes = 1

sonar abnormalities	no = 2 IUGR = 1 bowel dilatation = 2 other congenital anomalies = 3 no other abnormalities = 4

Gastroschisis

type	simple = 1 complex = 2
defect size	< 4cm = 1 > 4cm = 2
antenatal diagnosis	yes = 1 no = 2
method of defect closure	manual reduction = 1 silo reduction = 2 primary closure = 3 combination (silo + then surgical closure) = 4

day of life of surgical closure

Complications/ Morbidity

Ventilator days

length of ICU stay

length of hospital stay

bowel related complications	abdominal compartment syndrome =1 wound dehiscence = 2 bowel perforation = 3 NEC = 4 bowel adhesions/obstruction = 5 no complications = 6

Sepsis	yes = 1 no = 2
suspected	1
confirmed	2
early onset (< 72 hours)	1
late onset (> 72hours)	2

type of sepsis CLABSI=1 (central line associated sepsis)
VAP = 2
Wound sepsis = 3
Bowel related/ peritonitis = 4
blood borne = 5
presumed sepsis = 6
meningitis = 7

Microbiology/organism cultured 2= no organism cultured

duration of central venous access 2 = no central line

duration of TPN 2 =no TPN

PNAC (conj bilirubin > 34umol/l) yes = 1
no=2
not documented = 3

IFALD yes = 1
no = 2
not documented = 3

days post op initiation of feeds

days post op full feeds

ICU readmission yes = 1
no = 2

day of readmission

length of readmission

reason CVP placement = 1
bowel stricture/obstruction = 2
NEC with bowel perforation = 3
feeding intolerance = 4
sepsis = 5
closure stoma = 6

neonatal death yes = 1
no = 2

relook surgery yes = 1
no = 2

day of relook surgery	
no. of relook surgery	
findings at relook surgery	nil = 1 bowel necrosis = 2 NEC = 3 adhesions = 4 atresia = 5 perforation = 6
no. of sepsis episodes	
type of sepsis	CLABSI=1 (central line associated sepsis) VAP = 2 Wound sepsis = 3 Bowel related/ peritonitis = 4 blood borne = 5 presumed sepsis = 6 meningitis = 7
microorganism	2 = no organism