GASTROSCHISIS AND OMPHALOCOELE: AUDIT AT TWO REFERRAL HOSPITALS IN JOHANNESBURG, SOUTH AFRICA: 2000-2005

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DECLARATION

I, Elaine Mary Philippa Beckh-Arnold, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in Genetic Counselling in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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ABSTRACT

Gastroschisis and omphalocoele are serious birth defects which differ in many aspects. There are numerous reports of an increase in the incidence of gastroschisis but not omphalocoele.

A retrospective analysis was conducted including all infants with gastroschisis and omphalocoele admitted to two tertiary institutions in Johannesburg over six years from 2000-2005. The study aimed to describe the frequency of gastroschisis and omphalocoele, assess maternal characteristics, evaluate clinical details and factors that may affect mortality, describe additional abnormalities and determine if there was appropriate use of genetic services.

The prevalence of gastroschisis and omphalocoele was 0.36 per 1 000 live births and between the years 2000 and 2005, there was a 2.7 fold increase in the number of patients with gastroschisis compared to omphalocoele. Sixty percent of the patients were transferred into the hospitals and 47% of these patients demised. Twenty-one percent (3/14) of patients with additional abnormalities were referred for a genetic assessment. Fifty-eight percent (7/12) of patients with omphalocoele and additional congenital abnormalities demised. Fifty-eight percent (7/12) of the patients with sepsis demised.

From this study, improvement in certain areas such as prenatal diagnosis, interhospital transfer and education of staff involved in the care of patients with gastroschisis and omphalocoele is recommended to facilitate a reduction in the high mortality observed.

DEDICATION

This work is dedicated to my husband, Francis Thuynsma Beckh, my mother, Dorothy Arnold, my children Gabrielle and Graham and my sisters Coretta and Frances. Thank you for all the love, care and support during this difficult period.

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LIST OF ABBREVIATIONS

ANC – antenatal clinic

HIV – human immunodeficiency virus

MTC – mother to child

HAART – highly active antiretroviral therapy

MSAFP – maternal serum alpha fetoprotein

AFP – alpha fetoprotein

PCR – polymerase chain reaction

CHBH – Chris Hani Baragwanath Hospital

JH – Johannesburg Hospital

ICU – intensive care unit

OEIS – omphalocoele-exstrophy-imperforate anus-spinal defects complex

IVH – intraventricular haemorrhage

NEC – necrotizing enterocolitis

HMD – hyaline membrane disease

CHAPTER 1

INTRODUCTION

1.1 BIRTH DEFECTS

Birth defects, also known as congenital disorders, are defined as disorders of structure or function which are present from birth.[1] Globally, thousands of birth defects have been identified. Birth defects may be minor or serious. Serious birth defects are life threatening or have the potential to cause disability. The birth prevalence of serious birth defects is reported to be approximately 20% higher in middle- and low-income countries[2] and South Africa is regarded as a middle-income country. The number of recorded births in South Africa has increased from 1 006 000 to 1 092 000 between 2003 and 2005.[3] A figure of the exact number of babies delivered annually in South Africa with serious birth defects is not readily available. Annually, approximately two to three percent of neonates are diagnosed with a serious birth defect globally.[4]According to the Modell Birth Defects Database, the estimated birth prevalence of genetic birth defects in South Africa is 53.4 per 1 000 live births every year.[1] Gastroschisis and omphalocoele are serious birth defects which are clinically obvious at birth and are the focus of this study.

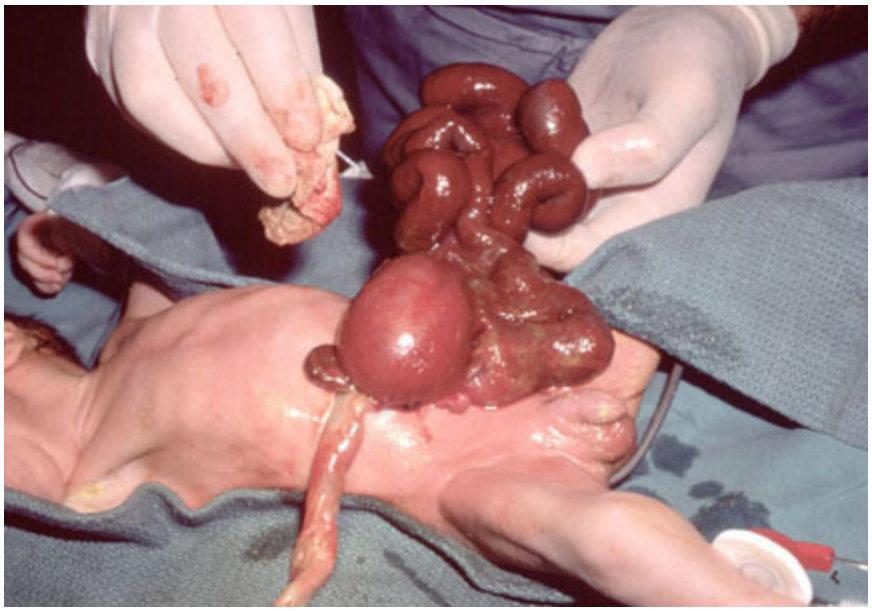
1.2 LITERATURE REVIEW

Gastroschisis and omphalocoele are rare congenital abdominal wall defects, occurring in about 0.4 per 1 000 live births.[5] They differ in their aetiology, incidence and pathology.

1.2.1 Gastroschisis

Gastroschisis is an abdominal wall defect characterized by evisceration of bowel through a defect in the abdominal wall, with no membrane covering, usually to the right of an intact umbilical cord. The abdominal defect tends to be small and is usually less than 4cm in diameter.[6] The sex distribution in published reports varies from no gender difference in larger cohorts to predominance of females.[7-8] Figure 1.1 demonstrates a baby with gastroschisis.

Figure 1.1 Baby with gastroschisis.[9]



Aetiology

It has been speculated that gastroschisis may be a primary malformation, or disruption secondary to fetal teratogen exposure. Some of the teratogens implicated include radiation damage at the preimplantation stage, aspirin, pseudoephedrine and

acetaminophen. Other factors associated with gastroschisis include young maternal age, cigarette smoking, drug abuse and low socioeconomic status.[6]

Embryology

The embryological basis of gastroschisis involves the maldevelopment of the abdominal wall. The ventral body wall is formed by the endoderm and mesoderm layers of the embryonic disc.[10] Failure of closure of the ventral body wall results in defects such as gastroschisis. Different embryological processes that have been proposed in the formation of gastroschisis include:

1) Failure of mesoderm to form in the body wall due to teratogen exposure during the fourth week after conception.[11]
2) Rupture of the amnion around the umbilical ring either during the period of physiologic herniation or later in the fetal period.[12]
3) Abnormal involution of the right umbilical vein leading to weakening of the body wall.[13]
4) Disruption of the right vitelline artery resulting in body wall damage.[14]
5) Abnormal folding of the body wall resulting in the ventral body wall defect.[15]

Epidemiology

The birth prevalence of gastroschisis ranges from 0.5 to 4 per 10 000 births and varies in different countries or regions of the world.[6,16-20] Gastroschisis is associated with a still birth rate, and up to 10% of cases which are diagnosed prenatally by sonar die prior to delivery.[21]

There have been numerous reports in the literature that the birth prevalence of gastroschisis has been steadily increasing. Analysis of cases with gastroschisis in almost half of the registries from Europe, Australia, Japan and the Americas demonstrated an increase in the birth prevalence of gastroschisis, though the birth prevalence varied in different regions.[17] Data from the National Congenital Malformation Notification System showed an increasing trend in the birth prevalence of fetuses with gastroschisis but a decline in the birth prevalence of omphalocoele in England and Wales between 1987 and 1993.[22] This large study demonstrated an almost doubling in the birth prevalence of gastroschisis from 0.65 to 1.11 per 10 000 births during the study period.[22]

Associated anomalies

Approximately 10 % of cases with gastroschisis are associated with another major birth defect.[19] These include intestinal atresias, malrotations and, rarely, intestinal duplications.

A*ssociated genetic conditions*

Gastroschisis is not commonly associated with chromosomal or genetic syndromes. One study reported that less than 2 % are associated with a recognizable syndrome.[19] However, in a hospital based study in Utah, USA, up to 3.7% of cases with gastroschisis were syndromic.[7]

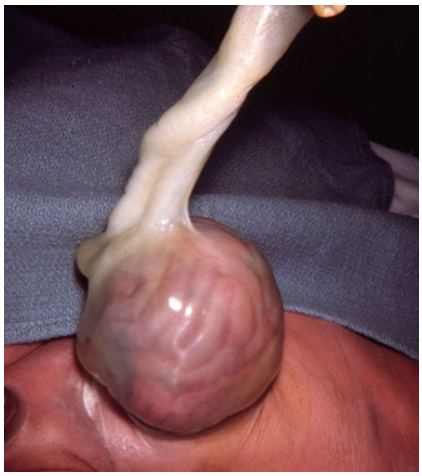
It is important to differentiate cases of isolated gastroschisis from cases where the gastroschisis is secondary to another pathological mechanism. Close examination of all cases of apparently isolated gastroschisis is essential to ensure no subtle deformities are

missed. For example, infants with limb-body-wall complex, secondary to early amnion rupture sequence, may be incorrectly classified as having gastroschisis alone. In limb-body-wall complex there is an association of abdominal wall defects with a variable spectrum of anomalies including limb reduction defects, neural tube defects, anal atresia and absent external genitalia. Similarly, patients with amyoplasia congenita may have gastroschisis with atypical and/or asymmetrical limb involvement.[23]

1.2.2 Omphalocoele

Omphalocoele, also known as exomphalos, results from herniation of abdominal contents into the intact umbilical cord. The abdominal contents are covered by a membrane consisting of peritoneum and amnion, unless the membrane ruptures. Omphalocoeles may be classified as small or giant. Giant omphalocoeles contain bowel, stomach and liver but small omphalocoeles do not contain liver. Figure 1.2 demonstrates a baby with omphalocoele.

Figure 1.2 Baby with omphalocoele.[9]



Aetiology

The precise aetiology of omphalocoele is unknown. If the omphalocoele is associated with multiple congenital anomalies, single gene mutations have been proposed as a potential aetiology.[24]

Embryology of the ventral abdominal wall

In early fetal life the small intestine lies outside the abdominal cavity in the extra-embryonic coelom, within the umbilical cord, because there is insufficient space to accommodate the bowel in the peritoneal cavity. The bowel returns to the abdomen by the tenth week post conception. The embryonic events responsible for the closure of the abdominal wall involve a process of folding. The abdominal wall defect is closed when the somatic layers of the cephalic, caudal and lateral folds of the embryonic disc join. Failure of abdominal wall infolding is thought to result in omphalocoele.[25]

Epidemiology

The birth prevalence of omphalocoele ranges between 1.5 and 3 per 10 000 births.[16] The birth prevalence of omphalocoele varies by ethnicity and geographical location.[6,22] Omphalocoele tends to be more than 20 times more common in still born infants.[6] A large multicentre study showed a slight predominance in the number of male patients with omphalocoele.[26] Omphalocoeles are not usually associated with maternal age. However, the incidence of cases rises with advanced maternal age as a result of the increase in chromosomal abnormalities, namely the trisomies.

Associated anomalies

Patients with omphalocoele have a high rate of associated anomalies. Up to 88% of fetuses with omphalocoele may have multiple defects.[6] These congenital anomalies include cardiac defects, gastrointestinal anomalies, musculoskeletal, genitourinary and central nervous system anomalies. Cardiac defects are reported in up to 50% of cases, and include tetralogy of Fallot, septal defects and ectopia cordis.[6] The literature reports that small omphalocoeles are more likely to have associated gastrointestinal anomalies where as giant omphalocoeles are more likely to have cardiac, renal and limb anomalies.[27]

Associated genetic conditions

Approximately 30% to 40% of individuals with omphalocoele have chromosome abnormalities which include trisomy 13, 18 and 21, Turner syndrome, triploidy and Klinefelter syndrome.[6] Other genetic syndromes that are commonly associated with omphalocoele include Beckwith-Wiedemann syndrome, pentalogy of Cantrell, and cloacal exstrophy and limb defects. Non syndromic or isolated cases of omphalocoele are generally sporadic with no significant increase in the recurrence risk.

The differences between gastroschisis and omphalocoele are summarized in Table 1.1.

Table 1.1 Differences between gastroschisis and omphalocoele

Gastroschisis	Omphalocoele
Evisceration of bowel through abdominal wall defect	Herniation of abdominal contents into intact umbilical cord
No membrane covering	Membrane covering
Defect is usually to right of umbilical cord	Umbilical cord inserts into defect
Defect usually small (<4cm diameter)[6]	Defect size may vary (2-15cm)[9]
May be associated with vascular disruptions of the bowel	Tend to be associated with abnormalities in other organ systems
Rarely associated with chromosome abnormality[19]	30-40% have chromosome abnormality[6]
High incidence in mothers < 20 years old[6]	Maternal age a factor if >35yrs (higher risk of trisomies) [6]
Equal male to female ratio[7-8]	Slight male predominance[26]
90% survival in high-income countries[28]	Prognosis affected by presence of abnormal karyotype and associated abnormalities[6]

1.2.3 Antenatal care

Attendance at antenatal clinics (ANC) is advocated during pregnancy. The main objective of antenatal care is to prevent or facilitate the early identification of complications in order to reduce maternal and perinatal mortality and to ensure the best possible health of the mother and fetus during the pregnancy. At ANC in South Africa, ultrasound facilities are not available on a routine basis but may be offered to patients with certain risk factors. Routine special investigations are performed which include serology for the diagnosis of syphilis, Rhesus status, and voluntary counselling and testing for human immunodeficiency virus (HIV).

In South Africa, at least 25% of the women who attended ANC in 2006 in Gauteng Province tested positive for HIV. [29] Human immunodeficiency virus can be transmitted from an infected mother to her baby before, during or after birth, and through breast milk. Direct exposure to infected blood through breaks in the skin of the baby at the time of delivery increases the risk of vertical transmission of HIV. Hence it can be assumed that newborn patients with gastroschisis and omphalocoele born to HIV positive mothers are at increased risk of contracting HIV. There are no published studies investigating the risk of contracting HIV in patients with gastroschisis and omphalocoele. Mother to child (MTC) transmission can be reduced by the provision of antiretroviral therapy (ARV) to pregnant women who are infected with HIV. One of the modalities used in South Africa to reduce MTC transmission of HIV is single-dose nevirapine, although it does not offer as much protection as more complex regimes such as highly active antiretroviral therapy (HAART). To date there is no evidence to show that combinations of antiretrovirals have a teratogenic effect and therefore are unlikely to increase the incidence of gastroschisis and omphalocoele. However, neural tube defects have been reported in fetuses exposed to efavirenz.[30]

1.2.4 Prenatal testing for gastroschisis and omphalocoele

Gastroschisis and omphalocoele can be diagnosed antenatally using ultrasound and by measuring maternal serum alpha-fetoprotein (MSAFP). Alpha-fetoprotein (AFP) is a glycoprotein synthesized by the yolk sac, fetal gastrointestinal tract and liver and is excreted by the renal system. It can be detected in the amniotic fluid and maternal serum. Maternal serum AFP levels reflect the levels of AFP in the amniotic fluid.[31] Maternal

serum AFP is usually elevated in fetuses with omphalocoele and gastroschisis but can also be elevated in fetuses with chromosomal abnormalities and open neural tube defects. Maternal serum AFP at 15-20 weeks gestation followed by routine ultrasound at 16-22 weeks can identify up to 80% of fetal abdominal wall defects.[32]

Not only can prenatal ultrasound potentially identify most cases of abdominal wall defects, it can accurately distinguish omphalocoele from gastroschisis. Ultrasound evaluation for omphalocoele is useful after 14 weeks gestation. Factors that may affect the accuracy of the prenatal ultrasound include the fetal position, the experience of the operator and whether the omphalocoele has ruptured. If an abdominal wall defect is suspected on a routine antenatal scan, referral to a tertiary centre for a detailed sonar is recommended to confirm the finding and screen for other structural abnormalities. Genetic tests such as PCR for the common anueploidies, or chromosome analysis from an amniocentesis or cordocentesis, are recommended because of the high incidence of chromosome abnormalities associated with omphalocoeles.[33]

The prognosis of a patient with gastroschisis and omphalocoele is dependent on the presence of associated anomalies. Therefore, when gastroschisis or omphalocoele is detected on ultrasound, it is important to screen for other structural anomalies.

1.2.5 Genetic counselling and postnatal care

In *Clinical Genetics and Genetic Counselling*, Kelly defines genetic counselling as "An educational process that seeks to assist affected and/or at risk individuals to understand

the nature of the genetic disorder, its transmission, and the options open to them in management and family planning."[34] Genetic counselling is therefore ideal when a prenatal diagnosis of multiple congenital abnormalities has been made in a fetus, or if features suggestive of a recognizable syndrome are seen in a neonate with either an omphalocoele or gastroschisis.

Following counselling, if the parents decide to terminate the pregnancy, it is important that a karyotype as well as a detailed post mortem examination is performed. The fetus should be examined closely to delineate all birth defects present in order to see if the features fit with a particular syndrome which may assist in giving accurate recurrence risks. If an abnormal karyotype is detected it may be necessary to perform chromosome analysis on both parents. This is done to determine whether either parent has a balanced chromosome rearrangement which may affect the recurrence risk and management of future pregnancies.

If the parents elect to continue with an affected pregnancy, part of the obstetric care includes close monitoring of the pregnancy for fetal growth and liquor volume to assess fetal well being. The fetus with gastroschisis or omphalocoele should be delivered at a tertiary institution with appropriate perinatal facilities for surgical management. The best mode of delivery of the fetus with gastroschisis and omphalocoele has been debated, and vaginal delivery is advocated.[35] The mode of delivery may be influenced by a number of factors such as the size of the abdominal wall defect, severe intrauterine growth retardation, pathological cardiotocograph or abnormal presentation. Care in the perinatal

period involves a multidisciplinary team including obstetricians, neonatologists, paediatric surgeons and, where appropriate, clinical geneticists.

Prematurity tends to occur less often in cases with isolated omphalocoele than gastroschisis. The incidence of prematurity may be higher in patients with omphalocoele who have multiple anomalies. Intrauterine growth retardation is also more common in patients with gastroschisis.[22]

The newborn management of these defects begins with the basic principles of newborn resuscitation. Once stabilized, extra care is necessary to prevent heat loss, monitor fluid replacement, establish gastric decompression, protect any exposed viscera, maintain serum glucose levels, and prevent sepsis. The ultimate goal in the surgical management of gastroschisis and omphalocoele is to reduce the herniated viscera and close the fascia and skin.[31]

Closure of the abdominal wall may be performed by primary fascial closure or staged reduction using a silastic sac ("silo"). A factor that may play a role in primary closure of the abdominal wall is visceral-abdominal disproportion. If primary closure of the abdominal wall is not possible the intestines are gradually reduced into the abdominal cavity using a "silo".[28] Figure 1.3 demonstrates the use of a "silo".

Figure 1.3 "Silo" in a patient with gastroschisis. [36]

When patients with omphalocoele are too unstable to have surgical reduction, the omphalocoele may be coated with an antimicrobial agent. The ventral defect can then be closed at a later stage.

1.2.6 Morbidity and mortality

Various factors can affect the morbidity and mortality in patients with gastroschisis and omphalocoele. The factors include the size of the defect, prematurity, and associated congenital anomalies.

Survival rates of infants with omphalocoele are highest if the karyotype is normal and there are no associated anomalies.[37] In omphalocoele the mortality is as high as 80% when associated with cardiac abnormalities, whereas if there is no cardiac abnormalities, up to 70% of cases survive.[6]

There appears to be a disparity in the survival rates of cases with gastroschisis between high- and low-income countries. Ninety percent, or more, of individuals with gastroschisis in high-income countries survive compared to around 50 % in less developed countries.[28] Some of the risk factors for adverse outcome of newborns with gastroschisis in a low-income country include delivery outside the tertiary centre, no prenatal diagnosis, prematurity, low birth weight, sepsis and delayed surgery.[38]

Another important factor that may affect the outcome of patients with gastroschisis and omphalocoele is the length of time taken to full enteral feeds. Patients with gastroschisis tend to be more affected because they have a gradual return of intestinal motility compared to patients with omphalocoele where there is prompt recovery of intestinal function. Indwelling lines for total parenteral nutrition tend to increase the susceptibility to infections which increases the risk of morbidity and mortality.[28]

1.2.7 Present state of local problem

As mentioned in section 1.2.1, page 4, there have been numerous reports of an increase in the incidence of gastroschisis in the literature compared to the incidence of omphalocoele, which is declining or static.[6,7,16,32] A study looking at the prevalence of gastroschisis and omphalocoele in two hospitals in Pretoria, South Africa, demonstrated a significant increase in gastroschisis compared to omphalocoele over a 21 year period.[39] The author reviewed 48 cases of gastroschisis and 139 cases of omphalocoele out of 21 495 paediatric surgical ward admissions and demonstrated a 35-fold increase in gastroschisis when comparing two seven year periods (1981-1987 and 1995-2001). Over

the same time period the cases of omphalocoele only showed a 1.82-fold increase.[39] The results from this study may be interpreted in various ways:

- True increase in gastroschisis
- The results are skewed due to the improvement in referral, although this should have an equivalent effect on gastroschisis and omphalocoele
- Skewed results may indicate better antenatal care and detection because of improved technology
- Patients with omphalocoele demise prior to admission to the surgical ward

Teenage fertility rates in South Africa have been documented to have dropped by at least 10% between 1996 and 2001.[40] This would suggest that there are other factors impacting the increase in the incidence of gastroschisis apart from young maternal age.

A retrospective study performed over a six year period, 2002-2007, at Inkosi Albert Luthuli Central Hospital in Durban, South Africa, demonstrated a nine percent increase in the cases of gastroschisis in the neonatal surgical units. A large percent of the patients with gastroschisis were referred into the hospital. They also reported a high overall mortality rate of 43% in these cases, and sepsis was the most common cause of death.[41]

1.3 BACKGROUND TO CURRENT STUDY

Whilst working in the Neonatal Unit at Chris Hani Baragwanath Hospital (CHBH) the general perception was that there was an increase in the number of cases of gastroschisis that were being treated in the unit. We were interested to determine whether the changing trend in the number of cases with gastroschisis and omphalocoele reported in the

literature was also observed elsewhere in Johannesburg. No studies have been performed in Johannesburg, South Africa, to analyze the frequency of gastroschisis and omphalocoele or to describe the associated clinical features of affected individuals, which makes this study unique.

Patients with gastroschisis and omphalocoele are usually cared for at medical institutions with intensive care facilities, paediatric surgeons and neonatologists. In Johannesburg, CHBH and Johannesburg Hospital (JH) are the only hospitals in the public sector which offer care for patients with gastroschisis and omphalocoele. Patients with gastroschisis and omphalocoele noted to have dysmorphic features, congenital anomalies or a recognisable syndrome may have additional genetic tests such as chromosome analysis and may be referred for genetic counselling. Other investigations may be requested depending on the clinical features. Patients may be admitted to the Neonatal Unit, in the high care area, to the Intensive Care Unit (ICU) if they require ventilation or directly to the Pediatric Surgical Unit. Post surgical closure of gastroschisis and omphalocoele, the patients may be admitted to the Neonatal ICU if they require ventilation.

Chris Hani Baragwanath Hospital and JH are both tertiary referral centres. Chris Hani Baragwanath Hospital is situated in Soweto and is one of the largest hospitals in the southern hemisphere. It has a large referral area covering southern Gauteng and parts of the Northwest province. The number of deliveries at CHBH is increasing. From 2000 - 2005 there were on average approximately 19 000 live births annually (personal communication, Prof S Velaphi, neonatologist, CHBH). Johannesburg Hospital is

situated in the centre of Johannesburg and is a referral centre for the inner city and the north eastern parts of Johannesburg. Patients are also referred from provinces neighbouring Gauteng. Johannesburg Hospital has approximately 6 900 live births per annum (personal communication, Sr E Hennessy, assistant manager, Department of Obstetrics and Gynaecology, JH). In 2008, the name of JH was changed to Charlotte Maxeke Johannesburg Academic Hospital, but will be referred to as JH in this study.

Using an overall or combined prevalence of 0.4 per 1 000 live births, for gastroschisis and omphalocoele, from the annual number of deliveries at each hospital it was approximated that 11 new patients with gastroschisis and omphalocoele would be seen at these hospitals annually, excluding referral cases (three patients at JH and eight patients at CHBH).

1.4 STUDY OBJECTIVES AND AIMS

The aim of the study was to undertake an audit of newborns with gastroschisis and omphalocoele, seen at two teaching hospitals in Johannesburg, over a six year period, from 2000-2005. The objectives of the study include the following:

- to describe the frequency of gastroschisis and omphalocoele in infants treated by the Neonatology and Paediatric Surgical Divisions at the JH and CHBH in Johannesburg
- assess the following maternal characteristics in patients with gastroschisis and omphalocoele: age, booking status (attended ANC) and blood results (HIV, WR), residential area and exposure to cigarette smoke or recreational drugs

- evaluate the clinical details and factors that may influence whether or not affected babies survived. These would include: antenatal diagnosis, mode and place of delivery, gestational age, growth parameters and the need for ventilation and surgery.
- describe what additional abnormalities were detected
- determine if there was appropriate use of genetic services (that is how many patients were referred for a genetic assessment and the use of karyotyping).

1.5 LIMITATIONS OF THE STUDY

Being a retrospective study, some of the problems anticipated include inaccurate or incomplete data in the patient files plus the inability to locate some of the files.
The area of residence recorded in the patient file or summary may not be accurate because some of the mothers may come from another province to deliver in Gauteng and give a local address. The numbers will not be representative of the Johannesburg population especially because cases with gastroschisis and omphalocoele are referred from neighbouring provinces. In addition, patients seen in the private sector are not included. The study only included live babies that are seen at the hospitals and did not include still born babies, terminations of pregnancies, or babies that demised prior to transfer to the referral hospital.

CHAPTER 2

SUBJECTS AND METHODS

2.1 METHOD

The study is retrospective and descriptive, reviewing the patient hospital records of newborn infants with gastroschisis and omphalocoele. Data was reviewed over a six year period from January 2000 to December 2005 at two hospitals in Johannesburg: CHBH and JH.

When patients with gastroschisis and omphalocoele are admitted to the Neonatal and Surgical Units, their clinical, and in most cases, maternal information, is recorded. Patients that are seen in the Neonatal Units are entered into registers and a database. At the JH Neonatal Unit a clinical summary is generated by the doctor and filed. At CHBH a brief clinical summary is generated on the computer and the patient file is kept in the Neonatal Unit. At CHBH and JH the registers were reviewed and an attempt was made to retrieve the patient files. The patient files and clinical summaries at CHBH and JH were reviewed by the investigator to retrieve the patient information, which was entered into a data collection sheet (see Appendix A) and closely analysed. The registers in the Pediatric Surgical Units were also reviewed. Patients with insufficient clinical details were excluded from close analysis.

2.1.1 Data collection sheet

The information collected from the data collection sheet included the mother's and baby's details. The maternal details included maternal age, address and booking status. The maternal age was considered because of reports that young maternal age is a risk factor for gastroschisis. The maternal address was recorded to assist with the calculation of the frequencies of gastroschisis and omphalocoele in Gauteng and to determine if certain areas have higher frequencies than others. The booking status of the mothers was recorded to determine how many mothers were unbooked (did not attend ANC) and whether or not any prenatal testing was performed. If the mothers were unbooked and/or did not have prenatal diagnosis of gastroschisis and omphalocoele it would be expected that these factors would be associated with poor outcome.

The data collected of the infants born with gastroschisis and omphalocoele included factors that may affect their outcome such as if they were transferred in, the presence of other defects and the duration of ventilation. Other details included mode of delivery, sex of the baby and growth parameters. These factors were correlated with the cases that demised to assess which factors may have played a significant role in affecting the outcome.

To determine whether there was appropriate use of genetic services, the number of cases that had genetic testing and/or had a genetic assessment were assessed. The records of patients with gastroschisis and omphalocoele seen at JH and CHBH were cross

referenced with the database at the National Health Laboratory Service to determine how many of the patients had genetic testing and received genetic counselling.

Ethics approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Protocol M060820, see Appendix B).

2.2 STATISTICAL ANALYSIS

Data were entered on a Microsoft Excel XP datasheet. Frequencies, means and percentages of the demographic data were calculated using this programme. Intergroup comparisons between patients with gastroschisis and omphalocoele were performed to determine whether there were significant differences between the data sets. P-values of less than 0.05 were taken as significant. Comparisons were made for maternal and child characteristics.

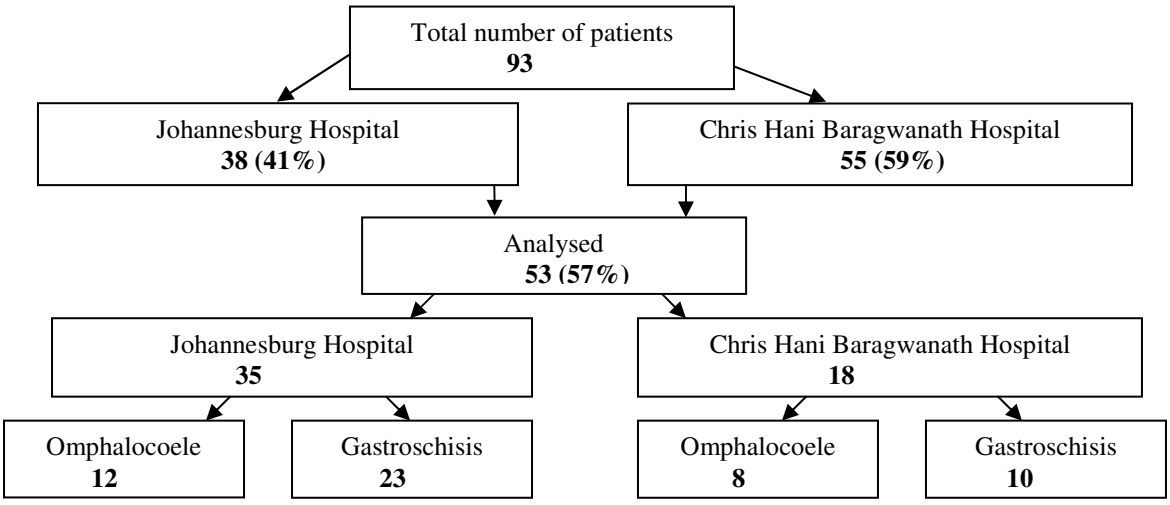
CHAPTER 3

RESULTS

3.1 PATIENT NUMBERS

At the Neonatal Units of JH and CHBH a total of 93 patients with gastroschisis and omphalocoele were registered during the study period. Fifty-nine percent (55/93) had gastroschisis and 41% (38/93) had omphalocoele. Forty patients were excluded from the study either because their files could not be found or because of insufficient information in the clinical summaries. The clinical summaries and files of 57% (53/93) of cases were reviewed and closely analysed (92% (35/38) from JH and 32% (18/55) from CHBH). Of these, 33 (33/53, 62%) patients had gastroschisis and 20 (20/53, 38%) omphalocoele. (See Figure 3.1).

Figure 3.1 Total number of cases of gastroschisis and omphalocoele analysed at Chris Hani Baragwanath Hospital and Johannesburg Hospital

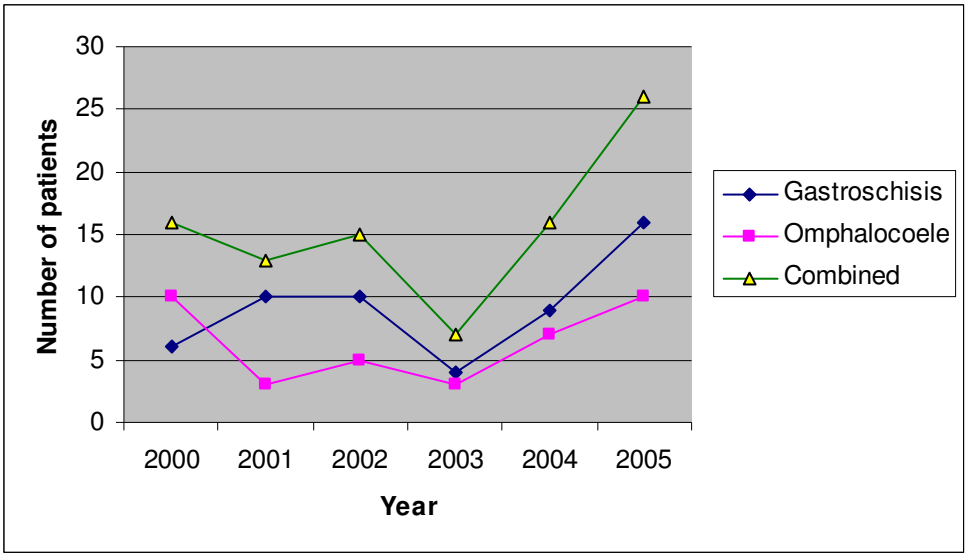


A larger proportion of the analysed cases were from JH (35/53 or 66%). Over the study period there were 6376 admissions to the Neonatal Unit at JH. The cases with gastroschisis and omphalocoele therefore represent 0.55% (38/6376) of the admissions. From calculations, the expected number of inborn patients with gastroschisis and omphalocoele over the study period was 16 (see section 1.3, page 17) but there were only 11 inborn cases at JH. There were 41 344 live births at JH over the study period so the calculated birth prevalence of gastroschisis and omphalocoele at this hospital is 0.27 per 1 000 live births (see Appendix C, page 52).

Thirty-three percent (18/55) of cases from CHBH with gastroschisis and omphalocoele were analysed. Over the study period there were 21 943 admissions to the Neonatal Unit at CHBH. Of the admissions, the cases of gastroschisis and omphalocoele account for 0.25% (55/21 943). There were 44 inborn patients with gastroschisis and omphalocoele at CHBH and 112 822 live births over the 6 year period hence the birth prevalence for gastroschisis and omphalocoele at this hospital is 0.39 per 1 000 live births. With a total of 154 166 live births at JH and CHBH and 55 inborn patients the birth prevalence of gastroschisis and omphalocoele is 0.36 per 1 000 live births over the six year study period. The total number of live births and admissions at each hospital are shown in Appendix C (page 52).

Over the study period, when numbers of total admissions from both hospitals are combined, there was an increase in the number of patients seen with gastroschisis as reflected in Figure 3.2.

Figure 3.2 All cases of gastroschisis and omphalocoele seen at Chris Hani Baragwanath and Johannesburg Hospitals from 2000-2005



The percentage of patients of the total number of admissions per annum to CHBH Neonatal Unit with gastroschisis and omphalocoele increased from 0.27% (9/3286) in 2000 to 0.5% (21/3881) in 2005, whereas at JH the number declined from 0.56% (7/1250) in 2000 to 0.36% (5/1389) in 2005. Comparison between the numbers of cases seen in 2000 and 2005 show a 2.7 fold increase in the number patients with gastroschisis, whereas there was no increase in patients with omphalocoele noted over the same period.

In 2003 there was a drop in the patients with gastroschisis and omphalocoele seen at both hospitals. The numbers of patients with gastroschisis and omphalocoele in subsequent years increased.

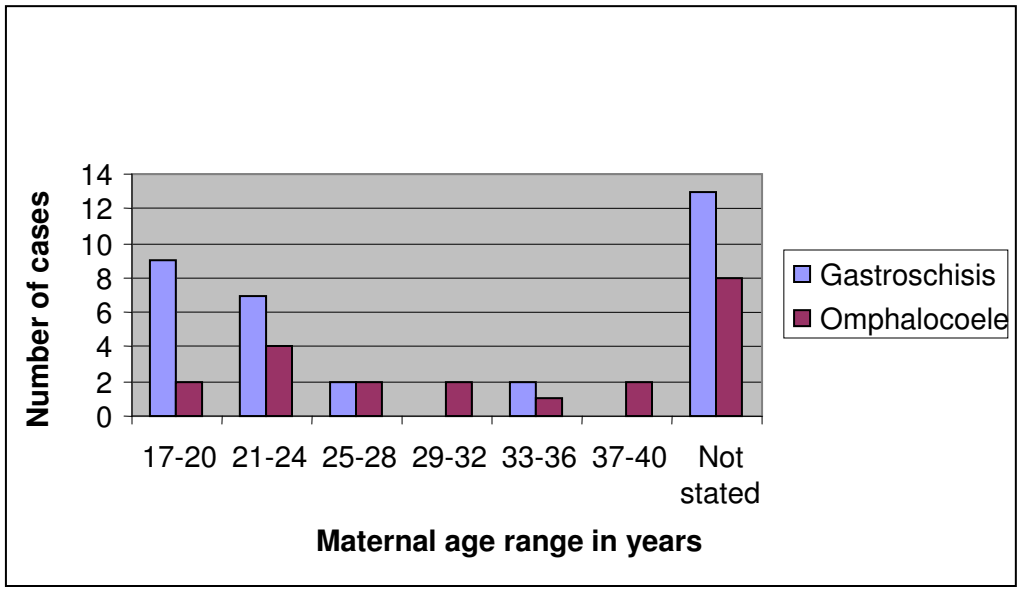
From section 3.2 to 3.5 the results reported are on all the analysed cases.

3.2 MATERNAL CHARACTERISTICS

3.2.1 Age of mothers

The recorded maternal age ranged from 17-39 years (mean 23.9 years). In 48.5% of cases (16/33) with gastroschisis the maternal age was recorded in the range of 17-24 years and of these, nine (56%) were in the 17 – 20 years age range. The maternal age was significantly lower in the patients with gastroschisis than in those with omphalocoele (p value 0.037). The maternal age was not recorded in 40 % (21/53) of the files. Data shown graphically in Figure 3.3

Figure 3.3 Maternal age range for patients with gastroschisis and omphalocoele at Chris Hani Baragwanath Hospital and Johannesburg Hospital.



3.2.2 Maternal booking status and results

In 66 % (35/53) of cases the maternal booking status was not recorded. Ten cases were recorded as booked and eight unbooked. The HIV status in 26% (14/53) of cases was recorded and of these 43% (6/14) were HIV positive. From the patient records documentation on whether or not antiretrovirals were given to the mother and/or child was poor.

3.2.3 Residential area

Most of the patients with gastroschisis and omphalocoele (40/53 or 75%) were from Gauteng Province, one from Mpumalanga Province and two from North West Province. The patients were not clustered in any particular area. For 21% (11/53) of the patients no residential address was recorded.

3.2.4 Exposure to cigarette smoke or recreational drugs

Maternal exposure to cigarette smoke and/or recreational drugs was not recorded in the clinical summaries or patient files despite provision being made to document this information in the bedletters.

3.3 PATIENT DETAILS

3.3.1 Antenatal diagnosis

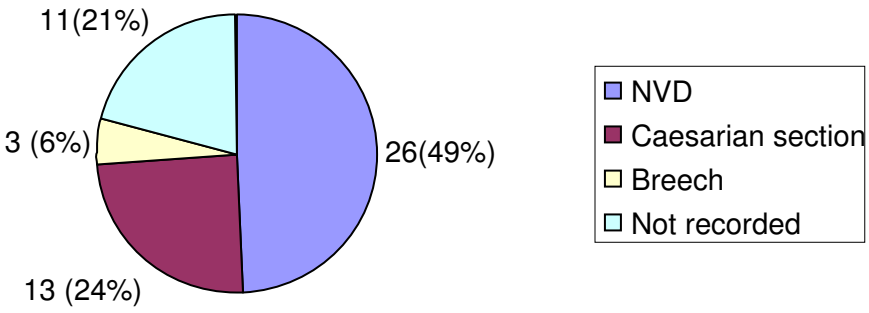
In this study antenatal diagnosis was made in two patients (2/53, 3.8%). Antenatal diagnosis was made in one patient with gastroschisis at CHBH who was delivered by Caesarian section at a gestation of 36 weeks. At JH one prenatal diagnosis was made in a

twin pregnancy. One of the twins had an omphalocoele and was delivered by Caesarian section at a gestation of 33 weeks. In two other cases at CHBH it was recorded that antenatal sonar was performed but no prenatal diagnosis of gastroschisis or omphalocoele was made.

3.3.2 Mode of delivery

The mode of delivery of cases with gastroschisis and omphalocoele are combined graphically and demonstrated in Figure 3.4.

Figure 3.4 Mode of delivery of cases with gastroschisis and omphalocoele



Forty-five percent (15/33) of patients with gastroschisis had a normal vaginal delivery, 27% (9/33) delivered by Caesarian section and 3 % (1/33) were breech deliveries. Of patients with omphalocoele, 55% (11/20) had a normal vaginal delivery, 20% (4/20) delivered by Caesarian section and 10% (2/20) were breech deliveries.

3.3.3 Place of delivery

Thirty-two patients, which accounts for 60% of the cases (19 gastroschisis and 13 omphalocoele) were referred to either JH or CHBH from elsewhere.

3.3.4 Gestational age and growth parameters

Overall, 29 of the patients with gastroschisis and omphalocoele were recorded as being term (54.7% or 29/53). Nineteen cases (19/53, 35.8%) were preterm, one was postdates and four did not have a gestational age recorded.

In the cases with gastroschisis, 51.5% (17/33) were term, 42.4% (14/33) were preterm and 6. 1% (2/33) did not have a gestational age recorded. In the cases with omphalocoele 60% (12/20) were term, 25% (5/20) were preterm, 5% (1/20) were postdates and 10% (2/20) did not have a gestational age recorded.

Birth weights were plotted on a standard growth chart against the recorded gestational age and birth weight. Forty-nine percent (26/53) of babies were appropriate for gestational age (16 gastroschisis, 10 omphalocoele), 17% (9/53) were small for gestational age (6 gastroschisis, 3 omphalocoele), one patient with an omphalocoele was large for gestational age. In 32.1% (17/53: 11 gastroschisis and 6 omphalocoele) it was not possible to plot the weight because the gestational age was not recorded.

3.3.5 Sex of cases

Overall, 64% (34/53) of the patients with gastroschisis and omphalocoele were male and 36% (19/53) were female. The male to female ratio was 1.6:1. There were 21 males and 13 females with gastroschisis (male: female ratio = 1.6:1), and 14 males and six females with omphalocoele (male: female ratio = 2.3:1).

3.3.6 Need for IPPV and surgery

Eighty-one percent of the patients with gastroschisis and omphalocoele were ventilated (31/53 (58%) gastroschisis; 12/53 (23%) omphalocoele).

In patients from CHBH, surgery was performed within the first day of life although the exact time of birth and surgery were not recorded. In patients from JH insufficient data is available to comment on when the surgery was performed. From the data retrieved it was difficult to ascertain whether primary surgical closure or a staged reduction using a "silo" was performed.

3.4 ADDITIONAL ABNORMALITIES AND USE OF GENETIC SERVICES

Genetic syndromes were only documented in cases with omphalocoele. A genetic diagnosis was made in eight of the patients: four patients had Pentalogy of Cantrell, three with suspected Beckwith-Weidemann syndrome and one had trisomy 18. On review of the data, another patient with omphalocoele had features suggestive of omphalocoele-exstrophy-imperforate anus-spinal defects complex (OEIS). A further three cases were noted to be dysmorphic but there were no results of any genetic testing having been

performed. Therefore 9/20 (45%) patients with omphalocoele definitely had a genetic condition but the figure may be as high as 12/20 (60%).

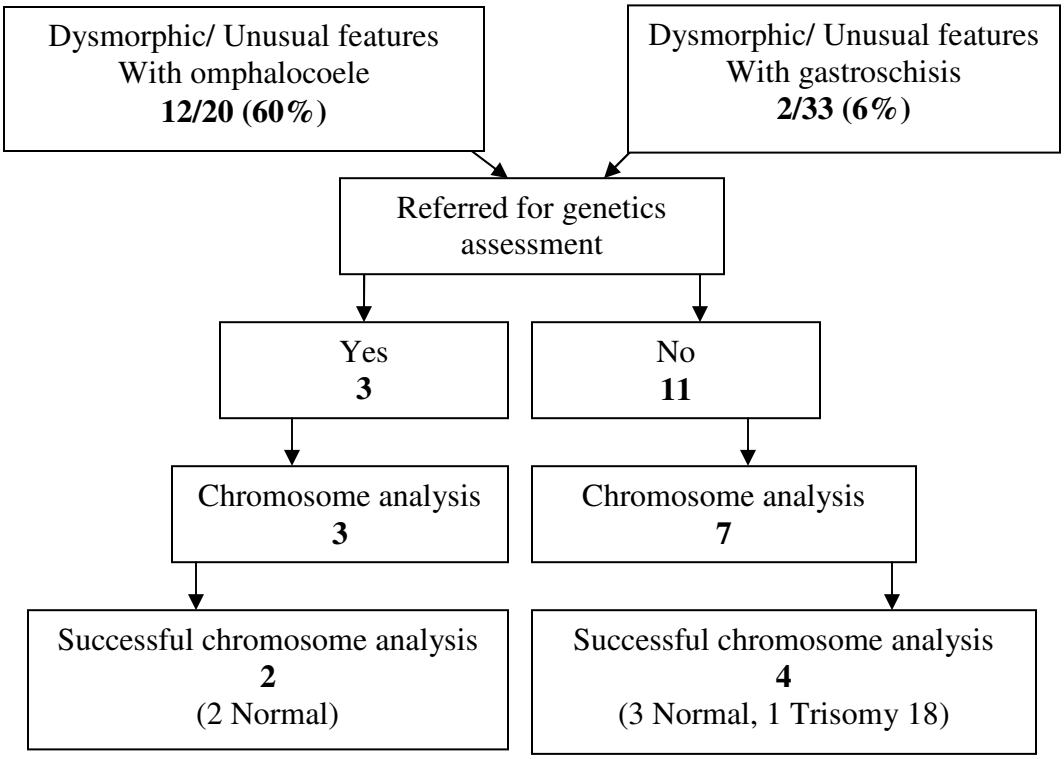
One patient with gastroschisis was documented as having small bowel atresia and volvulus and another patient had a patent ductus arteriosus and coarctation of the aorta. Therefore 2/33 (6%) of patients with gastroschisis had associated abnormalities.

A clinical geneticist was consulted about three of the 14 (21%) patients with additional abnormalities (1 omphalocoele, 2 gastroschisis).

Chromosome analysis was requested in a total of ten patients with gastroschisis and omphalocoele (10/53 or 18.9%). Of these, seven were not assessed by a clinical geneticist hence only three (3/53 or 5.6%) patients were seen by the clinical geneticist. Of the patients seen by the clinical geneticists, chromosome analysis was requested in these three patients. In two of these patients the chromosome analysis was normal but analysis failed in the third patient. From the seven who were not assessed by a clinical geneticist three patients had a normal karyotype and one had trisomy 18. Chromosome analysis was unsuccessful in the remaining three patients for technical reasons.

The use of genetic services in patients with omphalocoele and gastroschisis noted to have additional congenital abnormalities is summarized in Figure 3.5.

Figure 3.5 Summary of the use of genetic services in patients noted to have dysmorphic or unusual features

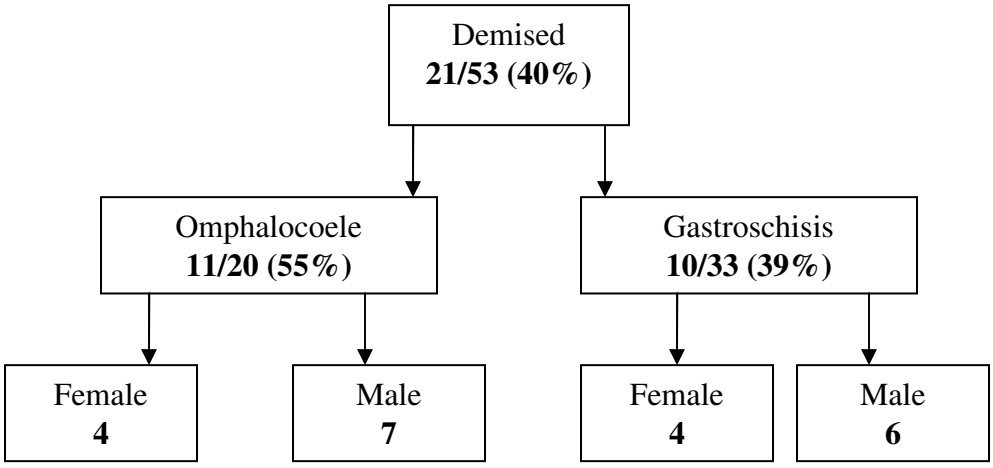


3.5 OUTCOME: MORTALITY

3.5.1 Sex of patients

Despite an overall higher proportion of male patients in the cohort, proportionally fewer male than female patients demised. Thirteen male patients demised (13/34, 38%) (6 with gastroschisis and 7 with omphalocoele) compared to eight female patients (8/19, 42%) (4 with omphalocoele and 4 with gastroschisis). The sex distribution in the cases that demised is summarized in Figure 3.6.

Figure 3.6 Number of male and female patients with gastroschisis and omphalocoele who demised.



3.5.2 Cause of death

Of the four patients with Pentalogy of Cantrell, three demised before discharge, and two of the three patients suspected to have Beckwith-Weidemann syndrome demised before discharge. The patient with trisomy 18 and an omphalocoele also demised prior to discharge. This accounted for 54.5% (6/11) of the patients with omphalocoele who demised. The patient with suspected OEIS was seen at the Genetic Clinic and demised after discharge from hospital. Therefore, overall, 58.3% (7/12) of patients with omphalocoele and additional abnormalities demised.

At least 12 of the patients in the study were documented to have sepsis and 7 (7/12, 58%) of these patients demised. The causes of death are summarized in Table 3.1.

Table 3.1 Cause of death in patients with gastroschisis and omphalocoele at Chris Hani Baragwanath and Johannesburg Hospitals prior to discharge

	Gastroschisis		Omphalocoele	
Year	**Number demised**	**Cause of death**	**Number demised**	**Cause of death**
2000	2	Necrotic bowel	1	Gestational diabetes mellitus with suspected trisomy 13/18
		Sepsis		
2001	2	Sepsis and infective endocarditis	1	Not recorded
		Liver and mesenteric tear		
2002	2	Small bowel atresia	1	Not recorded
		IVH* 4 and HMD‡		
2003	1	Not stated	2	Pentalogy of Cantrell
				Pentalogy of Cantrell and sepsis
2004	1	Not stated	3	BWS§
				Pentalogy of Cantrell and sepsis
				BWS§
2005	2	Infarcted bowel	3	Trisomy 18
		NEC † totalis with sepsis		Sepsis
				1 patient not recorded
Total	**10**		**11**	

IVH*- Intraventricular hemorrhage; NEC†-Necrotising enterocolitis; HMD‡-Hyaline membrane disease; BWS§ - suspected Beckwith-Weidemann syndrome

3.5.3 Age at time of demise

The age at the time of demise ranged from 1-58 days (median 9 days).

3.5.4 Transferred patients

A comparison of the outcome of patients with gastroschisis and omphalocoele that were transferred into either CHBH or JH Hospitals, or were inborn, is demonstrated in Table 3.2

Table 3.2 Summary of features of patients with gastroschisis and omphalocoele who demised compared to those who survived to discharge

	Demised		**Not demised**	
	Gastroschisis	Omphalocoele	Gastroschisis	Omphalocoele
Transfer in **Inborn**	8 2	7 4	11 12	6 3
GA* **Term** **Preterm**	 6 5	 7 3	 11 9	 5 2
Sex **Male** **Female**	 6 4	 7 4	 14 7	 7 2
Other anomalies	0	8	0	5
Sepsis	3(3CHBH) -*A Baumanii* -Infective endocarditis - suspected sepsis x2	4(2CHBH) -suspected sepsis - *Alcaligenes* sp CNS† + MRSA ☒ in 2patients)	4(3CHBH) -*Staphylococcus epidermidis* -*Acinetobacter sp* -Suspected sepsis *H Influenza* & ?fungal sepsis +MRSA‡ & *Klebs Pneumonia* + *Candida albicans* + CNS §	1(1CHBH) -septic abdominal wall (CNS §)

GA* gestational age CNS †Coagulase negative *Staphylococcus aureus* MRSA ‡ Methicillin resistant *Staphylococcus aureus*

Forty-seven percent (15/32: 8 gastroschisis and 7 omphalocoele) of the patients transferred in to the referral hospitals demised compared to 29% that were inborn (6/21: 2 gastroschisis and 4 omphalocoele). If analysed further 42% (8/19) of the patients with gastroschisis that were transferred in demised compared to 14% (2/14) that were inborn. In the cases with omphalocoele 54% (7/13) that were transferred in demised compared to 57% (4/7) that were in born. Therefore a higher proportion of the transferred patients who had omphalocoele (7/13, 54%) demised compared to those with gastroschisis (8/19,

42%). Because the number of patients are small, these figures need to be interpreted with caution.

Ten of the 31 patients (32%) with gastroschisis who were ventilated demised. Seven of the 12 patients (58%) with omphalocoele who were ventilated demised. The age in days when these infants demised range from 1-58 days of life (average 15.7 days). Twelve patients (12/17, 71%) demised between 1-15 days of life.

3.6 SUMMARY OF RESULTS

The study shows a 2.7 fold increase in the number of patients with gastroschisis seen at JH and CHBH over the study period compared to patients with omphalocoele, where no increase is seen when the figures are compared between 2000 and 2005. A high percentage (75%) of the patients were from Gauteng Province. Sixty percent of the patients with gastroschisis and omphalocoele were transferred in and 47% of those demised. In this study the birth prevalence of gastroschisis and omphalocoele is 0.36 per 1 000 live births.

The maternal age was significantly lower in patients with gastroschisis. There was poor recording of maternal data such as ANC booking status and exposure to cigarette smoke or recreational drugs. Only two cases (4%) of gastroschisis and omphalocoele were diagnosed antenatally. In the patients with gastroschisis, 42.4% were premature compared to 25% of those with omphalocoele. A higher percentage of patients in the study were male. The male to female ratio was higher in patients with omphalocoele. A higher proportion of female patients demised and sepsis appears to have played a role.

Additional congenital abnormalities suggestive of a syndrome were noted only in cases with omphalocoele (up to 60%) and 58.3% of these cases demised. Only 21% (3/14) of patients with additional abnormalities were referred for a genetic assessment.

CHAPTER 4

DISCUSSION

4.1 EPIDEMIOLOGY

This is the first study in Johannesburg to audit newborns with gastroschisis and omphalocoele seen at two tertiary institutions over a six year period, from 2000-2005. Over the study period, there was an increase in the total number of patients seen with gastroschisis and omphalocoele. In 2003 there was a drop in the number of patients with gastroschisis and omphalocoele seen at both JH and CHBH. The reason for this decline is unclear. The numbers of patients seen with gastroschisis and omphalocoele then increased, but the increase was higher in the patients with gastroschisis. There was an annual increase in the number of admissions to each of the units over the study period. However, this increase would have affected the number of patients with gastroschisis and omphalocoele equally. Due to the short time frame of the study the total number of cases seen are low, and the increase therefore must be interpreted with caution. However, the increase in the number of patients with gastroschisis is comparable to reports in the literature.[17,22]

In the study, the calculated expected number of patients with gastroschisis and omphalocoele was higher than the actual number of inborn patients seen at the two units. The estimated birth prevalence of gastroschisis and omphalocoele at JH and CHBH of 0.36 per 1 000 live births is only slightly lower than 0.4 per 1 000 live births calculation

used. A high proportion of patients with gastroschisis and omphalocoele were from Gauteng Province but did not appear to be clustered to a particular area of Gauteng. A difference was noted between the birth prevalence at the two hospitals and the reason for this difference is unclear. The movement of pregnant mothers into those geographic areas from surrounding areas however may affect the birth prevalence. From personal experience, when patients from neighbouring provinces register at one of the hospitals they give a local residential address. Without accurate information on the permanent maternal address it is difficult to comment on what impact this has on birth prevalence rates.

4.2 MATERNAL CHARACTERISTICS

In this study, the maternal age of patients with gastroschisis was significantly lower than that for patients with omphalocoele, which is comparable to other published studies.[6] Considering that in patients with gastroschisis, the maternal age clustered in the lower age range, 17-20 years, one might question whether the general trend in the population studied is toward a younger maternal age. This appears unlikely from data documenting a decline in teenage fertility rates.[40]

The maternal antenatal booking status and exposure to cigarettes, drugs and teratogens was poorly recorded in the study. If these mothers were booked at ANC and received antenatal care it would be interesting to examine what impact this practice would have on the rate of prenatal detection and outcome of the patients with gastroschisis and

omphalocoele. One cannot correlate the presented data with reports in the literature that maternal exposure to cigarettes or drugs are factors associated with gastroschisis.[6]

Antenatal diagnosis was made in only two cases in the study. According to the literature at least 80% of cases with gastroschisis and omphalocoele can be detected antenatally.[31] Lack of antenatal diagnosis impacts on the care of the patient because it reduces the chance of delivery at a suitable medical institution. Possible reasons why antenatal diagnoses were not made include: limited access to sonar equipment, trained sonographers and fetal medicine specialists; no maternal serum screening tests performed in the state hospitals; and mothers not attending ANC.

4.3 PATIENT DETAILS

According to the literature, the vaginal mode of delivery in patients with gastroschisis and omphalocoele is advocated.[35] In this study the recorded mode of delivery in 49% was by normal vertex deliveries and by Caesarian section in 24%, reflecting a high Caesarian rate. A number of factors may have affected this. One may speculate that the hospitals in the study are tertiary care centres where high risk patients are referred and hence have a lower threshold to perform Caesarian sections. Due to the low number of prenatal diagnoses it can be inferred that the mode of delivery was not influenced by the presence of either gastroschisis or omphalocoele. A higher proportion of patients with gastroschisis (42%) were recorded to be preterm compared to those with omphalocoele (25%), which is comparable to reports in the literature.[22]

4.4 OUTCOME

The disparity in the mortality of patients with gastroschisis and omphalocoele in low or middle-income countries and high-income countries was evident in this study (see section1.2.6).[28] The overall mortality of patients in the study was higher in patients with omphalocoele than those with gastroschisis; 61% of patients with gastroschisis survived compared to 45% of those with omphalocoele. The survival rates in gastroschisis reported here are slightly better than those reported in other middle- and low-income countries, where an average of 50% survive, but are lower than the 90% or more who survive in high-income countries.[28] At least 54.5 (6/11) of patients with omphalocoele that demised had additional congenital abnormalities which is comparable to reports in the literature.[6, 37] In order of importance, factors which appeared to impact whether or not a patient with gastroschisis or omphalocoele demised included: whether the patient was transferred to the referral hospital, if the patient was noted to have additional congenital abnormalities, sepsis and the sex of the patient.

From the literature, in the low- or middle-income countries, sepsis is reported as one of the factors associated with a high morbidity.[38] This finding was verified in this audit (see section 3.5.2, page 33). Unfortunately from this study one is not able to comment on factors that may have impacted whether an individual with gastroschisis and omphalocoele developed sepsis such as delayed time to surgery, and the duration of total parenteral nutrition along with indwelling lines

4.5 TRANSFER

The literature recommends transfer in utero of a patient with gastroschisis and omphalocoele to suitably equipped medical institutions because it lowers the risk of transporting a critically ill infant. Sixty percent of patients with gastroschisis and omphalocoele were outborn and were transferred to either JH or CHBH. This figure is likely the result of insufficient number of prenatal diagnoses, which would impact negatively on the outcome. Possible reasons for a higher mortality in the transferred infants seen in the study include the type of transport used, training of staff who transfer these ill neonates, time taken for the transfer (i.e. from time of birth and distance to the referral hospital). Information regarding the general condition of the babies transferred with gastroschisis and omphalocoele was not assessed in this study, but may be an important factor that needs to be closely analysed.

4.6 SEX DISTRIBUTION

An interesting finding of this study was that the sex distribution was different between patients with gastroschisis and omphalocoele. There was a higher male to female ratio in this study (1.6:1) and if split further, there was even a higher ratio of males in the patients with omphalocoele (2.3:1). The sex ratio of patients with gastroschisis and omphalocoele reported in the literature is generally 1:1 although smaller reports show a slightly higher female predominance in gastroschisis.[7-8] The higher male ratio has been previously reported in patients with omphalocoele.[26] The cause of this result is unknown.

4.7 CARE AND SURGERY

The study revealed that 81% of patients with gastroschisis and omphalocoele were ventilated in the intensive care units. This documents the importance of availability of intensive care facilities for patients with gastroschisis and omphalocoele. In the files from CHBH, surgery tended to be performed within the first 24 hours of life. The surgery ranged from primary closure of the abdominal wall to staged reduction as recommended in the literature.[28] It would have been interesting to analyze whether the time taken to surgery affected the outcome of these infants, and whether a shorter time to surgery influenced the development of sepsis. One would expect that the longer the time taken to close the defect the higher the chance was of developing sepsis.

4.8 USE OF GENETIC SERVICE

From this study additional congenital anomalies suggestive of a genetic syndrome were documented in 60% (12/20) of the patients with omphalocoele. Fifteen percent (3/20) of the patients with omphalocoele had chromosome analysis. Given that as many as 40% of patients with omphalocoele are reported to have chromosome abnormalities[6], submission of blood for karyotyping in patients with omphalocoele is too low. Further, of all the patients with gastroschisis and omphalocoele who had chromosome analysis, the analysis failed in 40%. Possible explanations for this may include samples being sent in the wrong tubes, the use of expired tubes and a delay in the samples arriving in the laboratory.

As reported in the literature, gastroschisis is uncommonly associated with chromosome abnormalities or genetic syndromes.[19] In this study two patients with gastroschisis had

additional abnormalities, namely, a cardiac abnormality and small bowel atresia and volvulus. From this study one is unable to comment whether or not there were subtle unusual features in the patients with gastroschisis, and whether genetic conditions may have been present.

Referral of all cases with gastroschisis and omphalocoele to the Genetic Clinic for a thorough examination and for genetic counselling would be ideal. This may assist to document accurate antenatal information and subtle unusual examination findings in these patients. The main role of genetic counselling would be to help the parents of the affected child understand the congenital anomaly, to dispel incorrect beliefs of possible causes of the birth defects and to discuss the risk of recurrence. This study reflects poor use of the genetic service because only 21% (3/14) of the patients with additional congenital anomalies were referred. Possible reasons why few patients were referred may include: patients or parents of the patients may have been referred to the Genetic Clinic but did not attend the clinic; doctors feel that they can make their own diagnosis and do not require specialist clinical genetics advice; ignorance of doctors who are not aware of the link between gastroschisis and omphalocoele and genetic conditions and doctors not understanding the role of genetic counselling.

4.9 LIMITATIONS AND PROBLEMS

This study highlights some of the challenges associated with data collection and doing research in South Africa. The numbers of patients analysed in the study are small making it difficult to accurately interpret the figures. The availability of files and data varied in

the different hospitals, with a higher proportion of analysed data coming from JH. Incomplete patient data and the inability to locate some of the files of patients with gastroschisis and omphalocoele was encountered. Hence the study failed to identify maternal risk factors such as exposure to cigarettes and drugs, thought to be important in the aetiology of gastroschisis. Patients with gastroschisis and omphalocoele from the private sector, and patients that demised prior to transfer to the referral hospitals, were omitted from the study. It would have been interesting to analyse and compare the patients from the private sector to those in the public sector especially with regard to factors affecting the morbidity and outcome.

CHAPTER 5

CONCLUSION

This is the first study of its kind to perform an audit of newborns with gastroschisis and omphalocoele seen at two teaching hospitals in Johannesburg over a six year period. This research met most of the study objectives. Firstly, this study demonstrated an increase in the number of patients seen with gastroschisis over the study period although this should be interpreted with caution. Secondly, it identified the factors which affected the mortality in patients with gastroschisis and omphalocoele. Thirdly, it documented and described the additional congenital anomalies that were seen mainly in patients with omphalocoele. And, finally, the study also demonstrated the poor use of the genetic counselling service. Unfortunately the study was unable to adequately assess maternal exposure to factors postulated in the aetiology of gastroschisis.

5.1 RECOMMENDATIONS

This study has highlighted a high mortality in the patients with gastroschisis and omphalocoele transferred into JH and CHBH. In order to address this issue, some recommendations can be made. Firstly, an improvement in prenatal screening would advance the treatment and outcome of patients with gastroschisis and omphalocoele in many respects. The screening of the high risk pregnancies would facilitate prenatal diagnosis and referral to the genetic service to ensure genetic counselling and appropriate genetic testing. This would facilitate the opportunity for couples to choose selective

termination of pregnancy after genetic counselling. Prenatal diagnosis would also play a role to ensure delivery at appropriate institutions and hence reduce the likelihood of transferring critically ill neonates. Secondly, an improvement in the quality of transport used to transfer neonates with gastroschisis and omphalocoele would help improve the chance of survival of the transferred infants.

Another broad area that may require attention to improve the care and reduce the mortality in patients with gastroschisis and omphalocoele is education. This education can target different aspects such as periconceptual care, prenatal care, and also target staff involved in transferring neonates with gastroschisis and omphalocoele and in-hospital management. Periconceptual care would provide an opportunity to educate women about factors that may have a detrimental effect on the pregnancy such as teratogen exposure, and would be a good starting point to encourage women to book early at ANC. This would allow for screening for high risk pregnancies. Education of staff at institutions where patients with gastroschisis and omphalocoele are delivered or cared for is ideal. This would involve the nursing staff, obstetricians, neonatologists, paediatric surgeons, and paramedics involved in inter-hospital transfer of patients. The education would need to target the care of patients with gastroschisis and omphalocoele including the use of the available genetic services.

In this study maternal and infant information was poorly documented. Improved documentation of clinical findings and treatment would be helpful in future retrospective studies. Education of staff involved in record capturing and physical storage of files,

documents or records would help to improve the collection of maternal and infant information and give information on trends in certain medical conditions, factors affecting outcome and may be useful to guide changes in clinical practice.

It may be beneficial to approach the doctors in tertiary institutions and encourage referral to the genetic service. This would include gynaecologists, obstetricians, fetal medicine specialists, neonatologists and paediatric surgeons. The referrals could take place when omphalocoele or gastroschisis is diagnosed in pregnancy, in a stillborn or live baby at the tertiary institution. Referral from all the different disciplines would help to ensure that all patients with gastroschisis and omphalocoele are fully examined and cared for. Referral to the genetic services would ensure genetic counselling for the parents, advice to medical staff on appropriate genetic tests and could assist to screen for other congenital anomalies. This would benefit the parents to ensure they have a clear understanding of the abnormality seen, may assist decision making by doctors and parents, and help with interpretation of the results (e.g. if a chromosome abnormality was detected).

The study numbers may have been small but it has identified many areas that are similar to reports in the literature, factors that need to be improved and several aspects regarding gastroschisis and omphalocoele that need to be investigated further. Exposure to teratogens and cigarettes in the South African population in mothers who have infants with gastroschisis remains unanswered from this study. Another factor that needs to be looked at is what impact antenatal diagnosis would have on patients with gastroschisis and omphalocoele in the local population. It would be interesting to see whether this

would improve the mortality, as is suggested in published literature. It would also be interesting to compare the differences between the cases with gastroschisis and omphalocoele seen at the private and public sector especially since the private sector facilities are similar to those offered in developed countries.

It may be beneficial to perform a larger prospective multicentre study, over a longer period of time, ideally also including still born infants and the private sector. This may help to obtain a more complete picture about gastroschisis and omphalocoele in South Africa.

APPENDIX A

DATA COLLECTION SHEET

Study number | | | | | |

Maternal details

Age | |

Address: Area _____

Province _____

Booked at antenatal clinic Y/N

Booking results HIV pos/neg, Wr pos/neg

Antenatal drugs Y/N

If Y specify which drugs and when taken

_____

_____

Smoker Y/N

Antenatal sonar Y/N/not recorded

If Y details _____

Was Prenatal diagnosis made Y/N

Baby details

DOB | | | | | | |

Inborn at CHB/JHB Y/N

If N state which hospital referred from _____

Approximate age on arrival (hrs) _____

Mode of delivery; NVD/Breech/Caesar/Not stated

Gestational age | |

specify how determined Ballard/ Dates/Sonar/ not specified

Birth weight(gm) | | | | |

Length(cm) | | | |

Head circumference (cm) | | | |

Sex M/F

Defect Gastroschisis/Omphalocoele
Other anomalies Y/N
If Y specify below

_____
_____
_____
_____
_____
_____

Chromosomes sent Y/N
If Y: date sent and results _____

Seen at genetics Y/N
If Y mother/baby/both
Surgery Y/N
Date of first surgery _____
IPPV Y/N
If Y how many days _____
Outcome- demised Y/N
If Y age in days _____

APPENDIX B

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Beckh-Arnold

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M060820**
PROJECT	Gastroschisis and mphalocoele: Audit at Two Referral Hospitals in Johannesburg, South Africa .....
INVESTIGATORS	Dr E Beckh-Arnold
DEPARTMENT	Human Genetics
DATE CONSIDERED	06.08.25
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 06.08.28 **CHAIRPERSON** .....
(Professor A Dhai)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr N Gregersen

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

9/11/06

APPENDIX C

Total live births and number of all cases with gastroschisis and omphalocoele at Chris Hani Baragwanath and Johannesburg Hospitals from 2000-2005

Year	2000	2001	2002	2003	2004	2005
Live births						
JH*	6831	6927	6827	7034	6920	6760
CHBH†	17693	18150	18667	18973	19572	19767
No of cases seen						
Gastroschisis						
JH*	5	5	5	2	3	3
CHBH†	1	5	5	2	6	13
Omphalocoele						
JH*	2	0	2	3	3	2
CHBH†	8	3	3	0	4	8

JH* Johannesburg Hospital; CHBH†Chris Hani Baragwanath Hospital

REFERENCES

1. "Management of birth defects and haemoglobin disorders: report of a joint WHO-March of Dimes meeting. Geneva, Switzerland 17-19 May 2006". www.who.int/genomics/publications/WHO-MODreport-final.pdf (September 2009)
2. Christianson A, Howson CP, Modell B. March of Dimes Global report on birth defects. March of Dimes Birth Defects Foundation, 2006 .
3. UNICEF "Statistics" www.unicef.org/infobycountry/southafrica_statistics.html (September 2009)
4. International Clearinghouse for birth defects Monitoring Systems (ICBDMS). 1998. World Atlas of Birth Defects. 1st edition. ICBD and European Register of Congenital Abnormalities and Twins (EUROCAT)
5. Magnuson DK, Parry RL, Chwals WJ. Selected abdominal gastrointestinal anomalies. In: Martin RJ, Fanaroff AA, Walsh MC eds. Fanaroff and Martin's Neonatal-Perinatal Medicine, Diseases of the fetus and infant. 8th ed., Philadelphia. Mosby Elsevier, 2006;1381-1403
6. Wilson RD, Johnson MP. Congenital wall defects: an update. Fetal Diagn Ther 2004;19:385-398.
7. Hougland KT, Hanna AM, Meyers R, Null D. Increasing prevalence of gastroschisis in Utah. J Pediatr Surg 2005;40:535-540.
8. Goldkrand JW, Causey TN, Hull EE. The changing face of gastroschisis in southeast Georgia. J Matern Fetal Neonatal Med 2004;15:331-335.

9. Picture references (Omphalocele and gastroschisis) J Glasser. “Gastroschisis and omphalocoele”. Updated Jul 22, 2009 http://emedicine.medscape.com/article/975583-overview (September 2009)
10. Sadler TW, Feldkamp ML. The embryology of body wall cosure: Relevance to gastroschisis and other ventral body wall defects. Am J Med Genet 2008;148C:180-185.
11. Duhamel B. Embryology of exompholos and allied malformations. Arch Dis Child 1963;38:142-147
12. Shaw A. The myth of gastroschisis. J Pediatr Surg 1975;10:235-244
13. deVries PA. The pathogenesis of gastroschisis and omphalocoele. J Pediatr Surg 1980;15:245-251
14. Hoyme HE., Higginbottom MC, Jones KL. The vascular pathogenesis of gastroschisis: Intrauterine interruption of the omphalomesenteric artery. J Pediatr Surg. 1981;98:228-231
15. Feldkamp MI, Carey JC, Sadler TW. Development of gastroschisis: Review of hypothesis, a novel hypothesis, and implications for research. Am J Med Genet 2007;143A:639-652
16. Ledbetter DJ. Gatroschisis and omphalocele. Surg Clin N Am 2006;86:249-260.
17. Di Tanna GL, Rosano A, Mastroiacovo P. Prevalence of gastroschisis at birth: Retrospective study. BMJ. 2002: 325:1389-1390.
18. Kazura MR, Lie RT, Ingrens LM, Diriksen A, Kapstad M, Egenaes J et al. Increasing risk of gastroschisis in Norway: An age-period-cohort analysis. Am J Epidemiol. 2004:159:358-363.

19. Mastroiacovo P, Lisi A, Castilla EE. The incidence of gastroschisis: Research urgently needs resources. BMJ 2006;332:250-251.

20. Nichols CR, Dickinson JE, Pemberton PJ. Rising incidence of gastroschisis in teenage pregnancies. J Matern Fetal Med 1997;6:225-229.

21. Opitz JM, Pysher TJ. Invited editorial comment: Further reflections on Gastroschisis. Am J Med Genet 2008;148C:192-198

22. Tan KH, Kilby MD, Whittle MJ, Beattie BR, Booth IW, Botting BJ. Congenital anterior abdominal wall defects in England and Wales 1987-93: retrospective analysis of OPSC data. BMJ 1996;31(7076):903-6.

23. Hunter AGW, Stevenson RE. Gastroschisis:clinical presentation and associations. Am J Med Gen 2008;148C:219-230

24. Robertson SP, Twigg SR, Sutherland-Smith AJ, Biancalana V, Gorlin RJ, Horn D et al. Localized mutations in genes encoding the cytoskeletal protein filamin A cause diverse malformations in humans. Nat Genet 2003;33(4): 487-491)

25. Vermeij-Keers C, Hartwig NG, van der Werff JF. Embryonic development of the ventral body wall and its congenital malformations. Semin Pediatr Surg 1996;5(2):82-9.

26. Lisi A, Botto L, Rittler M, Castilla E, Bianchi F, Botting B et al. Sex and congenital malformations: an international perspective. Am J Med Genet A. 2005 Apr 1;134A(1):49-57

27. Groves R, Sunderajan L, Khan AR, Parikh D, Brain J, Samuel M. Congenital anomalies are commonly associated with exomphalos minor. J Pediatr Surg 2006;41(2): 358-361.

28. Nichol PF, Bryne JLBB, Dodgion C, Saijoh Y. Clinical considerations in gastroschisis: Incremental advances against a congenital anomaly with severe secondary effects. Am J Med Genet 2008;148C:231-240
29. UNAIDS.2007. "AIDS epidemic update: December 2007". http:www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2007/default.asp (Sept 2009)
30. DeSantis M, Carducci B, DeSantis L, Cavaliere AF, Straface G. Periconceptional exposure to efavirenz and neural tube defects. Arch Intern Med 2002;162(3):355
31. Hanna JS, Neu RL, Lockwood DH. Prenatal cytogenetic results from cases referred for 44 different types of abnormal ultrasound findings. Prenat Diagn 1996;16(2):109-115
32. Saada J, Oury J, Vuillard E, Guibourdenche J, De Lagausie P, Sterkers G et al. Gastroschisis. Clin Obstet Gynecol. 2005;48(4):964-972.
33. Mann S, Blinman TA, Wilson RD. Prenatal and postnatal management of omphalocoele. Prenat Dagn 2008;28: 626-632
34. Harper P. Genetic Counselling: an introduction. In: Practical genetic counselling. 6th ed., Oxford Univ Press, 2004, 3-20.
35. Segel S, Marder S, Parry S, Macones G. Fetal abdominal wall defects and mode of delivery: a systematic review. J Obstet Gynaecol 2001;98:867-873.
36. Ryckman J, Aspirot A, Laberge J, Shaw K. Intestinal venous congestion as a complication of elective silo placement for gastroschisis. Semin Pediatr Surg.2009; May:18(2), 109-112

37. Heider AL, Strauss RA, Kuller JA. Omphalocele: clinical outcomes in cases with normal karyotypes. Am J Obstet Gynecol 2004;190(1):135-141

38. Vilela PC, de Amorim, Falbo GH, Santos LC. Risk factors for adverse outcome of newborns with gastroschisis in a Brazilian Hospital. J Pediatr Surg 2001;36(4):559-564

39. Arnold M. Is the incidence of gastroschisis rising in South Africa in accordance with international trends? A retrospective analysis at Pretoria Academic and Kalafong Hospitals, 1981-2001.S Afr J Surg. 2004;42:86-88.

40. Moultrie T, McGrath N. Teenage fertility rates falling in South Africa. Scientific letter. SAMJ 2007;97(6):442-443).

41. Sekabira J, Hadley GP. Gastroschisis: a third world perspective. Report. Pediatr Surg Int 2009; Apr 25(4):327-9