# EPIDEMIOLOGY OF OMPHALOCELE AND GASTROSCHISIS IN GLASGOW

by

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To the memory of my father, who guided my paths and filled my life with love and confidence.

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## DECLARATION

The work, study design and statistical analysis contained in this thesis was performed by myself.

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| | |
|---|---|
| GGHB | Greater Glasgow Health Board |
| GRCA | Glasgow Register of Congenital Anomalies |
| AWDs | Abdominal wall defects |
| O&G | Omphalocele plus gastroschisis |
| OM | Omphalocele |
| GAS | Gastroschisis |
| IA | Induced abortions |
| PND | Prenatal diagnosis |
| MSAFP | Maternal serum alpha-fetoprotein |
| NTD | Neural tube defects |
| RR | Relative risk |
| OR | Odds ratio |
| NS | Not significant |
| U/K | Unknown |
| MAL | Malformed |
| NON-MAL | Non-malformed |
| M H | Mantel-Haenszel test |
| CI | Confidence interval |
| R | References |
| EUROCAT | European Register of Congenital Anomalies and Twins |

## ABSTRACT

Omphalocele and gastroschisis (O&G) are relatively common congenital anomalies. Omphalocele (or exomphalos) is defined as herniation of some intra-abdominal contents through the umbilical ring in to the cord. This defect has a membrane over it, and may contain abdominal organs. Gastroschisis is defined as a full-thickness defect in the abdominal wall without herniation or a covering membrane.

The aetiology of omphalocele and gastroschisis is still in doubt. Epidemiological studies suggest that the cause of these defects might be multifactorial, but hypotheses relating to gastroschisis have focused more on environmental factors.

This study reports descriptive and case-control epidemiological findings from an investigation of abdominal wall defects in Greater Glasgow Health Board, Scotland, United Kingdom between the birth years 1980 and 1993. All registered cases (live births, stillbirths and induced abortions following prenatal diagnosis) of O&G, primary and secondary were included.

The aims of the study were, firstly, to establish the epidemiology of O&G in Glasgow; secondly, to determine the extent of any association between the prevalence of O&G and a number of the hypothetical risk factors, particularly maternal age, cigarette smoking, and socio-economic status; thirdly, to assess the extent and epidemiological impact of prenatal diagnosis on the prevalence of O&G.

During 1980-1993, 73 cases of omphalocele (4.1 per 10,000 births) and 24 cases of gastroschisis (1.3 per 10,000 births) were registered. The pregnancy prevalence of gastroschisis (but not omphalocele) showed a significantly increasing trend over time. The prevalence rate of omphalocele in Glasgow appears to be the highest in the United Kingdom.

The male to female ratio was 2.0 for gastroschisis and 0.8 for omphalocele.

The risk of gastroschisis was inversely correlated maternal age (chi-square= 8.8; $p<0.003$). The highest rate was found for maternal age under 20. There was a greatly

increased risk for young mothers of isolated gastroschisis (under 20 years) compared to those aged over 20 years: these young mothers were 7.8 times more at risk (95% CI= 3.08 to 19.79). In the case-control study, age remained a significant risk factor in the multivariate analysis.

The prevalence of the two malformations showed no significant seasonal variation, nor a strong and consistent association with socio-economic status, as determined by postcode of maternal residence.

Both defects were associated with early birth and low birth weight, an effect that was more pronounced for multiple malformed than for isolated cases. Isolated cases of gastroschisis had significantly lower birth weights than isolated cases of omphalocele.

There was a significant association of omphalocele with other malformations ($p< 0.0001$). The most common abnormalities among O&G were musculoskeletal anomalies (26%), genital and urinary abnormalities (15%), neural tube defects (13%), and GI in the upper alimentary tract (13%). Omphalocele was also associated with trisomies 13, 18 and Beckwith-Wiedemann syndrome.

The percentage of smokers in isolated cases of gastroschisis was significantly higher than that in associated cases (Fisher's exact test, two tailed = 0.01). In the case-control study, after logistic regression smoking remained a significant risk factor among gastroschisis cases compared to non-malformed controls (RR= 3.8, 95% CI =1.16 to 12.45) and malformed+ non-malformed controls (RR= 2, 95% CI =1.12 to 3.4).

The length of survival during first week and first year was significantly longer among infants with gastroschisis than omphalocele ($p=0.005$ up to first week; $p=0.001$ up to one year). Perinatal deaths were more frequent among omphalocele cases than gastroschisis ($p=0.09$).

While the proportion of gastroschisis prenatally diagnosed significantly increased from 1980-1986 to 1987-1993 (Fisher's exact test=0.01), the proportion terminated did not. Although the proportion of omphalocele prenatally diagnosed non-significantly increased

in that time, the proportion of prenatally diagnosed cases that were terminated showed a non-significant decrease.

Although the numbers of cases are small, this study has highlighted several epidemiological features of O&G that could be important aetiologically.

A comprehensive public health strategy, including antenatal screening, is probably required to prevent these anomalies.

## DEFINITIONS

ABDOMINAL WALL DEFECTS: Between five and ten weeks of gestation, most of the small intestine is located outside the abdominal cavity as a result of a discrepancy between rapidly enlarging intestines and the abdominal cavity. By the 11th week of gestation, all of the bowel should return to the abdominal cavity. Omphalocele and gastroschisis are defects of the anterior abdominal wall.

OMPHALOCELE: Failure of anterior extension of the embryonic folds during the process of closing of the abdomen of the embryo results in a defect of variable size in the umbilical region which is covered by amnion. Omphalocele is a large abdominal wall defect with herniation of midgut, liver and other abdominal organs into a translucent sac at the umbilical ring. The size of defect is variable and can range from four to > 10 cm. The umbilical cord inserts in the sac. The sac may contain small and large bowel, stomach, liver, spleen, bladder, uterus and ovaries.

GASTROSCHISIS: Errors in development of the somatopleure lateral to the apex of the embryonic folds results in the formation of a paraumbilical full thickness defect in the abdominal wall. Gastroschisis is a small abdominal wall defect occurring just to the right of the umbilical cord. There is no sac, and midgut alone appears outside the abdominal wall.

PRENATAL DIAGNOSIS: Prenatal diagnosis is defined as any specific investigation undertaken after prenatal screening (usually serum alpha-fetoprotein assay, or ultrasound, or both) with a view to establishing the presence or otherwise of a fetal abnormality.

EPIDEMIOLOGY: Epidemiology is a term derived from the Greek language (epi= upon; demos= people; logos= science). It is a science concerned with health events in human populations. In practical terms, it is the study of how various states of health are distributed in the population and what environmental conditions, life-style, or other circumstances are associated with the presence or absence of disease. Epidemiology is "the study of the distribution and determinants of health- related states or events in specified populations, and the application of this study to control of health problems" (Last, 1988). Epidemiologists are essentially medical detectives concerned with the

who, what, where, when, and how of disease causation. When an agent is finally identified, public health officials can take steps to prevent or control the occurrence of the disease. So "epidemiologists are concerned not only with death, illness and disability, but also with more positive health states and with the means to improve health" (Beaglehole *et al.*, 1993).

The objectives of epidemiology are:

- To describe the distribution and size of disease problems in human populations.
- To provide the data essential to the planning, implementation and evaluation of services for prevention, control and treatment of disease and to the setting up of priorities among those services.
- To identify aetiological factors in the pathogenesis of disease.

Epidemiological investigations employ one or more of the following approaches:

*Descriptive epidemiology.* The first phase of epidemiological investigation; applying epidemiological methods to generate descriptions of the time, place, and person characteristics of disease distribution.

*Analytical epidemiology.* Use of epidemiological methods to test hypotheses about causality; the second phase of epidemiological investigations.

*Experimental epidemiology.* Use of experimental studies to establish disease causality.

*PREVENTION.* The act of hindering or forestalling development or progression of disease.

*Primary prevention.* Actions directed toward intervening in the natural history of disease during the stage of susceptibility, before any pathological changes occur in a host. These actions seek to keep the agent away from the host or to increase host resistance.

*Secondary prevention.* Actions directed toward early detection and treatment of disease.

*Tertiary prevention.* Actions directed toward limiting disability from disease or restoring function.

PREVALENCE RATE: The total number of all individuals who have an attribute or disease at a particular time (or during a particular period) divided by the population at risk of having the attribute or disease at this point in time or midway through the period.

AETIOLOGY: Postulated causes that initiate the pathogenic process.

PERINATAL MORTALITY RATE: Literally, mortality around the time of birth. Conventionally this time is limited to the period between 28 weeks before 1992 and 24 weeks after 1992 gestation and one week postnatal. This is defined as;

$$\text{Perinatal mortality rate} = \frac{\text{Fetal deaths + postnatal deaths (first week)}}{\text{Fetal deaths + live births}} \times 1000$$

STILLBIRTHS: All fetal deaths after 28 completed weeks from 1980-1991 and after 24 completed weeks from 1992.

SECULAR TRENDS: Changes over long periods of time, generally years or decades.

BIRTH DEFECTS REGISTRIES: They seek to document congenital anomalies that are apparent at or soon after birth. They may suffer from incompleteness due to omission of stillbirths and of congenital anomalies that do not declare their presence until later in life, such as certain forms of congenital heart lesion, mental deficiency, and neurological disorders.

SOCIO-ECONOMIC STATUS: Descriptive term for a person's position in society, which may be expressed on an ordinal scale using such criteria as income, educational level attained, occupation, value of dwelling place, etc. or by means of a proxy indicator (education, address etc.).

CASE-CONTROL STUDY: A study that starts with the identification of persons with the disease of interest and a suitable control group of persons without the disease. The controls should be representative of the population from which the cases come. The relationship of an attribute to the disease is examined by comparing the disease and non-disease with regard to how frequently the attribute is present, or if quantitative, the levels of the attribute, in each of the groups.

CONTROLS, MATCHED: Controls who are selected so that they are similar to the study group, or cases, in specific characteristics. Some commonly used matching variables are age, sex, race, and socio-economic status.

ISOLATED DEFECT: Omphalocele and gastroschisis are considered isolated if there are no associated anomalies or if anomalies present (such as intestinal atresia or stenosis, undescended testicles or lung hypoplasia) were thought to be a consequence of these conditions.

MULTIPLE MALFORMED INFANTS: All cases of congenital anomaly associated with major and minor omphalocele and gastroschisis were considered to be multiple malformed.

MALFORMED CHILDREN: Data are collected on all children with major and /or minor congenital malformations detected.

VARIABLE: Any attribute, phenomenon, or event that can have different values.

*Confounding Variable*. A factor that causes change in the frequency of a disease and also varies systematically with a third, potentially causal factor being studied. When uncontrolled, a confounding variable masks or distorts the effect of the study variable.

*Dependent Variable*. A variable which is dependent on the effect of other variables; a manifestation or outcome we seek to explain through the influence of exposure variables.

*Independent Variable*. The exposure or characteristic being observed or measured that is hypothesized to influence the outcome of interest or in statistics, an independent variable is one of (perhaps) several variables that appear as arguments in a regression equation.

CONFOUNDING:

1. A situation in which the effects of two processes are not separated. The distortion of the apparent effect of an exposure on risk brought about by the association with other factors that can influence the outcome.
2. A relationships between the effects of two or more causal factors as observed in a set of data.
3. A situation in which a measure of the effect of an exposure on risk is distorted because of the association of exposure with other factor(s) that influence the outcome under study.

FACTOR: One of the elements, circumstances, or influences that contribute to product a result.

RISK FACTOR: An attribute or exposure that is associated with increased probability of a specified outcome, such as the occurrence of a disease.

This term is used in three ways:

1. An attribute or exposure associated with an increased probability of a specified outcome; a risk marker.
2. An attribute or exposure that increases the probability of occurrence of disease or other specified outcome; a determinant.
3. A determinant that can be modified by intervention, thus reducing the probability of occurrence of a disease or other specified outcome; (a modifiable risk factor).

RELATIVE RISK: The ratio of the risk (probability) of disease among those exposed and the risk among those not exposed.

MULTIVARIATE ANALYSIS: Techniques used when the variation in several variables has to be studied simultaneously. In statistical terms, any analytic method that allows the simultaneous study of two or more dependent variables.

# SECTION I: INTRODUCTION

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## 1.1. *HISTORICAL NOTE*

Omphalocele has been known as long as medicine has been practised. It was never clearly described by the physicians of antiquity and it was only at the time of the Renaissance that detailed descriptions appeared in the medical literature (Rickham, 1970). In 1634, Ambrose Pare' was the first to describe an infant with omphalocele. Calder is given for credit for describing the first detailed reported case of gastroschisis in 1733. Scarpa, in 1803, was credited with separating congenital from acquired forms of abdominal wall defects (Grosfeld and Weber, 1982).

Omphalocele has been designated by many names, such as "tunicular hernia of the umbilicus", "hernia into the cord", "umbilical eventration", "amniotic hernia", "exomphalos", or omphalocele (Gross, 1953). Tarrufi, in 1894, introduced the word gastroschisis in referring to all congenital malformations of the abdominal wall (Grosfeld and Weber, 1982) and the term of "gastroschisis" ('belly-cleft') was used by teratologists in the nineteenth century and early twentieth century to designate lesions which are now referred to as omphalocele (Irving, 1990). Moore and Stokes (1953) suggested that the term gastroschisis should be reserved for those cases in which the abdominal wall defect lies adjacent to a normally inserted umbilical cord and in which there is no evidence of a sac covering the extruded viscera (Irving, 1990). In this classification "gastroschisis" and "omphalocele" were selected from the multiple terms then in use as appropriate terms from their Greek derivation e.g. "belly rent, cleft, or separation" for gastroschisis and "hollow navel" for omphalocele. The newer terms also bore a similarity to terms in use for uncovered and covered dorsal midline birth defects, rachischisis and meningocele (Moore, 1977).

Rare surgical cures were reported in the nineteenth century, but no significant progress was made until 1948, when Gross introduced a staged method to cover large omphalocele (Allen, 1980). Gastroschisis is such a fatal condition that it is not surprising that successful operation for this anomaly has become possible only during recent years. Watkins was the first to report a successful surgical cure in 1943 (Rickham, 1970). By 1937, 350 cases of omphalocele had appeared in the medical literature; however, it was not entirely clear if some of the these cases with rupture were not actually instances of gastroschisis. Due to the very high neonatal mortality noted in the past in infants with omphalocele and particularly with

gastroschisis, it is highly probable that many cases were neither treated nor accurately recorded (Grosfeld and Weber, 1982).

## 1.2. *PATHOLOGY AND EMBRYOLOGY*

### 1.2.1. **Pathology**

Omphalocele is the herniation of some of the intra-abdominal contents through the open umbilical ring. It differs from umbilical hernia in that the protrusion is not covered by skin but by a translucent, avascular membrane consisting of peritoneum inside and amniotic membrane outside, separated by Wharton's jelly. The umbilical cord is usually inserted into the apex of the sac and the umbilical vein and arteries run within its walls (Rickham, 1970). Rupture of the omphalocele sac either *in utero* during labour or after birth is a well known complication. The size of the abdominal wall defects in omphalocele varies from a small opening through which only one or two knuckles of small intestine or a Meckel's diverticulum protrude, to an enormous defect with the stomach, all the small and large intestine, most of the liver, the pancreases, spleen, bladder, etc., all contained in the sac, leaving the peritoneal cavity virtually empty.

Irving (1990) suggested that the term 'hernia' of the cord should be used to define those cases with an umbilical defect of less than 4 cm and a sac which contains only loops of intestine. Moore's (1977) suggested classification is into types 1, 2 and 3 with defect diameters of <2.5 cm, 2.5 to 5 cm and >5 cm respectively. Rickham (1970) reported that omphalocele is often divided into omphalocele minor, where the diameter of the abdominal wall opening is less than 5 cm, and omphalocele major, where it is larger than 5 cm, so the size of the omphalocele sac is very variable; it may occasionally be so large as to interfere with delivery. The covering membranes are at first translucent, soft and pliable, and it is possible to observe coils of intestine, liver and other intra-abdominal organs through them.

The size of the omphalocele sac depends to a certain extent on the distension of the loops of intestine which fill it. At birth the sac may be small, but once the infant starts swallowing air and the intestine becomes distended, the size of the sac may rapidly increase. The abdominal skin may stop at the neck of the omphalocele, but it may extend for a distance up the side of

the sac. Occasionally the sac ruptures during, or just before, delivery. The child is born with eviscerated intestine protruding through the abdominal defect. The intestines appear normal and, provided no contamination occurs and the defect is closed immediately, peritonitis may not result. If the sac has ruptured *in utero* some time before delivery, the appearance of the intestine is similar to that in gastroschisis. The condition can be distinguished from gastroschisis by the fact that the abdominal defect is centred at the umbilicus and, in addition, remnants of the sac are frequently discovered between the coils of eviscerated intestine (Rickham, 1970). In most cases the membrane is shiny and intact at birth, but because of the lack of blood vessels it begins to die immediately and becomes opaque, malodorous and necrotic within 12 hours. If untreated, rupture and evisceration follow (Jones, 1976). In omphalocele, at birth the sac consists of a thin translucent membrane composed of peritoneum internally, and amniotic membrane externally.

While the sac is usually intact at delivery, rupture occasionally occurs *in utero* or during delivery. This complication creates an emergency, and return of the intestines to the peritoneal cavity with repair of the abdominal defect should not be delayed (Swenson, 1969). Particular care is necessary for gastroschisis during transport to hospital to prevent severe hypothermia due to heat lost from the extruded viscera. Operation is performed as soon after birth as possible. The condition is one of the group of neonatal emergencies (Jones, 1976).

Gastroschisis is a full-thickness defect in the abdominal wall which takes the form of a smooth edged cleft either immediately adjacent to the umbilical cord or, much less commonly, separated from it by a strip of skin (Irving, 1990). The opening in the abdominal wall is small (less than 5 cm), lies adjacent to the umbilicus and no remnant of sac is found (Allen, 1980). The defect is usually located to the right of the umbilicus, and few left-sided defects have been described in the literature. Stomach and intestine are frequently herniated but, in contrast to omphalocele, other intra-abdominal organs have rarely eviscerated (Rickham, 1970). The eviscerated intestines usually show evidence of foetal peritonitis because of the irritative effect of the amniotic fluid on the intestinal serosa. They are markedly dilated with grossly thickened and oedematous walls. The intestines are often adherent to each other and surrounded by oedematous gelatinous material. The intestinal circulation is always impaired. No peristaltic movements can be observed. The caecum is usually cone-shaped with the

appendix arising from its apex and the intestine are frequently abnormally short (Jones and Woodward, 1986).

### 1.2.2. **Embryology**

There is still considerable controversy about the precise embryogenesis of omphalocele and gastroschisis, the main point at issue being the question of whether the two lesions represent distinct developmental anomalies or whether they have a common embryogenesis (Irving, 1990).

According to one view, between five and 10 weeks of gestation most of the small intestine is located outside the abdominal cavity as a result of a discrepancy between rapidly enlarging intestines and the abdominal cavity (Moore and Persaud, 1993; Nyberg and Mahony, 1993). By the 11th week of gestation, all of the bowel should return to the abdominal cavity (Paidas *et al.*, 1994).

During the past two decades, many of the early concepts of embryology relating to defects of the abdominal wall were based on Duhamel's work on the subject reported in 1963 (Grosfeld and Weber, 1982). Duhamel suggested that abdominal malformations result from developmental or structural defects in the embryonal folds responsible for ventral closure of the embryo (Duhamel, 1963). The final appearance of the abdominal wall defects is dependent on a number of factors including the return of the midgut from its extracoelomic location in the yolk sac and the circumferential infolding of the four abdominal wall defects folds: cephalic, caudal and two lateral components (Grosfeld and Weber, 1982). These folds contain a dorsal somatic and ventral splanchnic layer and are condensations of embryonic mesenchyme. The folds fuse around the umbilical ring. Duhamel felt that a central omphalocele resulted from a major defect of inhibition of the lateral abdominal wall folds that occurred early in gestation (week 3 or 4) (Duhamel, 1963). Abnormal development of either the cephalic or caudal folds could lead to an epigastric or lower midline omphalocele respectively. These observations have been frequently referred to and supported by other investigators.

According to the concept of Izant *et al.* (1966), the early embryo for anterior abdominal wall formation is a flat oval disk composed of three layers: (1) a dorsal ectoderm, continuous with the amnion; (2) a ventral entoderm, continuous with the yolk sac; and (3) an intermediary

mesoderm. Condensation, then division of the mesenchyme adjacent to the amnion and yolk sac form the extra-embryonic coelom. Separation of the condensed mesenchyme adjacent to the ectoderm (somatopleure) and the entoderm (splanchnopleure) provides the intra-embryonic coelom. As growth proceeds, the lateral walls fold over to form the ventral wall of the embryo. The foregut is formed by the distal growth of the cephalic fold; this is the origin of the thoracic and epigastric wall and the septum transversum. A caudal fold closes the hindgut and forms the hypogastric wall; from this area the allantois develops. Formation of the ventral wall by these four folds, with the apex at the umbilicus, is completed in the third week. Inhibition of this morphologenesis (closing the body of the embryo) leads to a general category of defects called celosomias. When the upper fold is involved, omphalocele (exomphalos) is accompanied by defects of the sternum, diaphragm, and heart. A simple omphalocele is the result of teratogenic effects on the lateral folds. The omphalocele type of malformation can be differentiated from abnormalities resulting from interference with other phases of embryonic development.

Gastroschisis results from a failure of differentiation of the embryonic mesenchyme forming the somatopleure of the lateral abdominal wall. Resorption of the ectoderm adjacent to the somatopleure leads to the formation a paraumbilical defect; there is no peritoneal-amnion sac as in an omphalocele. A minor variation of gastroschisis is localized hypoplastic abdominal musculature with intact overlying skin. The hernia of the cord results from a failure of the extra-embryonic coelom to close; bowel remains outside the abdominal cavity or "prolapsing" through the persisting peritoneal defect (Irving, 1991). Gray and Skandalakis (1972) considered omphalocele a result of faulty migration of myotomes resulting in incomplete muscular closure of the abdominal wall. They postulated that failure of the return of the bowel from the yolk sac into the developing peritoneal cavity removes a necessary stimulus for both enlargement and growth of the abdominal wall. Margulies (1945) suggested that small hernias of the umbilical cord resulted from a failure of closure of the umbilical ring itself occurring a number of weeks later in gestation (at 8-10 weeks). Studies of human embryos by Wyburn (1953) do not support Duhamel's contention that the formation of the ventral abdominal wall was related to differentiation of the mesoblast of the lateral lamina induced by para-axial mesoblast. Wyburn concluded that ventral extension of somites initiated abdominal wall development. According to study of serial sections of human embryos from the Carnegie Collection, by DeVries (1980) also refutes Duhamel's report and agrees with the finding of Wyburn. DeVries defined an omphalocele as a persistence of the body stalk in

the region normally occupied by somatopleure. Duhamel (1963) postulated that omphalocele was a "monstrosity", and therefore more commonly associated with multiple anomalies.

The embryogenesis of gastroschisis is still open to debate (Irving, 1990). Gastroschisis is a full-thickness cleft in the abdominal wall, which some believe occurs secondary to incomplete closure of the lateral folds during the sixth week of gestation (Moore and Stokes, 1953; Moore and Persaud, 1993). Duhamel considered gastroschisis the result of a minor defect in the lateral embryonic fold due to inhibition of differentiation of somatopleuric mesenchyme (Duhamel, 1963). Deprived of its mesenchymal support, the epiblastic layer of the somatopleure will be resorbed resulting in formation of a lateral paraumbilical defect (Grosfeld and Weber, 1982). In contrast to this suggestion, Show (1975) considers gastroschisis a consequence of an intrauterine rupture of the amniotic membrane at the base of a hernia of the umbilical cord. The defect is thought to occur where involution of the primitive right umbilical vein results in a weakened site. Rickham (1970), had previously observed that the position of the right umbilical vein probably determined the site of a gastroschisis defect in its usual position just to the right of the umbilical cord. Grosfeld and Weber (1982) suggest that antenatal epithelialisation may be the mechanism for the development of the skin bridge that is occasionally observed between the defect margin and the umbilical cord. They concluded that these events suggest that gastroschisis may represent a mechanical accident rather than a teratogenic occurrence. DeVries (1980) suggested that gastroschisis results from a rupture of the paraumbilical somatopleure, but does not represent a ruptured omphalocele. He concluded that gastroschisis and omphalocele were actually distinct entities. Grosfeld and Weber (1982) believe that the observation that associated anomalies and chromosomal syndromes are commonly observed in infants with omphalocele but almost never seen in instances of gastroschisis supports this development concept. Hoyme *et al.* (1981) suggest that most cases of gastroschisis are the result of an intrauterine vascular accident involving the omphalomesnteric artery. Glick *et al.* (1985) claim to have established the "missing link" between omphalocele and gastroschisis by documenting *in utero* rupture of a small omphalocele, between 27 weeks and 34.5 weeks of gestation the ultrasound appearances changed from those of a small hernia of the cord to a typical gastroschisis. The condition of the bowel at delivery was consistent with relatively late evisceration. Intrauterine ischemia has been implicated in the pathogenesis of gastroschisis (De Vries, 1980) and Bulut *et al.* (1989) have reported what they term a

"pregastroschisis", namely, a gastroschisis-like anomaly, with a sac, within which lay distal ileum with an atresia but without evidence of contact with amniotic fluid. The description suggest that this was a true sac, but unfortunately there is no histological information about it.

Several experimental models of gastroschisis have been studied. Sherman *et al.* (1973) produced evisceration by creating small abdominal wall defects in fetal rabbits. Decreased intestinal length and enteritis were produced after only four days of exposure to amniotic fluid. Haller *et al.* (1974) used a similar technique in fetal lambs and were able to study bowel that had been eviscerated for ten to 30 days. They documented progressive damage to the neural plexuses. Klück *et al.* (1983) developed a gastroschisis model in the chick embryo and found that the characteristic picture of gastroschisis only evolved when the eviscerated bowel was exposed to urine. From a combined study by Tibboel *et al.* (1986) in Rotterdam and Glasgow which involved further chick experiments as well as clinical (including prenatal) observations, it was concluded that the fibrous coating of the eviscerated bowel is a late occurrence and directly related to changes in amniotic fluid composition, and that both associated intestinal atresia and postoperative hypoperistalsis in the absence of obstruction are also late gestational events caused by ischaemia due to compression of bowel and mesentery in a small defects.

It has been recognized that omphalocele is frequently associated with other abnormalities, indicative of a general interference with early embryonic development Moore (1977) found that they occurred in 37% of 236 collected cases.

In summary, omphalocele is embryologically and anatomically distinct from gastroschisis (Table 1.1). There is a lack of agreement among the various hypotheses proposed (Warkany, 1971; Hershey *et al.*, 1989; Torfs *et al.*, 1990). The most accepted hypothesis for omphalocele is a failure of migration and fusion of the two lateral embryonic folds of the anterior abdominal wall, and there are two hypotheses for gastroschisis, early intrauterine rupture of an omphalocele with complete resorption of the sac (Show, 1975) or intrauterine vascular accident involving the omphalomesenteric artery (Hoyme *et al.*, 1981).

Table 1.1.- Comparison of omphalocele and gastroschisis

| Factor | Omphalocele | Gastroschisis |
|---|---|---|
| Location | Umbilical ring | Lateral to cord |
| Size of defect | 2 to 10 cm | Small (< 4 cm) |
| Umbilical cord | Insert in sac | Normal insertion |
| Sac | Present (amnion and peritoneum) | None |
| Contents | Liver, bowel, etc. | Bowel, stomach |
| Bowel appearance | Normal | Matted, foreshortened exudate |
| Malrotation | Present | Present |
| Small abdominal cavity | Present | Present |
| Postoperative alimentary | Normal | Prolonged ileus |
| Associated anomalies | Common (37-67%) | Rare (10%) |
| Coexisting syndromes: | | |
| Trisomy 13-15,16- 18, 21 | | |
| EMG (exomphalos, macroglossia, gigantism) | | |
| Beckwith-Wiedemann (BWS)[1] | Relatively common | Not reported |
| Exstrophy of bladder, cloaca | | |
| Pentalogy of Cantrell | | |

Adapted from Allen (1980) and Grosfeld and Weber (1982)

[1] This syndrome, which is also known as the EMG (exophthalmos, macroglossia, gigantism) syndrome was recognized independently by Beckwith in 1963 and Wiedemann in 1964. The aetiology of BWS appears to be a genetic contribution, but little is known about the pathogenesis of the condition. Elevated concentrations of plasma grouth hormone and somatomedin have been detected at birth, however, suggesting that there is an abnormality in the production of fetal-regulating peptides (Irving, 1990).

## 1.3. *AETIOLOGY*

The aetiology of the conditions is unknown. It is obvious that omphalocele and gastroschisis are caused by some fault in embryonic development during very early intrauterine life (Rickham, 1970; Irving, 1990). The aetiology of omphalocele and gastroschisis in humans is not known, but they have been produced experimentally in rodents. In a strain of mice with a genetic predisposition to omphalocele, the incidence was increased tenfold by exposure on the ninth day of gestation. Abdominal wall defects have been induced in rats by folic acid deficiency and by the administration of trypan blue salicylate and streptonigrin (Irving, 1990). Although regarded since 1953 as a distinct clinical entity separate from omphalocele, the developmental pathology and aetiology of gastroschisis have been the subject of considerable controversy (Hoyme, 1981). On the other hand, the occurrence of both of these types of abdominal wall defects in two families suggests that some cases of omphalocele and gastroschisis have a similar genetic cause (Gaillard, 1980; Hershey *et al.*, 1989), but Novotny *et al.* (1993) reported no family history of abdominal wall defects.

Omphalocele, but not gastroschisis, is a well recognized feature of the chromosomal trisomy syndrome and association with other anomalies. The great majority of cases of omphalocele are sporadic, but from time to time familial cases are reported. Moore and Nur (1986) observed that positive family history for defect was found in 3 of 39 omphalocele mothers and 5 of 38 omphalocele fathers. Angerpointer *et al.* (1981) reported that the father of one infant had omphalocele, and he concluded that no clear pattern of inheritance exists, and considered the aetiology to be multifactorial.

On the other hand, familial recurrence of gastroschisis is rare, and there have been few reports of familial recurrence of gastroschisis (Salinas *et al.*, 1979; Hershey *et al.*, 1989., Torfs *et al.*, 1991; Haddow *et al.*, 1993). Haddow *et al.* (1993) reported the first population-based study and showed a sib recurrence rate of 4.3%. Nelson and Toyama (1995) reported that the first published case of a mother who had gastroschisis and gave birth to a son with gastroschisis, which supports a genetic aetiology. Baird and MacDonald (1981) concluded that because the majority of cases of gastroschisis are not inherited in a Mendelian pattern so a sporadic or multifactorial profile could exist. Moore and Nur (1986 b) observed that a negative family history for defect was obtained from 32 gastroschisis fathers.

Clinical data and an appreciation of the embryology of the umbilical region support the concept that most instances of gastroschisis are disruptions of the abdominal wall that result from early gestation (Hoyme *et al.*, 1983), and Hoyme (1981) suggested that because of the recognition of the disruptive vascular nature of the structural defects associated with gastroschisis and appreciation of the embryology of the umbilical region, gastroschisis results from an intrauterine interruption of the omphalomesenteric artery.

Haddow *et al.* (1993) have concluded that the absence of evidence for a strong genetic predisposition strengthens the possibility that a behavioural or environmental factor (or factors) could be responsible for at least some cases of gastroschisis and might also explain the apparent recent increase in birth prevalence observed in several countries.

Aetiological hypotheses for gastroschisis have focused on environmental factors that may be teratogenic through their effect on the vascular system. Several studies have shown an association between gastroschisis and exposure to chemicals that have a primary vasoactive effect or that potentiate the vasoactive effect of other chemicals, including pseudoephedrine (Werler *et al.*, 1992a), cocaine (Drongowski *et al.*, 1991; Torfs *et al.*, 1994), oral contraceptives (Drongowski *et al.*, 1991), tobacco (Goldbaum *et al.*, 1990 and Haddow *et al.*, 1993; Torfs *et al.*, 1994), salicylates (Drongowski *et al.*, 1991; Werler *et al.*, 1992a), drugs (Werler *et al.*, 1992a ), and alcohol (Werler *et al.*, 1992b; Torfs *et al.*, 1994). Experiments in animals have shown that teratogens could exert an effect on the vasculature system: e.g. salicylates in mice (Kimmel *et al.*, 1971); ethanol in mice (Randall *et al.*, 1994); hyperthermia in rats (Nilsen, 1986; Sasaki *et al.*, 1995); early exposure to X-Ray irradiation (Pampfer and Streffer, 1988).

Recently Torfs *et al.* (1996), in a case-control study, found significantly elevated risks for high levels of solvents, colorants, and for medications, aspirin and ibuprofen. Periconceptional exposure to x rays was also associated with gastroschisis. They also found elevated risks for two decongestants, pseudoephedrine and phenylpropanolamine. For the group of all decongestants, including also oxymetazoline and ephedrine, the risk was significantly elevated. They concluded that most of these associations are for vasoactive substances, which supports a vascular hypothesis for the pathogenesis of gastroschisis.

Reports from several countries have shown an increase in prevalence of gastroschisis in the past three decades (Lindham, 1981; Hemminki *et al.*, 1982), perhaps suggesting either an environmental aetiology or improved ascertainment (Torfs *et al.*, 1990). While no secular trends has been noted by Baird and MacDonald (1981). Some maternal factors have been associated with gastroschisis in previous investigations e.g., age and reproductive history (Colombani and Cunningham, 1977; Gierup and Lundkvist, 1979; Lindham, 1981; Hemminki *et al.*, 1982; Martínez-Frías *et al.*, 1984; Roeper *et al.*, 1987; Goldbaum *et al.*, 1990). The defect is known to occur at the highest rate in infants of youngest mothers (Lindham, 1981; Baird and MacDonald, 1981; Hemminki *et al.*, 1982). However, to date, no biological mechanism has been postulated to explain this strong inverse association with maternal age. Some investigators suggest that exposure to an aetiological factor may be related to maternal age. Haddow *et al.* (1993) concluded that the association of gastroschisis with maternal smoking during pregnancy suggests either that cigarette smoke itself might represent a causal or contributing agent, or that smoking might serve a marker for some other risk factor.

Some of the factors that have been hypothesized to be related to gastroschisis but have not been well studied in previous studies include vaginal bleeding, low gestational age, low birthweight, and low parity or gravidity (independent of maternal age). Hemminki *et al.* (1982) found that housewives and farmers' wives may be at reduced risk. Lindham (1983) reported no effect of prior miscarriage, previous serious or chronic disease, use of oral contraceptives, or drug use or smoking during pregnancy. Sarda and Bard (1984) reported twins whose gastroschisis may have been a consequence of *in utero* exposure to alcohol. Hemminki *et al.* (1982) reported increased risk in urban areas whereas Roeper *et al.* (1987) noted a slightly increased risk in rural areas. Neither Paulozzi and Milham (1986) nor Roeper *et al.* (1987) noted any seasonal risks. Neither Baird and MacDonald (1981); Gierup and Lundkvist (1979), nor Roeper *et al.* (1986) found gender to be a risk factor.

Tan *et al.* (1996) suggest that it is extremely doubtful that a genetic cause is responsible for gastroschisis, but the possibility of a nutritional or environmental aetiology remains. Chun *et al.* (1993) reported on two families with gastroschisis in successive siblings and proposed a multifactoral mediator. Genetic transmission has also been strongly suggested by Hershey *et al.* (1989) who were reported of monozygotic twins with gastroschisis. A genetic-epidemiological study reported by Yang *et al.* (1992) suggests a possible autosomal recessive mode of gastroschisis inheritance.

Moore and Nur (1986 b) suggest a non-genetic aetiology because of the sudden rise of gastroschisis in the early 1950s and its remarkable increase in incidence around 1973 and after. On the other hand, the relatively constant occurrence of omphalocele, its high incidence of serious associated anomalies, syndromes and trisomics, and the high incidence of multiplicity of these additional malformations suggest that the potential for omphalocele has long been in the gene pool of man.

The pathogenesis of gastroschisis is thus not fully understood. Environmental, multifactoral, and genetic aetiologies have been proposed.

In summary, the aetiology of omphalocele and gastroschisis is still unknown. Several studies suggest that these defects might be have a multifactoral origin, but hypotheses of gastroschisis aetiology have focused mainly on environmental factors. Some of these factors have been confirmed to be related to gastroschisis while others are still in doubt.

## 1.4. *EPIDEMIOLOGY*

### 1.4.1. **Prevalence**

Concern over a possible increasing prevalence of gastroschisis has prompted several epidemiological studies. Gastroschisis was first distinguished from omphalocele by Moore and Stock (1953). A reliable estimate of the frequency of gastroschisis before then is impossible. Jones and Woodward (1986) believe that for many years omphalocele was by far the more common, but commencing in the 1960s, the prevalence of gastroschisis inexplicably increased, at least in countries where accurate data are available. Several investigators from different geographic regions have found that the prevalence of gastroschisis has increased over the past few decades (Table 1.2).

The rate of abdominal wall defects is higher in Scotland than England and Wales. Recently a study in Scotland by Chalmers *et al.* (1997) was based on data collected from the record of a live birth (SMR 11), the record of discharge from a neonatal unit (SMR 11 (E)), the Scottish stillbirth and neonatal death survey, and the Registrar General's death records and the record of discharge from acute hospitals (SMR 1) for children

aged under 1 year. The overall rate of abdominal wall defects for the period 1988-1995 was 3.49 per 10,000 births (1.89 for gastroschisis and 1.22 for omphalocele). There was no pronounced upward trend in the number of cases of gastroschisis, although the number was high in 1994.

In England and Wales, a retrospective observational study by Tan *et al.* (1996) has been reported. They used data from the Office of Population Censuses and Surveys (OPCS) giving details of notified congenital abdominal wall defects and birth registrations for the years between 1987 and 1993. In the OPCS congenital malformation notification scheme, a standard record form (SD56) was completed by district health authorities to notify details of each malformed live birth or stillbirth. Only malformations detected at delivery or within ten days of birth were included. Abortion data were not included. The level of ascertainment is known to be low. Gastroschisis doubled in incidence from 0.65 in 1987 to 1.35 per 10,000 total births in 1991, with little further increase in 1992-93 ($p<0.0001$); in contrast, the incidence of omphalocele decreased from 1.13 to 0.77 per 10,000 births for the study period ($p<0.005$). The overall incidence of notified congenital abdominal wall defects was 2.15 per 10,000 total births (livebirths and stillbirths but not induced abortions).

**Table 1.2**. Time trend analysis for omphalocele and gastroschisis among live and stillbirths

| Place | Year | Omphalocele | | Gastroschisis | |
|---|---|---|---|---|---|
| | | Regression[2] | p value | regression | p value |
| England and Wales | 1974-94 | -0.05 | 0.02 | -0.12 | <0.01 |
| Finland | 1974-94 | 0.05 | 0.08 | 0.07 | >0.1 |
| Norway | 1974-94 | 0.14 | >0.1 | 0.07 | <0.01 |
| Czech Republic | 1974-94 | 0.00 | >0.1 | 0.00 | >0.1 |
| France (Central East) | 1976-94 | 0.01 | >0.1 | 0.03 | <0.01 |
| France (Paris) | 1981-94 | 0.07 | >0.1 | 0.23 | <0.01 |
| Italy (IPIMC) | 1978-94 | -0.01 | >0.1 | 0.00 | >0.1 |
| Italy (IMER) | 1978-94 | 0.02 | >0.1 | 0.04 | >0.1 |
| Spain | 1976-94 | -0.01 | >0.1 | 0.01 | >0.1 |
| Northern Netherlands | 1981-94 | 0.16 | 0.03 | -0.08 | >0.1 |
| Japan | 1978-94 | 0.16 | <0.01 | 0.07 | <0.01 |
| Israel | 1974-94 | -0.08 | 0.04 | -0.02 | >0.1 |
| South Africa | 1992-94 | 0.13 | >0.1 | 0.36 | >0.1 |
| USA (Atlanta) | 1974-94 | -0.11 | <0.01 | 0.08 | 0.03 |
| South America | 1974-94 | 0.09 | <0.01 | 0.07 | <0.01 |
| Mexico | 1980-94 | 0.00 | >0.1 | 0.08 | 0.05 |
| Australia | 1981-94 | -0.05 | 0.08 | 0.07 | <0.01 |
| New Zealand | 1980-94 | 0.01 | >0.1 | 0.14 | 0.05 |

Adapted from International clearinghouse for birth defects monitoring systems (1996)

[2] Regression analysis: coefficient value

Leck (1994) reported the prevalence of omphalocele was 0.3 per 1000 births in Europeans in England. A figure similar to that of whites in America but much higher than in Japan (see table 1.3).

**Table 1.3**. Birth prevalence of omphalocele

| | Prevalence per 1000 Births[3] | | | | | |
|---|---|---|---|---|---|---|
| | Hiroshima, Nagasaki, and Kure, Japan[4] | 12 centres, United States[5] | | Birmingham, England[6] | | |
| | | Black | White | European | South Asian | Afro-Caribbean |
| Omphalocele | 0.12 | 0.58 | 0.35 | 0.30 | 0.34 | 0.39 |

Adapted from Leck (1994)

[3] Including stillbirths at 28 or more weeks in England and 20 or more weeks elsewhere.

[4] Estimated from data for nonconsanguineous pregnancies registered from 1948 to 1954 (Neel, 1958) on the assumption that infants who underwent necropsy after stillbirth or neonatal death and those followed up at nine months were representative, respectively, of all who died before four weeks after birth (including stillbirths) and all who survived to this age.

[5] Single births following pregnancies booked in 1959 to 1965 (Heinonen et al., 1977)

[6] -1964 to 1984 births (Knox and Lancashire, 1991).

An international survey by questionnaire of gastroschisis and omphalocele (490 cases) by Moore and Nur (1986 a) from 16 paediatric surgery centres on four continents from 1954-1977 revealed a marked peak in the prevalence of gastroschisis in 1972 and after. The gastroschisis-to-omphalocele ratio was highest in Scandinavia, northern Europe and the United States, while the relative increase seemed to occur last in Japan. In Scandinavia, a 5-6 fold relative increase occurred in gastroschisis frequency from the period after 1971 (1961-1971), as compared with the period prior to 1972 (1972-76).

Report 6 of EUROCAT (EUROCAT Working Group, 1995) covered 28 EUROCAT registers in populations defined either by the residence of the mother ('population based') or by the place of birth ('hospital based'). The ascertainment of congenital anomalies was based on the use of active case-finding and of multiple sources of information such as birth and death certificates, maternity and hospital records, reports of cytogenetic laboratories and of pathology services, and reports of maternal and child health services. The total prevalence rate (per 10,000 births) of omphalocele between 1980 and 1992 was 2.6 (livebirths, fetal death and induced abortions), 1.9 (livebirths, fetal death) and 1.5 (livebirths). Glasgow had the second highest rate (4.4) followed by Mainz (5.6). For gastroschisis, the Glasgow rates were 1.3 (livebirths, fetal death and induced abortions), 1.0 (livebirths, fetal death) and 0.8 (livebirths) (Table 1.4 and 1.5).

**Table 1.4**[7]. Prevalence rate (per 10,000) of omphalocele in 28 EUROCAT registries, 1980-1992

| Centre | LB+FD+IA | | LB+FD | | LB | |
|---|---|---|---|---|---|---|
| | No | Rate | No | Rate | No | Rate |
| West Flanders | 15 | 1.8 | 15 | 1.8 | 12 | 1.4 |
| Hainaut | 28 | 2.2 | 19 | 1.5 | 13 | 1.0 |
| Antwerpen | 4 | 2.8 | 1 | 0.7 | 1 | 0.7 |
| Zagreb | 11 | 1.9 | 10 | 1.7 | 10 | 1.7 |
| Odense | 25 | 3.8 | 20 | 3.1 | 16 | 2.5 |
| Paris | 145 | 3.3 | 76 | 1.7 | 63 | 1.5 |
| Strasbourg | 39 | 2.7 | 20 | 1.4 | 12 | 0.9 |
| Marseille | 42 | 2.2 | 26 | 1.4 | 16 | 0.9 |
| Mainz | 7 | 5.6 | 7 | 5.6 | 7 | 5.7 |
| Magdeburg | 2 | 1.2 | 2 | 1.2 | 1 | 0.6 |
| Athens* | 4 | 1.6 | 4 | 1.6 | 3 | 1.2 |
| Toscana | 26 | 2.0 | 21 | 1.6 | 20 | 1.5 |
| Emilia Romagna | 53 | 1.9 | 53 | 1.9 | 52 | 1.9 |
| Umbria* | 10 | 1.3 | 10 | 1.3 | 8 | 1.0 |
| North-East Italy* | 45 | 1.2 | 45 | 1.2 | 39 | 1.0 |
| Dublin | 68 | 2.4 | 68 | 2.4 | 48 | 1.7 |
| Galway | 9 | 2.5 | 9 | 2.5 | 4 | 1.1 |
| Luxemburg | 6 | 2.3 | 6 | 2.3 | 6 | 2.3 |
| Malta | 5 | 1.3 | 5 | 1.3 | 3 | 0.8 |
| Groningen | 39 | 2.6 | 30 | 2.0 | 25 | 1.7 |
| Rotterdam* | 4 | 1.5 | 3 | 1.2 | 2 | 0.8 |
| Southern Portugal | 2 | 1.1 | 2 | 1.1 | 1 | 0.5 |
| Switzerland | 54 | 2.0 | 29 | 1.1 | 26 | 1.0 |
| Bilbao | 15 | 3.1 | 11 | 2.2 | 9 | 1.8 |
| Asturias | 4 | 1.7 | 0 | 0.0 | 0 | 0.0 |
| **Glasgow** | **74** | **4.4** | **38** | **2.3** | **28** | **1.7** |
| Liverpool | 60 | 3.3 | 43 | 2.3 | 34 | 1.9 |
| Belfast | 105 | 3.0 | 91 | 2.6 | 59 | 1.7 |
| Total | 838 | 2.6 | 602 | 1.9 | 467 | 1.5 |

Adapted from Report 6 of EUROCAT Working Group, 1995

[7] LB = Livebirths, FD = Fetal deaths from 20 weeks gestation, IA = Induced abortions following prenatal diagnosis.

*Athens, Umbria, North-East Italy and Rotterdam : Not included in the total cases.

**Table 1.5**[8]. Prevalence rate (per 10,000) of gastroschisis in 28 EUROCAT registries, 1980-1992.

| Centre | LB+FD+IA | | LB+FD | | LB | |
|---|---|---|---|---|---|---|
| | No | Rate | No | Rate | No | Rate |
| West Flanders | 2 | 0.2 | 2 | 0.2 | 2 | 0.2 |
| Hainaut | 23 | 1.8 | 15 | 1.2 | 13 | 1.0 |
| Antwerpen | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Zagreb | 14 | 2.4 | 14 | 2.4 | 14 | 2.4 |
| Odense | 8 | 1.2 | 6 | 0.9 | 5 | 0.8 |
| Paris | 62 | 1.4 | 46 | 1.1 | 40 | 0.9 |
| Strasbourg | 19 | 1.3 | 17 | 1.2 | 15 | 1.0 |
| Marseille | 20 | 1.1 | 16 | 0.9 | 11 | 0.6 |
| Mainz | 1 | 0.8 | 1 | 0.8 | 1 | 0.8 |
| Magdeburg | 4 | 2.4 | 4 | 2.4 | 4 | 2.4 |
| Athens* | 3 | 1.2 | 3 | 1.2 | 3 | 1.2 |
| Toscana | 5 | 0.4 | 2 | 0.2 | 2 | 0.2 |
| Emilia Romagna | 28 | 1.0 | 28 | 1.0 | 27 | 1.0 |
| Umbria* | 3 | 0.4 | 3 | 0.4 | 1 | 0.1 |
| North-East Italy* | 23 | 0.6 | 23 | 0.6 | 20 | 0.5 |
| Dublin | 12 | 0.4 | 12 | 0.4 | 11 | 0.4 |
| Galway | 4 | 1.1 | 4 | 1.1 | 2 | 0.6 |
| Luxemburg | 1 | 0.4 | 1 | 0.4 | 1 | 0.4 |
| Malta | 3 | 0.8 | 3 | 0.8 | 2 | 0.5 |
| Groningen | 16 | 1.1 | 12 | 0.8 | 8 | 0.5 |
| Rotterdam* | 1 | 0.4 | 1 | 0.4 | 1 | 0.4 |
| Southern Portugal | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Switzerland | 11 | 1.5 | 29 | 1.1 | 28 | 1.0 |
| Bilbao | 4 | 0.8 | 1 | 0.2 | 1 | 0.2 |
| Asturias | 1 | 0.4 | 1 | 0.4 | 1 | 0.4 |
| **Glasgow** | **21** | **1.3** | **17** | **1.0** | **14** | **0.8** |
| Liverpool | 28 | 1.5 | 18 | 1.0 | 16 | 0.9 |
| Belfast | 29 | 0.8 | 27 | 0.8 | 22 | 0.6 |
| Total | 346 | 1.1 | 276 | 0.9 | 240 | 0.8 |

Adapted from Report 6 of EUROCAT Working Group, 1995

[8] LB = Livebirths, FD = Fetal deaths from 20 weeks gestation, IA = Induced abortions following prenatal diagnosis.

*Athens, Umbria, North-East Italy and Rotterdam : Not included in the total cases.

The series of Calzolari *et al.* (1995) covered 21 EUROCAT registries. The population included livebirths, stillbirths and induced abortions. They used multiple sources of ascertainment, including birth certificates, paediatric records, maternity records, hospital discharge summaries, and pathology reports. The prevalence rate per 10,000 births (livebirths, stillbirths and induced abortions following prenatal diagnosis) was 2.52 (95% Cl=2.34 to 2.70) for omphalocele and 0.94 (95% CI = 0.83 to 1.05) for gastroschisis for the period 1980-1990. Glasgow had the highest rate of omphalocele (4.79 per 10,000).

The investigation of Lindham (1981) in Sweden between 1965 and 1976 drew information from (1) the Swedish Register of Congenital Malformations (RCM), (2) the Swedish Medical Birth Record Systems (MBRS) and (3) enquiries to all hospitals in Sweden where omphalocele and gastroschisis are treated. The MBRS records nearly all births in Sweden including stillbirths. The mean prevalence of abdominal wall defects, omphalocele and gastroschisis including stillborn was 1 in 3,900 births (2.55/10,000), one in 5,800 births (1.74/10,000) and 1 in 15,400 births (0.65/10,000) respectively. If stillbirths are excluded, the mean prevalence of omphalocele and gastroschisis was one in 6,900 births (1.49/10,000), one in 15,900 births (0.63/10,000) respectively. The mean prevalence of cases with indeterminate diagnosis (distinction between omphalocele and gastroschisis not possible) was one in 200,000 births (0.05/10,000) liveborn and one in 4,000 births (0.21/10,000) if stillbirths were included. The mean prevalence of abdominal wall defects among 10,579 stillbirths infants was one in 167 births (59.6/10,000). The prevalence of abdominal wall defects in stillborn was 20 times higher than in liveborn children. Thus, the incidence of gastroschisis increased significantly during the period of the study ($p<0.01$) while, the prevalence of omphalocele did not show any corresponding change.

Hemminki *et al.* (1982) in Finland, collected data from hospital and registry sources in Finland for the period 1970-1979. They reported that the birth prevalence of gastroschisis increased steadily in Finland during the time of study. The prevalence was 0.77/10,000 births in 1970-74 and 1.42/10,000 in 1975-79, resulting in a mean prevalence of 1.09/10,000 for the whole decade. The difference in the prevalence between the two five-year periods was statistically significant ($p<0.05$). By contrast, the prevalence of omphalocele 1.96/10,000 was unchanged during the decade.

An epidemiological study of gastroschisis and omphalocele was performed by Martinez-Frías *et al.* (1984) in Spain through the Spanish Collaborative Study of Congenital Malformation. The population included all livebirths in each of the participant hospitals. Data were collected on all children live born with major and/ or minor congenital malformations detected during in the first three days of life and internal malformations detected by necropsy if the child died during these three days. They reported that the prevalence of gastroschisis rose from 0.4 to 1.5 per 10,000 live births between 1976 and 1981. The incidence of gastroschisis showed a significant secular trend with an annual increase of 0.38 per 10,000 livebirths ($p<0.001$). Omphalocele, on the other hand, showed an irregular annual prevalence without a secular trend.

An epidemiological investigation of gastroschisis was reported by Roeper *et al.* (1987) in California. They used the birth certificate data for the period of 1968-1977. In the denominators, only live births were used because the numbers of fetal deaths were not available by maternal age and gravidity categories. The rate of gastroschisis increased significantly from 0.06 per 10,000 live births in 1968 to 0.89 per 10,000 by 1977. On the other hand, omphalocele did not demonstrate a statistically significant increasing or decreasing secular trend. Isolated gastroschisis had an increasing secular trend ($p<0.001$), while isolated omphalocele showed a significantly downward secular trend ($p< 0.05$).

In the 15 years experience of De Lorenzo *et al.* (1987) between 1971 and 1985, 59 cases of gastroschisis were treated at Hôpital Sainte- Justine in Montreal in Canada. The prevalence of gastroschisis more than doubled in the second half of the 15- year period reviewed while the birth rate in the province of Quebec was declining.

More recently, an investigation was performed by Puffinbarger *et al.* (1995) in Oklahoma using data derived from Children's Hospital of Oklahoma (CHO) medical records, inventory sheets completed by nurses and resident physicians on admission of gastroschisis infants at CHO, hospital records of Tulsa paediatric surgeons, and the state health departments of Oklahoma and Iowa between January 1989 and December 1993. They reported that the numbers of children born with gastroschisis appeared to be gradually increasing.

An Australian study from which was collected data from State and Territory perinatal data systems and birth defects registers showed that the national rate of omphalocele and gastroschisis varied between 1.6 and 2.7, and 0.7 and 1.7 per 10,000 births (respectively) in the period 1982-1992. The highest rate of gastroschisis occurred in 1992 (Lancaster and Pedisich, 1995).

A few reports have shown no increase in the prevalence of gastroschisis, for example in the report of Goldbaum *et al.* (1990) in Washington State using birth certificates for the years 1984 to 1987. The prevalence at birth of gastroschisis was 2.2 per 10,000 live births, and there was no trend over this period.

In British Columbia, Baird and MacDonald (1981) used the data from the records of a surveillance registry which employs multiple sources (the Hospital Discharge Diagnoses on infants, Physician's Notice of birth, and Vital Registrations of Death). Only live born cases were analysed. The prevalence rate per 10,000 was 2.4 for omphalocele and 0.8 for gastroschisis. No overall increase in the prevalence of anterior abdominal wall defects in livebirths was detected during the period 1964-1978 inclusive.

In the study of Calzolari *et al.* (1993) in Italy during 1984-1989, 116 cases of omphalocele and 42 cases of gastroschisis were detected in an area covered by five Italian congenital malformation registers, all part of the EUROCAT network. In calculating the prevalence of omphalocele and gastroschisis, only livebirths or stillbirths with an estimated gestational age of 28 weeks or more were included. No induced abortions were included. The prevalence rate (per 10,000 livebirths and stillbirths) was 1.6 (95% CI= 1.31 to 1.89) for omphalocele and 0.6 (95% CI= 0.42 to 0.78) for gastroschisis during 1984-1989. Three additional cases that were recognised among spontaneous abortions were included (one of omphalocele and two of gastroschisis). No significant secular trends in the prevalence rate of gastroschisis were observed.

In a survey in Newcastle upon Tyne, UK, by Dillon and Renwick (1995) from the Northern Region Fetal Abnormality Survey in the five years 1988 to 1992 (excluding terminations), gastroschisis occurred in 56 births, omphalocele in 43. They detected no rise in the incidence of gastroschisis or fall in the prevalence of omphalocele during this

period, and the mean prevalence for all cases of gastroschisis and omphalocele was 4.9 (95% CI= 3.94 to 5.84).

### 1.4.2. **Gender**

A predominance of males among gastroschisis cases has been observed in several studies (Moore and Stokes, 1953; Moore, 1977; Berseth, 1982; Hemminki *et al.*, 1982; De Lorenzo *et al.*, 1987; Torfs *et al.*, 1990; Torfs *et al.*, 1994), but not others (Lindham, 1981; Grosfeld *et al.*, 1981; Moore and Nur, 1986 a; Goldbaum *et al.*, 1990). On the other hand, Bergsma (1979) mention that sex ratio among omphalocele is M3:F2 while for gastroschisis it is unknown, and in some studies a male excess was reported among infants with omphalocele (Seashore, 1978; Grosfeld *et al.*, 1981; Lindham, 1981; Moore and Nur, 1986 a; Yazbeck *et al.*, 1986 (3:2); Calzolari *et al.*, 1995; (Lancaster and Pedisich, 1995) but not in study by Baird and MacDonald (1981). In a few studies, the same sex ratio was observed for two conditions (Roeper *et al.*, 1987; Calzolari *et al.*, 1993 ). In the study of Calzolari *et al.* (1995), a male excess was observed among omphalocele cases with multiple malformations (all types of association) except for those associated with NTD, where there was a female excess, and the difference in sex ratio between omphalocele cases with and without NTD was statistically significant ($p<0.01$). In the study of Novotny *et al.* (1993), there was no sex predilection (35 male, 34 female) among gastroschisis cases.

### 1.4.3. **Maternal age**

Young maternal age has been reported consistently as a risk factor. Both the older and the more recent data consistently demonstrate that young maternal age is associated with an increased risk of gastroschisis. An international survey of gastroschisis and omphalocele (490 cases) by Moore and Nur (1986 a) has shown that the average maternal age for 123 gastroschisis patients at the time of birth was 21.86±0.38 [standard error of mean (SEM)] years. This was considerably younger than 143 omphalocele patients, which were 27.05±0.51 (SEM) years. The ages of the mothers of patients born with gastroschisis were significantly lower than those of patients born with omphalocele ($p<0.0001$).

Calzolari *et al.* (1995) reported, through the data registered in 21 regional registers in Europe, that maternal age effects were much more marked for gastroschisis, where there was increased risk for young mothers (under 20 years) compared to those aged 25-29. These young mothers were 11 times more at risk (OR=11.24, 95% CI=7.8 1 to 16.16) and 15 times more at risk for isolated cases (OR=15.47, 95%CI=10.19 to 23.47) and gastroschisis was more than twice as common in this age group than was omphalocele (84 vs. 39 cases). Werler *et al.* (1992) reported their finding in the Slone Epidemiology Unit Birth Defects Study (BDS), which included patients from Boston, Philadelphia, and portions of Ontario and Iowa. They compared 76 cases of gastroschisis with 2,582 malformed controls and found a strong inverse association with maternal age: relative to women 30 years or older, relative risks for 25-29, 20-24, and, <20 year old women were 1.7, 5.4, and 16, respectively. In the study of Haddow *et al.* (1993), women under the age 20 were at significantly higher risk of having a pregnancy affected with gastroschisis (crude odds ratio 9.4; adjusted odds ratio 7.3). Roeper *et al.* (1987) concluded that the rate of gastroschisis decreased significantly with increasing maternal age ($p<0.001$), and the age of 19 years old had the highest rate. Martínez-Frías *et al.* (1984) reported that the maternal age in cases of gastroschisis (Mean=21.42, SD=2.87) differed significantly from the mean in cases of omphalocele (Mean=24.25, SD=5.55; $p<0.01$) and from the mean in the control group (non-malformed) (Mean=27.02, SD=5.65; $p<0.01$). Goldbaum *et al.* (1990) compared 62 infants who had gastroschisis with 617 randomly selected unaffected infants matched for birth year in the state of Washington. They found that maternal age less than 20 years was associated with a fourfold increased risk of having a baby with gastroschisis. Hemminki *et al.* (1982) found young age for gastroschisis (22.5 years) compared with all births (26.1) or to the omphalocele births (27.3). Their data demonstrated that the birth prevalence of gastroschisis decreased with the increasing age of the mother, whereas that of omphalocele increased.

Novotny *et al.* (1993) reviewed 18-years of gastroschisis from the records of 69 patients treated for gastroschisis at the Childrens's Hospital Medical Centre of Akron from 1972 to 1990. They found the average maternal age of gastroschisis was 21.1 years and 50% of all mothers were primiparous.

De Lorenzo *et al.* (1987) demonstrated that the maternal age of gastroschisis was lower than that of omphalocele (23.4±4.4 years versus 26.4±5.87 years, $p<0.05$) and Grosfeld

*et al.* (1981) have shown the mean maternal age of omphalocele was 24±4.9 years (range 17 to 38 years) while for gastroschisis was 20±2.9 years (range 15 to 28 years), with 66% being under 20 years and 50% being primigravida.

In the case-control study by Iskaros *et al.* (1996) over a three year period at a tertiary level fetal medicine centre, controls were selected as the next infant delivered, matched for maternal age, parity, gestational age and fetal sex (N=28) and also with a group of pregnancies with fetal omphalocele seen during the same period (N=27). This study showed that the mean maternal age was 21 years (range 16-19) and 25 mothers (89%) were nulliparous. Significantly longer hospital stay was associated with younger maternal age ($p<0.03$).

In Australia, Lancaster and Pedisich (1995) reported that prevelence of omphalocele was more than twice as common among births to mothers aged 40 years and over compared to mothers age under 20 while gastroschisis varied markedly with maternal age. The highest rate (5.9 per 10,000 births) of gastroschisis occurred in births to teenage mothers and the lowest rates in births to mothers aged 40 years and over (no cases). Lindham (1981) reported a highest rate of gastroschisis in mothers significantly younger than 21 years ($p<0.001$) but the mean age of omphalocele coincided with that of all births in Sweden. Drongowski *et al.* (1991) in a case-control study of congenital anomaly unrelated to gastroschisis, found the mean age of gastroschisis (23.2±4.8 years) significantly less than the controls. Seashore (1978) demonstrated, in a series of abdominal wall defects admitted to Yale-New Haven Hospital from 1964-77, gastroschisis cases (20.7±1.0) were significantly younger than omphalocele (27.0±1.4). In their series of 45 omphalocele cases and 42 gastroschisis cases between 1975 and 1985, they found that maternal age was younger in the gastroschisis group: 12 mothers (29%) were under 20 years of age and only three (7%) were over 30 years (Irving, 1990). Data presented by of Berseth (1982) showed that the mean age of gastroschisis was 19.5 (±0.75) years compared to 25.3 (±1.4) for omphalocele ($p<0.05$).

An increased risk was observed by Calzolari *et al.* (1995) for omphalocele among young mothers (under 20 years) compared to mothers 25-29 years old (OR Mantel-Haenszel=

2.08, 95% CI=1.56 to 2.78). This risk was slightly higher for isolated cases than for multiple malformed cases (this analysis excluded chromosomal defects).

Finally, the study of Tan *et al.* (1996), recently confirmed the association of gastroschisis with low maternal age (34% of mothers of gastroschisis infants were aged under 20 compared to 13% of omphalocele) (OR=3.45, 95% CI =2.48 to 4.79; $p< 0.001$).

Unlike gastroschisis, omphalocele is associated with older rather than younger women (Lindham, 1981; Hemminki *et al.*, 1982; Berseth, 1982; Martínez-Frías *et al.*, 1984; Roeper *et al.*, 1987; Calzolari *et al.*, 1993; Lancaster and Pedisich, 1995).

Only the study of Angerpointer *et al.* (1980) suggested that maternal age of omphalocele and gastroschisis at the time of delivery was not significantly different from controls.

### 1.4.4. **Social and Environmental Factors**

Socio-economic status has not been well studied in relation to the risk of AWDs. Torfs *et al.* (1994) showed a significantly increased risk associated with poor maternal education (incomplete high school education or trade school education), and membership in the lowest or middle income group in univariate analyses of this variable. In contrast, mothers with no high school education or with a college education were at lowest risk, as were mothers in the highest income group. In the multivariate analysis, the only factor that remained significant was income, both low (less than $ 10,000) and medium ($ 10,000-$ 49,000). In the study of Hemminki *et al.* (1982), data were available for only 62% of gastroschisis and 55% of cases of omphalocele, allowing for these low figures, commercial and sales work was overrepresented after age-standardisation in gastroschisis cases; service work was slightly overrepresented both in gastroschisis and omphalocele either. There were more cases of gastroschisis in urban communities than in rural, and more babies with gastroschisis were born to sales personnel and fewer to economically inactive women, housewives and farmers' wives, than to all working women.

In the case-control study of Drongowski *et al.* (1991) using controls with a congenital anomaly unrelated to gastroschisis, they found a greater proportion of control mothers

(30%) had post-secondary education compared to study group mothers (21%), and household incomes greater than $30,000 per year (20 vs. 0%), and residence in towns with a population greater than 30,000 (67% vs. 44%). They concluded that there were no differences between cases (gastroschisis) and controls in exposure of mothers to environmental substances at the work place during the first trimester of pregnancy. Werler *et al.* (1992a) showed in a case-control study that mothers of gastroschisis infants had fewer years of education, but with maternal age taken into account, no associations were identified for 12 or less years of education, and they suggest that education may not be a significant factor because of its dependency on age. They concluded that this may be true for other typical measures of socio-economic status (occupation and income), because young women have not yet had the opportunity to obtain academic degrees, higher level jobs or income.

Roeper *et al.* (1987) demonstrated there was no apparent clustering for gastroschisis or omphalocele by geographically adjacent countries while, recently, Tan *et al.* (1996), reported the incidence of abdominal wall defects was higher in the regions of northern England than in regions in south east England.

An international survey by Moore and Nur (1986 a) showed that the rural-to-urban ratio of omphalocele was fairly uniform in all parts of the world reviewed, whereas that of gastroschisis varied widely from area to area with a range of 13% to 61%.

In the case-control study by Iskaros *et al.* (1996), the majority of gastroschisis cases were of low socio-economic class (68% class V and class IV, 25% class III and 7% class II). After stepwise regression analysis, and linear regression analysis of the demographic and sonographic factors as independent variables, more complex closure procedures were associated with poor socio-economic status ($p<0.01$). The authors concluded that maternal age and poor socio-economic status in combination with bowel dilatation, may improve the prediction of adverse outcome and long duration of hospitalisation.

### 1.4.5. Birthweight and Gestational Age

According to some reports, prematurity and low birthweight seem be risk factors particularly for gastroschisis and to a greater extent for multiple malformed cases than

isolated cases. In the survey of three million births between 1980 and 1990 in 21 regional registers in Europe, both omphalocele and gastroschisis, whether isolated or multiple malformed, were associated with early birth and low birthweight, although this effect was greater for multiple malformed cases than for isolated cases. Gastroschisis cases had a lower birthweight and were born earlier than isolated cases of omphalocele (Calzolari *et al.*, 1995). Another study in Italy by Calzolari *et al.* (1993), the birthweight in cases of omphalocele and gastroschisis was significantly lower than in controls, and among infants with associated omphalocele. The number of small for gestational age (less than 3rd centile) cases was significantly higher compared to controls ($p<0.001$). There were statistically significant differences in mean gestational age among cases of both omphalocele (isolated and associated) and gastroschisis (isolated and associated) compared to controls ($p<0.001$).

An international survey by Moore and Nur (1986 a) showed that 58% of gastroschisis patients had birth weights under 2500 grams as compared with 23% of the omphalocele group. Among gastroschisis cases, the period of gestation was under 38 weeks in 49% as opposed to only 16% among omphalocele cases. In an earlier report by Moore (1977), the 58% prevalence of prematurity in association with gastroschisis was significantly greater than the 10% incidence in omphalocele ($p< 0.001$).

In the series of Irving (1990) birthweight was considerably lower in gastroschisis than omphalocele, the proportion of babies weighing less than 2500 grams being 62% and 18% respectively.

Prematurity was common in both groups, and 58% of gastroschisis cases were premature among children admitted to Yale-New Haven hospital from 1964-77 (Seashore, 1978). Novotny *et al.* (1993) found the average birthweight was 2,473 grams, and gestational age was 36.5 weeks from 1972-1990 cases of gastroschisis who were treated at Akron Childrens's Hospital Medical Centre.

Among 92 cases of neonates with omphalocele admitted to Ste-Justine Hospital of Montreal between 1958 and 1983, birthweight ranged from 1,450 to 5,100 grams (mean 2,786 grams) (Yazbeck *et al.*, 1986). In the study by De Lorenzo *et al.* (1987) the

average birthweight was 2,137±795.3 grams and gestational age was 36.8±5.87 weeks with 19% born at less than 35 weeks.

During an eight-year period (1972 to 1980) 125 infants with abdominal wall defects were treated at the James Whitcomb Riley Hospital for children at the Indiana University Medical Centre, of whom 78 had gastroschisis and 47 had an omphalocele. The mean birthweight was 2520±0.560 grams with a range of 1100 to 3200 grams, and for omphalocele, it was 2910±1370 grams and 35% weighed less than 2500 grams . The mean gestational age among gastroschisis cases was 37±2.3 weeks, and 33% of cases were less than 36 weeks of gestation. The mean gestational age of omphalocele cases was 38±2.6 weeks; 25% of cases were premature (less than 36 weeks of gestation) (Grosfeld *et al.*, 1981).

In the case-control study by Iskaros *et al.* (1996), birthweight was significantly reduced in fetuses with gastroschisis (mean 2230 grams ; range 1300-3300 grams ) compared with controls (2751 grams; range 1744-3540, $p<0.0001$). The mean gestational age of gastroschisis cases at delivery was 36.3 weeks (range 32-38).

In Australia a study by Lancaster and Pedisich (1995) found that low birthweight (less than 2500 grams) occurred in 58% of infants with omphalocele and 62% of gastroschisis; 21% of omphalocele and 9% of gastroschisis were extremely low birthweight (less than 2500 grams). Preterm birth occurred in 53% of omphalocele and 55% of gastroschisis, and 16%.

In the case-control study of Drongowski *et al.* (1991) (using cases of congenital anomalies unrelated to gastroschisis as controls) they found that the mean birthweight of gastroschisis (2.49±0.38) was less ($p<0.001$) than that of the control infants (3230±610 grams).

In Spain, Martínez-Frías *et al.* (1984) reported low birthweight in gastroschisis ($p<0.02$) and omphalocele ($p<0.01$), and that the gestational ages of gastroschisis and omphalocele ($p<0.01$) both were significantly lower than controls.

### 1.4.6. **Associated Anomalies**

Omphalocele and gastroschisis are considered isolated defects if there are no associated anomalies or if the anomalies which are present (such as intestinal atresia or stenosis, undescended testicles or lung hypoplasia) are thought to be consequences of these conditions (Calzolari *et al.*, 1995).

Omphalocele is frequently associated with other abnormalities (Irving, 1990). Morrow *et al.* (1993) believes that omphalocele can be present as part of a syndrome, or as an isolated defect. The most important prognostic variable is the presence of associated malformations or chromosomal abnormalities. Omphalocele is often associated with trisomies (chromosomes 13 and 18) and Beckwith-Wiedemann syndrome (Calzolari *et al.*, 1995).

On the other hand, some reports in the literature have confirmed that chromosomal abnormalities are absent or rare in gastroschisis. Some studies found no association with chromosomal abnormalities (Mann *et al.*, 1984; Sermer *et al.*, 1987; Brun *et al.*, 1996).

In an international survey (Moore and Nur, 1986 b) of 16 paediatric surgery centres on four continents, data were presented on 490 cases of gastroschisis and omphalocele between 1954 and 1977. In the 203 cases of gastroschisis, additional malformations were found to be infrequent, comparatively mild, rarely multiple, largely limited to the eviscerated gut (atresias and stenosis), and most likely acquired as antenatal complications (volvulus) of the gastroschisis condition. Only two of the gastroschisis "malformations" were multiple and all were intra-abdominal and most likely acquired (1%). In 287 cases of omphalocele, 41 cases (14%) were classifiable as "syndrome" omphalocele (lower midline syndrome, upper-midline syndrome or Beckwith-Wiedemann syndrome) while 12 cases were trisomy associated. In omphalocele cases, additional malformations were frequent, serious and generally multiple (74%). The most frequent malformations in omphalocele cases involved the musculoskeletal and neurologic systems (32%), followed by the cardiac system (16%) where the malformations tended to be both multiple and serious. The geographic incidence of "syndrome" omphalocele varied from a high of 40% in southern Europe to a low of 7% - 9% in the United State, Japan

and Mexico with intermediate levels (12%-19%) in Scandinavia, northern Europe and Australia. The lower midline syndrome largely accounted for the high prevalence of syndrome omphalocele in southern Europe.

Among 21 EUROCAT registries, associated anomalies occurred in 54% of infants with omphalocele and 21% of those with gastroschisis, the difference being statistically significant ($p<0.001$). Among the omphalocele cases, 94 (22%) were chromosomal syndromes (60 cases of trisomy 18, 23 of trisomy 13, 4 of trisomy 21, and 7 with other chromosomal anomalies; 28 of Beckwith-Wiedemann syndrome). For gastroschisis, there were 9 (7%) chromosomal syndromes and 11 cases of amniotic bands. In infants with non-syndromic multiple malformations, NTD were the associated defects in 37% of omphalocele cases, compared to 24% of gastroschisis (non-significant difference); limb reduction defects represented 7% of the defects associated with omphalocele and 10% of those associated with gastroschisis. Terminal transverse defects were the commonest, suggesting that all cases with limb reduction defects can be classified as "limb body wall complex" (Calzolari *et al.*, 1995).

The frequency of trisomies in infants with omphalocele varied between 35 and 58 percent. Cardiac anomalies (ventricular and atrial septal defects, Tetralogy of Fallot) were found in 47% of patients, genitourinary abnormalities in 40%, and NTD in 39%. Gastrointestinal anomalies, either primary or secondary (for example, bowel obstruction), are a frequent finding. Intrauterine growth retardation has been reported in 20% of patients (Romero *et al.*, 1988). In contrast to omphalocele, gastroschisis is not associated with an increased incidence of other anomalies. However, in 25% of patients, gastrointestinal problems secondary to vascular impairment and adhesions are found, including bowel malrotation, atresia, and stenosis. Intrauterine growth retardation has been reported in 77% of gastroschisis infants (Romero *et al.*, 1988). Six neonates had trisomy syndromes (13-15 and 16-18), two had the Beckwith-Wiedemann syndrome, and one had a prune belly. Serious associated anomalies were observed in 12 (66%) of cases of omphalocele involving cardiac defects, gastrointestinal defects in 12, genitourinary anomalies in 21, musculoskeletal defects in 10, and abnormalities of the central nervous system in four. There were 13 deaths (28%), including 6 infants with chromosomal abnormalities (trisomy syndromes) (Grosfeld *et al.*, 1981).

In Italy (Calzolari *et al.*, 1993), associated anomalies occurred in 39% of omphalocele and 25% of gastroschisis cases (the difference was not significant). Among the recognized conditions, there were seven cases of Beckwith-Wiedemann syndrome, seven of trisomy 13, six of trisomy 18. In the series of Mabogunje and Oluwatope (1984), 32 of 57 patients with omphalocele (56%) and 13 of 64 with gastroschisis (20%) had associated anomalies. In Australia by Lancaster and Pedisich (1995), associated major malformation were reported in 41% of omphalocele and 21% of gastroschisis, 14% of omphalocele and 0.3% of gastroschisis had a chromosomal abnormality. Among abdominal wall defects admitted to Yale-New Haven hospital from 1964-77, associated anomalies occurred much more frequently in infants with omphalocele than gastroschisis. 77% of babies with omphalocele had other anomalies compared with only 16% of infants with gastroschisis (Seashore, 1978). In a series of 145 cases of omphalocele, 37% were found to have an additional "major" anomaly (Rickham *et al.*, 1970). If all additional anomalies were included, 58% of cases had an additional defect. 13% of their cases of omphalocele had a trisomy syndrome. On the other hand, gastroschisis had a low frequency of associated anomalies. In the data of Lindham (1981), concomitant malformations were found in 45% of omphalocele but only 5% of gastroschisis. In the California data, additional anomalies occurred in 33% of omphalocele as opposed to 13% of gastroschisis cases ($p < 0.01$). No chromosomal abnormalities were associated with gastroschisis (Roeper *et al.*, 1987). In a study in the West of Scotland, associated anomalies occurred in 30% of omphalocele and 6% of gastroschisis cases (Morrow *et al.*, 1993). In the England and Wales study by Tan *et al.* (1996), between 1987 and 1993 gastroschisis had a significantly lower proportion of associated anomalies (5%) than omphalocele (27%) ($p<0.001$) (OR=0.14, 95% CI= 0.09 to 0.22).

In the series of Novotny *et al.* (1993) 26% of gastroschisis cases had associated anomalies, the majority being intestinal atresia, volvulus, and / or undescended testicle.

Omphalocele was associated with another structural abnormality in 17 cases (40%) and a chromosome anomaly in 12 (28%); trisomy 18 (9), trisomy 13 (2) and Beckwith - Wiedemann's syndrome occurred in three babies. No cardiac abnormality was found in omphalocele cases. In contrast, gastroschisis was not associated with chromosome anomaly (Dillon and Renwick, 1995).

In the study of gastroschisis in a decade (1983-1993) of prenatal diagnoses in the Royal Hospital for Sick Children, Glasgow by Haddock *et al.* (1996), associated anomalies were seen in 26% of cases.

Several studies indicate that the large majority of infants with gastroschisis should survive (91%) and have a normal growth and development pattern and life expectancy (King *et al.*, 1980; Mayer *et al.*, 1980; O'Neill *et al.*, 1974; Touloukian and Spackman, 1971; Stringer *et al.*, 1991. Prognosis for infants with omphalocele must be somewhat guarded, especially if serious associated anomalies affecting other systems coexist (Grosfeld *et al.*, 1981).

### 1.4.7. Seasonality

In some studies, a seasonal trend is hypothesized for gastroschisis but not omphalocele. Some reports suggest that the month of birth, specifically the first quarter of the year is associated with an increased risk of gastroschisis. Hemminki *et al.* in Finland (1982) concluded that seasonal prevalence of the two malformations was apparently different, and the prevalence of gastroschisis was highest for children born in the early part of the year. Goldbaum *et al.* (1990) found that infants born during January, February, or March were at greater risk than infants born in any other months (OR=2.2, 95% CI=1.1 to 4.1).

On the other hand, three other studies did not. Roeper *et al.* (1987) reported no seasonal difference for the two conditions. In the series of Haddow *et al.* (1993), infant births in the first three months of the year were associated with a risk for gastroschisis similar to that in the later nine months of the year. Paulozzi and Milham (1986) found that the seasonality in gastroschisis births was not statistically significant.

Goldbaum *et al.* (1990) concluded that increased risk occurred in April, May, and June conceptions, prompting the hypothesis that this seasonal pattern may be due to an infectious aetiology, such as influenza and unidentified behavioural and environmental exposures which may explain the seasonal pattern. The data of Werler *et al.* (1992 a) for influenza or other infections in early pregnancy did not support this hypothesis. Hemminki *et al.* (1982) did not show any significant seasonality for omphalocele but

Paulozzi and Milham (1986) observed a possible influence of seasonality for omphalocele in Washington. They suggested that they may be a chance finding or may result from the use of different definitions of omphalocele in previous studies.

### 1.4.8. **Ethnicity, Consanguinity**

There have been a few reports on ethnicity as a risk factor for omphalocele and gastroschisis. It seems that ethnicity may play a role in these anomalies (Allen, 1980).

In a case-control study in which gastroschisis cases were compared with congenital anomalies unrelated to gastroschisis, there was no difference in frequency between whites and blacks (Drongowski *et al.*, 1991), while Goldbaum *et al.* (1990) reported that mothers of cases were more likely than those of controls to have been black.

Torfs *et al.* (1994) subdivided the variable maternal ethnicity into three groups: foreign-born Hispanics, United States (U.S.)-born Hispanics, and U.S.-born non-Hispanics. In this univariate analysis, foreign-born Hispanic mothers were at lower risk than Hispanic mothers born in the U.S., and lower than non-Hispanic whites. Both associations were of borderline significance.

The incidence of omphalocele among Filipino births in the survey of Paulozzi and Milham (1986) was 4.1 greater than non-Hispanic whites and 4.6 times that of non-whites. They concluded that the higher incidence of omphalocele in Filipinos in Washington seemed unlikely to be the effect of social status alone on either the causation or the reporting of this anomaly since the black, Indian, and Hispanic rates in the state were all lower than the Filipino rate and comparable to the non-Hispanic-white rate.

### 1.4.9. **Smoking**

Smoking has increased among young women and it has been associated with gastroschisis in some studies. Goldbaum *et al.* (1990) were the first to suggest this relationship. Smoking has been hypothesized to be aetiologicaly related to gastroschisis. This is logical since the aetiology of this defect is hypothesized to involve vascular

disruption (Hoyme *et al.*, 1983: Van Allen, 1981) and cigarette smoking has several vascular effects (Weler *et al.*, 1992 a).

Goldbaum *et al.* (1990) studied the Washington State birth certificates of 62 infants born with gastroschisis during the year 1984 to 1987. Residents were compared with 617 randomly selected unaffected infants matched for birth year. They found that women who smoked during pregnancy had double the risk (OR=2.0, 95% CI= 1.03 to 3.8) compared to non-smokers and concluded that smoking during pregnancy is a plausible risk factor that should be examined further as an explanation of the apparently increasing prevalence at birth of gastroschisis in developed nations. They added that of the four exposures identified in this study as potential risk factors, only smoking clearly affects the vascular system.

Haddow *et al.* (1993) designed a prospective, population-based study using 62,103 consecutive second-trimester singleton pregnancies in a maternal serum α-fetoprotein screening program between January 1980 and April 1989 in Maine. They used multiple ascertainment methods. Controls were selected from the pregnancies unaffected by gastroschisis. Their study showed that pregnant women who smoked cigarettes were at greater risk (OR= 2.1, 95% CI= 0.9 to 4.8) than non-smokers and they concluded that although this finding was not statistically significant, the trend is consistent with the report of Goldbaum *et al.* (1990). When they combined these data with two other studies (Goldbaum *et al.*, 1990 and Werler *et al.*, 1993a), the OR was 1.6 (95% CI= 1.2 to 2.2). They suggested that the association of gastroschisis with maternal smoking during pregnancy indicates either that cigarette smoke itself might represent a causal or contributing agent, or that smoking might serve as a marker for some other risk factors.

On the other hand, maternal age can be considered a firmly established risk factor for gastroschisis as Haddow *et al.* (1993) and Goldbaum *et al.* (1990) both demonstrated that, after smoking status is taken into account, the association between age and gastroschisis is slightly reduced, but remains highly significant.

In some studies, smoking was not associated with increased risk. Werler *et al.* (1993a) performed a case-control study of data drawn from the Slone Epidemiology Unit Birth Defects Study (BDS), an on-going hospital based case-control surveillance program

(1976-1990). They selected malformed controls for cases (excluding chromosomal, malformed and other abnormalities of the abdominal wall). They found that when age was taken into account, no association was identified for cigarette smoking, nor with cigarettes use in early pregnancy. A case-control study of Drongowski *et al.* (1991) compared 19 gastroschisis cases with 54 control infants born with a congenital anomaly unrelated to gastroschisis between 1978 and 1983. There were no differences between the gastroschisis cases and control mothers in the use of cigarettes.

In summary, several investigators from different geographic regions have found that the prevalence of gastroschisis has increased over the past few decades, especially after 1953 when gastroschisis was distinguished from omphalocele. The reported rate of abdominal wall defects is higher in Scotland than England and Wales. The overall prevalence of omphalocele in the world has been reported to vary from 0.77 to 2.7 per 10,000 and of gastroschisis to vary from 0.9 to 1.89 per 10,000 live and stillbirths. Young maternal age is associated with an increased risk of gastroschisis, a trend that studies from several different countries has confirmed. The average maternal age of gastroschisis patients at the time of birth ranges from 19.5 to 23.4 years. The ages of the mothers of patients born with gastroschisis are significantly lower than those of infants born with omphalocele. Associated anomalies occur in a greater percentage of infants of omphalocele (30-75%) than with gastroschisis (5-25%). Omphalocele is often associated with trisomies (chromosomes 13 and 18) and Beckwith-Wiedemann syndrome. On the other hand, reports in the literature have confirmed that chromosomal anomalies are absent or rare in gastroschisis. In addition to young maternal age, maternal cigarette use has been associated in some studies with an increased risk of gastroschisis, although rarely reaching statistical significance. Some studies suggested that the association of gastroschisis with maternal smoking during pregnancy indicates either that cigarette smoke itself might represent a causal or contributing agent, or that smoking might serve as a marker for some other risk factors.

Table 1.6 summarises the finding of key epidemiological studies of O&G reported in the period 1984-96.

**Table 1.6**. Summary of key epidemiological studies of O&G

| Study | Design | Sample | Results | Comments |
|---|---|---|---|---|
| Tan et al (1996), England and Wales | Retrospective of congenital anterior abdominal wall defects | -Data from the Office of Population Censuses and Surveys and the National Congenital Malformation Notification Scheme (1987 to 1993) | -Gastroschisis showed an increasing trend.<br>-Young maternal age of gastroschisis (less than 20) was significantly less than onphalocele cases ($p<0.001$) (OR=3.45, 95% CI= 2.48 to 4.79).<br>-Associated anomalies among omphalocele were significantly more than gastroschisis ($p<0.001$).<br>-Perinatal mortality among omphalocele cases significantly higher than gastroschisis ($p<0.001$). | -Possible selection bias (only live and stillbirths).<br>-Limitation of time (only malformations detected at delivery or within 10 days of birth were included.<br>-Validity of data uncertain. |
| Calzolari et al (1995), Europe | Retrospective | EUROCAT registers between 1980 and 1990, 732 cases of omphalocele and 274 cases of gastroschisis were registered | -The prevalence of omphalocele was 2.52 (95% CI=2.34 to 2.70) and 0.94 (95% CI=0.83 to 1.05) for gastroschisis.<br>-Associated anomalies among omphalocele were significantly more than gastroschisis ($p<0.001$).<br>-Young maternal age of gastroschisis (less 20) were 11 times more at risk 95% CI= 7.81 to 16.16).<br>-Omphalocele cases without NTD and omphalocele cases with NTD was significantly different ($p<0.01$). | -Good data (multiple ascertainment including live, stillbirths and induced abortions).<br>-Possible lack of standard criteria used by clinicians to distinguish between a major omphalocele and minor hernia of umbilical cord.<br>-Possible bias (varying abilities of participating registries to record induced abortions and in different laws regarding induced abortions in the countries involved).<br>-Possible misclassification (no information about how many of the prenatal diagnoses were verified by pathology). |

| | | | | |
|---|---|---|---|---|
| Haddow et al (1993), Maine | -Prospective<br><br>-Population-based | 62,103 consecutive second-trimester singleton pregnancies enrolling in a MSAFP screening, 1980-1989. Gastroschisis occurred in 21 of those pregnancies. | -Maternal age (pregnancies in women younger than 20 years old, 20-24, the OR were 7.3, 95% CI= 2.4 to 22 and 1.9, 95% CI= 0.7 to 5.0 compared to women aged 25 or older, respectively).<br>-Smoking (OR= 2.1, 95% CI= 0.9 to 4.8) | -No memory bias (information was collected during the second trimester).<br>-Possible sample bias (no multiple ascertainment).<br>-Possible selection bias ( if physicians were to select women as candidates for MSAFP screening if the pregnancies were considered high risk). |
| Calzolari et al (1993), Italy | case -control | 42 cases of gastroschisis and 116 cases of omphalocele in the area covered by five Italian congenital malformation registries between 1984 and 1989. | -Maternal age for isolated gastroschisis was significantly lower than in omphalocele and controls.<br>-Birthweight and gestational age in cases of omphalocele and gastroschisis were significantly lower than controls. | -Possible bias (only livebirths and stillbirths, not induced abortions).<br>-Possible bias (non-malformed control). |
| Werler et al (1992), Massachusetts | Case- control | 76 cases of gastroschisis in first trimester medication were compared with 2,142 malformed controls. | -Pseudoephedrine use (RR=3.2, 95% CI= 1.3 to 7.7).<br>-Salicylates, 1.6 (0.9 to 2.7).<br>-Acetaminophen, 1.7 (1.0 to 2.9).<br>-Ibuprofen, 1.3 (0.4 to 3.4).<br>-Phenylpropanolamine, 1.5 (0.4 to 5.4). | -Possible memory bias (interviewed within 6 months).<br>-Possible confounding (illness may confound the increased risks).<br>-No information on dosage, frequency, duration or timing of drug use.<br>-Possible Confounding (cocaine, which is strongly vasoconstrictive and a postulated risk factor for vascular defects).<br>-Recall bias. |
| Werler et al (1992), Massachusetts | -Case- control -hospital based | 76 gastroschisis cases (in first trimester) compared to malformed controls. | -Maternal age (relative to women 30 years or older, RR for 25-29, 20-24, and <20 years old were 1.7, 5.4, and 16, respectively).<br>-Alcohol (significantly RR for a maximum of >=5 drinks, 2.8 95% CI= 1.2 to 6.5). | -Possible selection bias (only malformed controls).<br>-Possible memory bias (interviewed within 6 months).<br>-Possible sample bias (hospital based).<br>-Possible recall bias (memory of histories of alcohol consumption can be unreliable). |
| Drongowski et al (1991), USA | Case- control | 19 cases of gastroschisis compared to malformed controls | -Cases more likely to have used aspirin during pregnancy, oral contraceptive at time of conception, and increased use of illegal drug (cocaine). | -Possible sample bias (hospital based).<br>-Possible memory bias (questionnaire was sent to mothers after delivery).<br>-Possible selection bias (only malformed controls). |

| | | | | |
|---|---|---|---|---|
| Goldbaum et al (1990), Washington, USA | Case-control | -Birth certificates<br>-62 infants born with gastroschisis (1984-1987) compared to 617 randomly selected unaffected infants matched for birth year. | -Month of the birth (January, February, or March) had greater risk (OR= 2.2, 95% CI= 1.1 to 4.1).<br>-Mothers less than 25 years old were at greater risk than mothers 25 years and older, with highest risk to mothers less than 20 (OR= 4.1, 95% CI= 1.4 to 12.0).<br>-Smoking (OR= 2.0, 95% CI= 1.03 to 3.8).<br>-Inadequate prenatal care (OR= 2.1, 95% CI= 1.09 to 4.6). | -Fetal deaths were not examined.<br>-No multiple ascertainment (confirmed just by surgeon).<br>-Possible recall (memory) bias (smoking habitats were collected after delivery.<br>-Possible selection bias (only livebirths).<br>-Possible selection bias (Only affected infants was selected as controls). |
| Roeper et al (1987), California | Retrospective | Using certificate data from California between 1968 and 1977 of gastroschisis cases. | -A clear upward secular trend of gastroschisis($p<0.001$).<br>-Young maternal age ($p<0.001$).<br>-Low gravidity ($p<0.001$). | -Possible selection bias (only livebirths no stillbirths and induced abortions).<br>-Possible bias (no multiple ascertainment). |
| Moore and Nur (1986), USA | Retrospective | International survey by questionnaire of 490 cases of gastroschisis and omphalocele from 16 paediatric surgery units (1954-1977). | -The mothers of gastroschisis cases were significantly younger than omphalocele cases ($p<0.0001$). | -Different data (Collection).<br>-Methods.<br>-No multiple ascertainment.<br>-Possible memory bias.<br>-Limited data. |
| Martinez-Frias et al (1984), Spain | Case control | Through the Spanish Collaborative Study of Congenital Malformation from 1976 to 1981, 12 gastroschisis and 40 omphalocele were identified and compared to malformed and nonmalformed controls. | -Prevalence of gastroschisis showed a significant secular trend with a mean annual increase of 0.38 per 10,000 livebirths.<br>-Maternal age of gastroschisis was significantly lower than control ($p< 0.01$).<br>-Maternal vaginal bleeding, gestational age, and birth weight were significantly different between gastroschisis and omphalocele and the controls. | -No memory bias (two different controls).<br>-Possible sample bias (hospital -based).<br>-Possible selection bias (nly livebirths).<br>-Possible memory bias (data was collected after delivery). |

## 1.5. *PREVENTION*

Prevention includes primary, secondary and tertiary forms of intervention.

### 1.5.1. **Primary Prevention**

The aim of primary prevention is to reduce the incidence of disease by controlling causes and risk factors. Primary prevention involves two strategies that are often complementary and reflect two views of aetiology. It can focus on the whole population with the aim of reducing average risk (the population strategy) or on people at high risk as a result of particular exposures (Beaglehole *et al.*, 1993).

Because the aetiology of these defects is unknown, no primary prevention is available (Bergsma, 1979), except for genetic counselling and possibly by using folic acid to prevent some defects particularly NTD (Czeizel and Dudas, 1992). Because omphalocele is associated with NTD, it appears this might offer prospects for prevention of abdominal wall defects as well, as suggested by a study done in experimental rats (Irving, 1990). Milunsky *et al.* (1989) observed a substantially reduced risk of NTD among women who took standard doses of multivitamin /folic acid supplements during the first 6 weeks of pregnancy. Czeizel (1996) recently found multivitamin supplementation appeared to result in a significant reduction in the rate of urinary tract abnormalities, mainly obstructive defects, and in the rate of sporadic cardiovascular malformations, mainly ventricular septal defects. Periconceptional multivitamin supplementation including 0.8 of folic acid appears to reduce significantly the first occurrence of NTD (Czeizel and Dudas, 1992). Tolarova (1982) reported a protective effect of periconceptional multivitamin supplementation for clef lip ± cleft palate. Czeizel *et al.* (1996) in a case-control study showed significant protection after folic acid supplementation during the critical period of cardiovascular defects, NTD, cleft lip ± cleft palate and posterior cleft palate.

### 1.5.2. **Secondary prevention**

The purpose of secondary prevention is to reduce the more serious consequences of disease through early diagnosis and treatment. It comprises the measures available to

individuals and populations for early detection and prompt and effective intervention. It is directed at the period between onset of disease and the normal time of diagnosis, and aims to reduce the prevalence of disease. Secondary prevention can be applied only to diseases in which the natural history includes an early period when it is easily identified and treated, so that progression to a more serious stage can be stopped. Secondary prevention is usually regarded as achievable through population screening.

### 1.5.2.1. *Screening*

Wilson and Jungner summarised the following principles of screening:

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognised disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognisable latent or early symptomatic stage.
5. There should be a suitable test examination.
6. The test should be acceptable to the population.
7. The natural history of the disease, including latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as whole.
10. Case-finding should be a continuing process and not a 'once for all' project.

Evaluation of screening is of vital importance and has to often been neglected in the establishment of screening programmes. Cochrane and Holland (1971) suggested several criteria for assessment or evaluation of any screening test.

- Simplicity: a test should be simple to perform, easy to interpret, and, where possible, capable of use by paramedical and other personnel. With increasingly complex technology certain screening tests, particularly for example in the antenatal and neonatal periods, can only be performed by doctors.
- Acceptability: since participation in screening is voluntary, a test must be acceptable to those undergoing it.

- Accuracy: a test must given a true measurement of the condition or symptom under investigation.
- Cost: the expense of the test must be considered in relation to the benefits of early detection of the disease.
- Precision or repeatability: the test should give consistent results in repeated trials.
- Sensitivity: the test should be capable of giving a positive finding when the person being screened has the disease being sought.
- Specificity: the test should be capable of giving a negative finding when the person being screened does not have the disease being sought.

The months before birth and in the first year of life are those in which most individuals receive more attention from the health care professions than at any other time during their lives. Screening at this stage of life relies increasingly on the use of complex technology and sophisticated equipment. The advantages of this are that potential problems can be clearly identified. Antenatal screening has for many years provided the focus for routine antenatal care. Routine antenatal care provides a convenient framework and opportunity for screening procedures to be carried out where necessary. There are those who argue that a clear distinction should be made between routine antenatal care and screening for specific fetal abnormalities, and from an academic point of view this is probably so. Antenatal screening tests vary from a simple blood test for anaemia to diagnostic tests for fetal abnormalities, for example, by amniocentesis (Holland and Stewart, 1990). Successful screening programmes need a high quality laboratory analysis, rapid and skilled communication between laboratory and physician, adequate resources for follow up testing, adequate counselling and epidemiological surveillance (Al-Omran, 1991).

Screening for O&G depends on the use of biochemical markers and / or ultrosonography leading to prenatal diagnosis.

#### 1.5.2.2. *Prenatal Diagnosis of O&G*

Fetal abdominal wall defects are being more frequently diagnosed as a consequence of widespread prenatal maternal serum alpha-fetoprotein (MSAFP) screening and by routine ultrasound fetal anomaly scanning (Mann *et al.*, 1984; Redford *et al.*, 1985). It

has been reported that MSAFP screening has a sensitivity of 42% for omphalocele. Therefore, the evaluation of the prevalence of abdominal wall defects is an important part of the sonographic assessment of pregnancies with elevated AFP. Conversely, since an increased incidence of NTD has been found in infants with omphalocele, identification of the latter lesion should not result in overlooking fetal spinal anomalies (Romero *et al.*, 1988).

With refinements in obstetric ultrasonography technique, it has become possible to distinguish accurately between omphalocele and gastroschisis and to recognize additional abnormalities. It is also possible to assess the size of the sac, if present, and of the abdominal wall defect as well as determining whether liver is present in the sac (Irving, 1990). Jones and Woodward (1986) noted that maternal ultrasonography is rapidly becoming routine in developed countries and that both conditions can be identified, and distinguished, in the first trimester. Amniocentesis and karyotyping are indicated when omphalocele has been diagnosed because of the high incidence of chromosomal trisomies (Irving, 1990).

The significantly higher incidence of co-existing abnormalities in a fetus with omphalocele is now widely accepted as grounds for termination. If this becomes standard practice, omphalocele should rarely arise as a clinical entity. In gastroschisis, the defect can be identified by ultrasound early in the pregnancy, even before evisceration, which may not occur until much later, and is not usually an indication to terminate the pregnancy (Jones and Woodward, 1986).

In the West of Scotland, Morrow *et al.* (1993) reported over seven years that omphalocele was prenatally diagnosed in 66% of cases, and in 30% of omphalocele cases it was associated with another major abnormality. Gastroschisis was prenatally diagnosed in 70% of all cases, and in the group who continued with the pregnancy there was a survival of 77% of gastroschisis and 20% of omphalocele who had no fetal anomaly and who opted to continue with pregnancy. Maternal serum α-fetoprotein was elevated in 89% of the cases with omphalocele and in 100% of the cases with gastroschisis.

In the study of gastroschisis in the decade (1983-1993) of prenatal diagnosis in the Royal Hospital for Sick Children in Glasgow, Haddock *et al.* (1996) reported that 39 of 50 cases were prenatally diagnosed (78%).

Le-Ha *et al.* (1995) in the study of impact of prenatal screening and diagnosis on the epidemiology of omphalocele and gastroschisis in Glasgow found a marked increase occurred over the period of 1980-91 in the proportions of cases diagnosed prenatally but not in the proportions terminated. They divided the study into two periods (1980-85 and 1986-91), and showed the frequency of prenatal diagnosis increased strikingly between the two periods, but the frequency of induced abortion showed almost no increase. The greatest difference between the prevalence at birth and during pregnancy was found for omphalocele.

Fisher *et al.* (1996) reviewed data during 24-months from the population-based Congenital Malformation Registry in the South East Thames Region of England, in 1992. Forty cases of omphalocele and 40 of gastroschisis were reported. Of these 39 cases of omphalocele (98%) and 38 of gastroschisis (95%) were diagnosed antenatally through routine antenatal ultrasound examination. The mean gestational age at the time of diagnosis was 18 weeks for omphalocele and 20 weeks for gastroschisis. After diagnosis, further ultrasound examinations were performed in all 38 antenatally diagnosed cases of gastroschisis. Antenatal karyotyping was carried out in 16 fetuses (40%) with omphalocele and three (8%) with gastroschisis. Additional abnormalities were identified in 25 (63%) of the 40 cases of omphalocele and in five (13%) of the 40 cases of gastroschisis. In 22 (56%) of the 39 antenatally diagnosed cases of omphalocele, the pregnancy was terminated because of suspected additional abnormalities; in three cases, the additional abnormalities were not confirmed after termination (in their data early spontaneous or social abortions were not included).

Dillon and Renwick (1995) reported that of 43 cases of omphalocele, 32 cases were prenatally diagnosed by ultrasound before 24 weeks, 10 cases at birth, one case spontaneous miscarriage. Two cases were misdiagnosed as gastroschisis. Of 56 cases of gastroschisis, 37 cases were diagnosed at 24 weeks, three cases in the third trimester, 14 at birth, had two ended in spontaneous miscarriage. Eight cases were misdiagnosed as omphalocele.

Surgery is another form of secondary prevention, which attempts to return the viscera to the abdominal cavity. Where the abdominal cavity is too small one must use silastic sheeting as temporary covering with serial removal for reconsitution of the abdominal wall for gastroschisis and operative correction by replacement of the viscera within the abdomen for small defects. In larger defects, when the return of the viscera to hypoplastic or underdeveloped abdominal cavity will result in respiratory deficiency, e.g. elevation of the diaphragm and diminised respiratory exchange, the fascia should remain open, the defect enlarged and a staged repair employed using temporary synthetic material, e.g. silastic rubber sheeting. Ultimate closure can be accomplished in stages by 2-4 weeks of age (Bergsma, 1979).

### 1.5.3. **Tertiary prevention**

The purpose of tertiary prevention is to reduce the progress or complication of established disease and is an important aspect of therapeutic and rehabilitation medicine. It consists of the measures intended to reduce impairments and disabilities, minimize suffering caused by departures from good health, and promote patients' adjustment to an incurable condition (Beaglehole *et al.*, 1993).

Rehabilitation is important after birth due to the possible damage either during the surgery, delay in surgery or association with other malformations. Therefore, children should be followed after birth, during school to optimise their quality of life.

In summary, the aetiology of omphalocele and gastroschisis is still unknown. Therefore, there is no available primary prevention. Genetic counselling and folic acid might offer prospects of preventing these defects but this remains to be established. Fetal abdominal wall defects are being more frequently diagnosed as a consequence of widespread prenatal maternal serum α-fetoprotein (MSAFP) screening and by routine ultrasound fetal anomaly screening. It has been reported that MSAFP screening has a sensitivity of 42% for omphalocele and about 70-95% for gastroschisis.

## 1.6. *PERINATAL MORTALITY AND SURVIVAL*

Perinatal mortality among omphalocele cases is usually higher than in gastroschisis cases, and the survival rate among omphalocele cases is less than gastroschisis cases because of the association of the former with other anomalies and syndromes. Several investigations have reported the impact of associated anomalies on survival in cases of omphalocele. According to the report of Berseth (1982), mortality for all babies was related to the presence of additional congenital anomalies, and most deaths of omphalocele were due to other congenital causes (83%). Seashore (1978) reported that among abdominal wall defects admitted to Yale-New Haven hospital from 1964-77, the survival rate was 57% for gastroschisis and 56% for omphalocele (74% excluding trisomies and one untreated patient). The overall survival rate in the study of Brun *et al.* (1996) was 94% for gastroschisis.

Bergsma (1979) reported that mortality rate was 20-30% for omphalocele. Causes of death are infection, inanition or unrelated congenital abnormalities for omphalocele, and for gastroschisis with staged repair and support, mortality dropped by 20-30% in most series.

In Australia by Lancaster and Pedisich (1995), 31% of omphalocele and 12% of gastroschisis were stillbirths: 34% of omphalocele and 10% of gastroschisis liveborn infants died in the neonatal period.

A survey of three million births between 1980 and 1990 in the 21 regional registers in Europe (Calzolari *et al.*, 1995) showed that 18% of cases were recorded as fetal deaths of gestational age of at least 20 weeks for omphalocele: the total proportion of induced abortions was 33% for omphalocele (23% for isolated cases), and the percentage of induced abortions following prenatal diagnosis was 27% (19% for isolated cases). Among the gastroschisis cases, 15% were recorded as stillbirths (18 of which were born between 20 and 27 weeks).

In Spain, Martínez-Frías *et al.* (1984), concluded that mortality during the first three days of life was higher in children with gastroschisis and omphalocele associated

syndrome or those associated with other anomalies, than in controls or children with isolated omphalocele.

Mckeown *et al.* (1953) found a very high prevalence of stillbirths in abdominal wall defects (1 in 170). Prevalence (1 in 167) was found in the study of Lindham (1981) 20 years later. In the study of Roeper *et al.* (1987), stillbirths occurred in 18% of the omphalocele cases and in 10% of gastroschisis but they were not significantly difference. In Taiwan, from 1982 to 1990, 31 neonates with omphalocele and 54 with gastroschisis were treated at Mackay Memorial Hospital. The overall survival rate for omphalocele was 71%, and 85% for gastroschisis. The mortality from omphalocele was almost exclusively due to the presence of serious associated congenital anomalies (Chang *et al.*, 1992). The overall mortality rate was 14% (8/59), and this was not affected by low birthweight or prematurity (De Lorenzo *et al.*, 1987). A retrospective study of 92 cases of omphalocele over a 25-year period reveals an overall mortality rate of 37%. Death was associated almost exclusively with additional congenital anomalies (Yazbeck *et al.*, 1986). In England and Wales, the perinatal mortality rate of gastroschisis (65 in 1000) was significantly lower than that of omphalocele (206 in 1000); OR= 0.32, 95% CI=0.21 to 0.48; $p<0.001$ (Tan *et al.*, 1996).

In the study of gastroschisis in the decade (1983-1993) of prenatal diagnosis in the Royal Hospital for Sick Children in Glasgow, Haddock *et al.*(1996) reported that mortality was 10%.

In summary, the prognosis (in term of survival) of gastroschisis is much better than that of omphalocele.

# SECTION II: SUMMARY OF LITERATURE, RATIONALE AND AIM OF THE PRESENT STUDY

# SECTION II: SUMMARY OF LITERATURE, RATIONALE AND AIM OF THE PRESENT STUDY

## 2.1. *SUMMARY OF LITERATURE, AND RATIONALE OF THE PRESENT STUDY*

The prevalence of anterior abdominal wall defects is approximately one in 2500 births (Mann *et al.*, 1984). The prevalence of livebirths with gastroschisis in the West of Scotland is approximately one in 6000 (Haddock *et al.*, 1996) . The ratio of omphalocele to gastroschisis is about 3:1. While the prognosis for omphalocele depends on whether there are any associated defects, especially chromosomal (Mann *et al.*, 1984; Schuster, 1986), gastroschisis is often an isolated lesion with an excellent outlook (Schuster, 1986).

Omphalocele and gastroschisis are the commonest malformations of the abdominal wall. While these defects are rare, they present clinically as emergencies. Their prevalence appears to be increasing in different geographic regions. Glasgow appears to have one of the highest prevalence rates in Europe and one that may have been increasing in recent years.

The reported prevalence of omphalocele in Glasgow is the highest in the United Kingdom, and these may be an increasing trend of omphalocele and gastroschisis prevalence from the South to the North of the United Kingdom.

The aetiology is unknown but epidemiological studies suggest that these defects might be a multifactorial. Hypotheses relating to gastroschisis have focused on environmental factors. Young maternal age has been confirmed to be a risk factor for gastroschisis.

The defects vary in their severity but most are potentially lethal if untreated surgically. An increasing proportion is being detected by prenatal diagnosis. Because of the wide availability of α-fetoprotein and ultrasound screening in pregnancy, it is now common for anterior abdominal wall defects to be diagnosed in the first half of pregnancy.

Omphalocele and gastroschisis are associated with other malformations. Omphalocele especially is associated with other malformations including trisomies. These severe malformations account to a large extent for the higher mortality rate of omphalocele.

Prenatal diagnosis is important in helping parents decide about termination of the pregnancy. On the other hand, for infants who have good prognosis, prenatal diagnosis facilitates the choice of place, time and method of delivery, and ensures that rapid surgery can be performed.

Glasgow is ideal for an epidemiological investigation for abdominal wall defects for several reasons. First, it appears to be a high risk geographical area. Second, it has a population based register of congenital malformations that includes induced abortions.

While the aetiology is unknown (except in the minority of cases associated with recognised genetic syndromes), various possible risk factors have been suggested including young maternal age, low socio-economic status and cigarette smoking in pregnancy. The importance of these factors is unclear, partly because of the paucity of high quality epidemiological data on these defects which have been published to date.

The present study was undertaken in order to determine to prevalence and early outcome of O&G in Glasgow, to investigate possible aetiological factors related to hypothesised maternal risk factors, and to asses the epidemiological impact of prenatal diagnosis.

## 2.2. *AIM AND OBJECTIVES*

The overall aim of the study was to undertake a detailed investigation of the epidemiology abdominal wall defects in Glasgow.

The specific objectives of the study were:

1-To establish the descriptive epidemiology of omphalocele and gastroschisis (O&G) in Glasgow for the birth years 1980-93.

2-To determine the extent of any association between the prevalence of O&G and a number of the hypothetical risk factors, particularly maternal age, cigarette smoking, and socio-economic status.

3-To assess the extent and epidemiological impact of prenatal diagnosis on the prevalence of omphalocele and gastroschisis.

# SECTION III: SUBJECTS AND METHODS

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## 3.1. *THE GLASGOW REGISTER OF CONGENITAL ANOMALIES*

The Glasgow Register of Congenital Anomalies (GRCA) commenced data collection on January 1st, 1972, under the auspices of the former Corporation of Glasgow Health Department. In 1974, following the abolition of municipal health authorities, responsibility for the Register was assumed by the GGHB, where it has remained ever since. Interest in the Register received a boost following the selection of Glasgow as one of the participating centres in the multi-national EUROCAT (European Register of Congenital Anomalies and Twins) project of the European Community in 1979 that is based in Brussels (Weatherall *et al.*, 1984). The GRCA is believed to have a high degree of validity of registered data relative to other centres in EUROCAT (Stone, 1986).

The initial geographical remit of the Register was the city of Glasgow followed by the GGHB area after 1974. Unlike many other registers, the Glasgow Register has always been population-based in that its denominator is the total number of births to residents of a defined area, rather than births occurring in one or more maternity hospitals (Stone, 1989).

All anatomical, metabolic and genetic congenital anomalies (except for minor defects such as umbilical and inguinal hernia) identified by a doctor, midwife or health visitor in a child born to a Glasgow resident are eligible for registration. Live births, stillbirths and therapeutic terminations are included. Since its involvement in EUROCAT, the Register has adopted the five-digit British Paediatric Association Code (based on the latest revision of the International Classification of Diseases) to assess, classify and code notified defects. Because Glasgow is one of the members of EUROCAT a special form called the EUROCAT Report on Congenital Malformations started to be used in 1980. One form is filed for each registered defect in births (live and still) and therapeutic terminations with relevant material including date and birth order. Data on terminations following prenatal diagnosis are collected and filed separately. Both multiple and singleton births are included. Multiple sources of ascertainment are employed, some 'active', requiring Registry staff to retrieve data, others 'passive', whereby data are routinely transmitted to the Register. The number and nature of these sources have

changed over the years (Table 3.1). The most important of them are the stillbirths and deaths registers, paediatric discharge letters, and routine hospital discharge forms (known as SMR 1, SMR 2, and SMR 11) which are completed for every hospital in-patient in Scotland and processed centrally by the Information and Statistics Division of the Common Service Agency of the Scottish Health Service.

In order to maximise ascertainment, the Register has no formal time limit for the registration of newly diagnosed cases. In theory, therefore, a congenital anomaly diagnosed in adult life is eligible for registration in the appropriate birth year.

All data processing is currently automated following transfer of the files to a dedicated microcomputer in 1980. Data linkage with other parts of the child health record system is feasible owing to the existence of a unique number allocated to every child born within the GGHB area (Stone ,1989).

A computerised search was performed of Medline (1975 to August 1997), Embase (1981-97), along with a manual search of relevant reports. Only English language papers were selected. The MeSH terms used in the computerised search were omphalocele, gastroschisis, exomphalos, abdominal wall defects. Only reports of epidemiological (rather than embryological or pathological) studies were included.

**Table 3.1**. The Glasgow Register of Congenital malformations: sources of ascertainment

| 'Active' sources | 'Passive' sources |
|---|---|
| Hospital records | Paediatric discharge letters |
| Post-mortem reports | Health visitor notifications |
| Prenatal meetings | Stillbirth and death registers |
| Department of medical genetics (cytogenetic reports, amniocentesis reports and files) | |
| Scanning of routine hospital discharge forms (SMR 1, SMR 2, SMR 11) | |

Adapted from Stone and Hamilton, 1987

## 3.2. *NUMERATOR AND DENOMINATOR DATA*

The population surveyed included live births, stillbirths and induced abortions following prenatal diagnosis. The term stillbirth refers to all fetal deaths after 28 completed weeks from 1980-1991 and after 24 completed weeks from 1992.

Numerator data were obtained from the GRCA. Cases comprised all registered cases of omphalocele and gastroschisis (ICD9 codes 75670, 75671) pregnancies leading to live births, still births or induced abortions following prenatal diagnosis for the birth years 1980-1993 inclusive (n=97). Spontaneous abortions were excluded from descriptive study (n= 97) but included in the case-control study (n= 108).

Denominator data (total births, live and still) were obtained from the Information Services Unit of GGHB. The denominator was the total number of births (live and still) to mothers who were resident in the GGHB at the time of births or abortions. Birth prevalence was calculated by dividing the number of infants (live+still) born with abdominal wall defects by the denominator for 1980-1993. Pregnancy prevalence was calculated by dividing the sum of affected live births, stillbirths and induced abortions following prenatal diagnosis by the denominator.

### 3.2.1. **Study Population**

The study population derived from all omphalocele and gastroschisis (minor and major) including live and stillbirths and induced abortions.

Omphalocele and gastroschisis were considered isolated if there were no associated anomalies or if anomalies were present (such as intestinal atresia or stenosis, undescended testicles or lung hypoplasia) were thought to be a consequence of these conditions. All cases of congenital anomaly associated with major and minor omphalocele and gastroschisis were considered to be multiply malformed.

## 3.3. *DESIGN OF STUDY*

Data from the registration forms and records of hospitals were transferred to coding forms. The coded data were then entered on a computer file and a series of computer print-outs generated for analysis.

### 3.3.1. **Descriptive Analysis**

To calculate birth and pregnancy prevalence rates (births and termination), the total births to GGHB residents were used, first for all years and then to the two periods 1980-1986 and 1987-1993. Induced abortions were allocated to a birth year according to the expected date of delivery (based on last menstral period). For gastroschisis, three periods were analysed (1980-84, 1985-88 and 1989-93), because from 1981-84, there were no cases and in some other years, there were few cases. Cases with omphalocele and omphalocele plus gastroschisis (O&G) were analysed in the same way.

Sex ratio was examined in isolated and associated cases, and in cases with and without NTD.

The data were divided into five maternal age groups (<20, 20-24, 25-29, 30-35, >35 years), and for trend analysis, total births in GGHB were included in the denominator to compare each group with each other particularly with <20 years old mothers. Cases were also separated into isolated and associated (chromosomal defects were excluded). For gastroschisis, mothers <20 were compared with >20 and their relative risk calculated (isolated, associated and total); similarly <20 were compared with 20-24 and their relative risk calculated. For omphalocele, mothers <20 were compared with >20 excluding chromosomal cases in terms of relative risk.

In the absence of adequate parental occupational data, maternal social class was examined using eight clusters of postcode sectors of maternal residents selected by the GGHB as representing, based on an analysis of census variables, gradations of socio-economic status (GGHB, 1991). These eight clusters or neighbourhood types range from the most prosperous (neighbourhood type 1) to the most deprived (neighbourhood type 8) postcode sectors in the city and are effectively proxies for maternal social class

(Lopez *et al.*, 1995). Neighbourhood types were divided into three groups; 1-2, 3-6, 7-8. The crude rate per 10,000 was calculated based on total births in each neighbourhood type grouping. Because in neighbourhood types 1-2 there were more older mothers than in the neighbourhood types 6-8, age standardisation was also performed, using the direct method.

For associated anomalies lung hypoplasia was excluded because it is thought to be a consequence of abdominal wall defects. The percentages of omphalocele and gastroschisis associated with other congenital malformations were calculated. Isolated, multiple malformations and syndromes were separated only for omphalocele because gastroschisis was associated with only one syndrome. In the group of infants with multiple malformations, syndromes were excluded and some malformation categories were combined ("other" congenital musculoskeletal anomalies with specific congenital musculoskeletal deformities, digestive system with upper alimentary tract, genital organs and urinary system, bulbus cordis anomalies and anomalies of cardiac septal closure with heart and circulatory system, "other" specified anomalies of brain with microcephalus).

Numbers and rates (per 10,000 total births) of omphalocele, gastroschisis and O&G were calculated for season (expected or actual) of births. Total births were calculated from 1983 because information before 1983 was inadequate.

Smoking was examined separately in isolated and associated defects. For the seasonal analysis, the prevalence rates were calculated by stratifying the data by month of last menstrual period.

Prenatal diagnosis was examined in both isolated and associated defects. Prenatal diagnosis was divided into two periods 1980-1986, 1987-1993. Total pregnancy (total prenatal diagnosis), live+still (prenatal diagnosis) and total induced abortions were the analytical categories. Proportions of omphalocele, gastroschisis and O&G were calculated among live births who had prenatal diagnosis or not for cases were survival.

For the calculation of prenatal deaths, cases were separated into isolated and associated defects and total live and still births of omphalocele and gastroschisis. For survival, the denominator was total births of omphalocele and gastroschisis up to one year of life.

Survival was also calculated up to birth, first week and first year among isolated and associated with other anomalies..

Some variables were dispensed with because of the high percentage of missing and unknown values recorded on the EUROCAT form (Table 3.2) and there were a low proportion of missing variables e.g drugs, smoking, illness before pregnancy, illness during pregnancy, History of spontaneous abortion, history of induced abortion and history of stillbirth (appendix $A_3$).

**Table 3.2.** Percentage of variables for which a high proportion of data were missing among omphalocele (OM), gastroschisis (GAS) and O&G (% cases with data).

| Variable | OM | GAS | O&G |
|---|---|---|---|
| | % | % | % |
| Family history | 52 | 75 | 58 |
| Unusual exposure | 85 | 63 | 79 |
| Father's age | 38 | 33 | 37 |
| Father's anomaly | 82 | 63 | 68 |
| Father's occupation | 85 | 63 | 79 |
| Mother's anomaly | 85 | 63 | 69 |
| Mother's occupation | 85 | 63 | 79 |
| Alcohol | 75 | 58 | 71 |

### 3.3.2. Case - Control Study

For each case, two controls (one malformed and one non-malformed) matched by sex, place and date of birth were randomly selected from all infants born to GGHB residents. The reason for selection of malformed and non-malformed controls was to minimise memory bias and selection (ascertainment) bias respective). The sample sizes were determined by a combination of two factors: statistical power (see figure, Appendix $A_4$) and feasibility of data collection. The sample size of about 100 gives a value of 0.80 for a standardised difference of 0.5 for continuos variables such as age.

#### 3.3.2.1. *Malformed Controls*

For each index case, one malformed control (excluding omphalocele and gastroschisis) was selected randomly by computer (SPSS), for whom the same data had been collected. The control was the next malformed live born infant (born to a Glasgow resident) of the same sex within same hospital on the same day (or subsequent). The information was available from the period 1980-1993 from the records of GGHB.

#### 3.3.2.2. *Non - malformed Controls*

For each index case one non-malformed control was selected from all of livebirths using the GGHB computer and was chosen randomly by SPSS package. The same data had been collected for controls as for cases. The control was the next non-malformed live birth to a Glasgow resident of the same sex within the same hospital on the same day. Detailed information on controls was collected from hospital records. There were three cases missing (no records) so they were replaced by random selection. The data were collected from 1983 because sufficiently detailed information on non-malformed controls was not available for the all infants born before 1983 in GGHB.

The case-control study was used to explore the association between omphalocele and gastroschisis and specific epidemiological variables. The following factors (abstracted by use of a specially designed registration form) were selected for analysis: demographic, reproductive, medical and a series of environmental factors. Cases and three categories of controls (malformed, non-malformed and malformed plus non-malformed) were compared with respect to the following maternal factors: Demographic: maternal age

(years) at time of delivery, reproductive history: parity (0, 1, 2 and ≥ 3), total pregnancies (0, 1, 2 and ≥ 3), history of spontaneous abortions (yes/no), history of induced abortions (yes/no), history of stillbirth (yes/no). Environmental factors: cigarette smoking during pregnancy; medical history, illness before and during pregnancy, drug (yes/ no), neighbourhood type (1-2, 3-6, 7-8), birth weight and gestational age.

The number of prior pregnancies was dichotomised as either no prior pregnancies or one or more prior pregnancies. Parity was dichotomised as either no prior live births or one or more prior live births.

First the variables were analysed separately from the demographic, reproductive, and environmental factors. Variables that were not associated with gastroschisis and omphalocele, or had numbers that were to small for analysis, were excluded from further analyses.

## 3.4. STATISTICAL METHODS

### 3.4.1. Univariate Analysis

The data were transferred to a microcomputer and a standard statistical package (SPSS for Window) was used for analysis. The graphics were produced by the Harvard Graphics software package.

The numbers are presented as percentages and rates per 10000 total births. To obtain an estimate of the prevalence, the numerators and the denominators were transformed into annual rates per 10000 total births (live and still).

The data are presented in tables, diagrams, and graphs. A variety of statistical tests were used to assess trends and associations between variables. Statistical analysis included the chi-squared test for presence or absence of the characteristic under study in the registered infants. Comparisons between the means of the different groups were carried out by T test or by Mann-Whitney (non-parametric test).

Statistical analysis consisted largely of the calculation of confidence intervals, chi-squared test or Fisher's exact test (two tails) if appropriate, Mantel-Haenszel test for trends and T test for comparison of two means (birth weight and gestational age). A chi-squared test was used to compare the frequency of anomalies associated with omphalocele and with gastroschisis. For survival, a log rank test was used.

Intergroup comparisons for continuous variables with a non-parametric distribution were made using the Mann-Whitney U test and T test (the results were same) as well to determine significant differences between the data sets. When the distribution was not normal, the Mann-Whitney (non-parametric test) was used, and categorical data were analysed using chi-squared test or Fisher's exact test and odds ratios and 95% confidence intervals. Significance was taken as $p<0.05$.

### 3.4.2. Multivariate Analysis

Variables that were not associated with omphalocele and gastroschisis, or had numbers that were too small for analysis, were excluded from further analyses. All variables were evaluated and included in the final model for possible interactions, but no interactive variable was retained due to lack of statistical significance. All remaining variables were then entered into the full multivariate logistic model. Logistic regression was used to compare maternal age in malformed controls and with non-malformed controls. Only maternal age and smoking variables were then entered into the full multivariate logistic model.

Conditional logistic regression was used to analyse parity and neighbourhood type in malformed, non-malformed and malformed + non-malformed controls. The analytical package BMDP was used for this analysis.

# SECTION IV: RESULTS

# SECTION IV: . RESULTS

## 4.1. *DESCRIPTIVE STUDY*

### 4.1.1. **Birth Prevalence**

Table 4.1 shows the numbers and rates (per 10,000 births) of omphalocele (OM), gastroschisis (GAS) and (O&G) (birth, terminations and pregnancies) in Glasgow, 1980-1993. The birth prevalence (live and still births) was 2.2 (OM), 1.1 (GAS) and 3.2 (O&G), and the pregnancy prevalence (births and terminations) was 4.1 (OM), 1.3 (GAS) and 5.4 (O&G) per 10,000. Of the 97 ascertained cases, 39 (40%) were terminated.

Figure 4.1 shows the birth prevalence of omphalocele and gastroschisis for 1980-1993. The pregnancy prevalence of gastroschisis showed a significant rising secular trend during the study period and although omphalocele did not show a significant increase.

Table 4.2 shows the numbers and rates (per 10,000 births) of O&G by birth year. The birth prevalence (live and still births) was 3.2, and the pregnancy prevalence (births and terminations) was 5.4 per 10,000. There was no significant trend either in pregnancy prevalence or birth prevalence (Mantel-Haenszel test=0.64, p=0.42 for total; Mantel-Haenszel test=0.26, p=0.61 for live and stillbirths).

Table 4.3 shows the numbers and rates (per 10,000 births) of omphalocele by birth year. The birth prevalence (live and still births) was 2.2, and the pregnancy prevalence (births and terminations) was 4.1 per 10,000. There was no trend either the pregnancy or birth prevalence over time.

Table 4.4 presents the numbers and rates (per 10,000 births) of gastroschisis. The pregnancy prevalence of gastroschisis showed a significant rising secular trend during the study period which was divided into three sub-periods (1980-1984; 1985-1988; 1989-1993) (Mantel-Haenszel test=5.46; df= 2; p=0.02) but the birth prevalence did not (Mantel-Haenszel test=2.76; df=2; p=0.25) (Table 4.5).

The pregnancy prevalence of omphalocele and O&G did not show any secular trend during the study period which was divided into three sub-periods (1980-1984; 1985-1988; 1989-1993) (Table 4.6 and 4.7).

Figure 4.2 shows that the relative frequency of O&G to all registered primary malformations rose significantly over the study period (chi-square test = 18.64; df=2, $p<0.0001$).

The prevalence rate of omphalocele in Glasgow is the highest reported in the United Kingdom, and this may be an increasing trend of O&G from the South to the North of United Kingdom (Table 4.8 a). According to report of Tan *et al.*, 1996, prevalence of all abdominal wall defects ranges from South West Thames region (1.23/ 10,000) to Northern region (3.11/ 10,000 births) (Table 4.8 b). Indeed, the prevalence found in the present study is more than four times higher than that reported from the ONS[1] for England and Wales. Data from EUROCAT for 1980-1992 indicate that the omphalocele / gastroschisis ratio in that system was 2.5, a figure much closer to that of Glasgow (3.0) than that (0.8) of the ONS. By contrast, the prevalence of gastroschisis in Glasgow is comparable with that of the area covered by the ONS, particularly its northern and western regions (Table 4.8 b).

[1] The Office for National Statistics

**Table 4.1**. Numbers and rates (per 10,000 births) of omphalocele (OM), gastroschisis (GAS) and omphalocele plus gastroschisis (O&G) (births, terminations and pregnancies) in Glasgow, 1980-1993 (total births= 179,067)

| Anomaly | Births | | | | Terminations | Pregnancies (births+ terminations) | | |
|---|---|---|---|---|---|---|---|---|
| | Live | Still | Total | | | Total | | |
| | No (%) | No (%) | No (%) | Rate /10,000 births | No (% of pregnancies) | No(%) | Rate* | 95% CI |
| OM | 27 (62.8) | 12 (80) | 39 (67.2) | 2.2 | 34 (46.6) | 73 (75.3) | 4.1 | 3.16 to 5.04 |
| GAS | 16 (37.2) | 3 (20) | 19 (32.8) | 1.1 | 5 (20.8) | 24 (24.7) | 1.3 | 0.77 to 1.83 |
| O&G | 43 (100) | 15 (100) | 58 (100) | 3.2 | 39 (40.2) | 97 (100) | 5.4 | 4.32 to 6.48 |

* Rate per 10,000 births

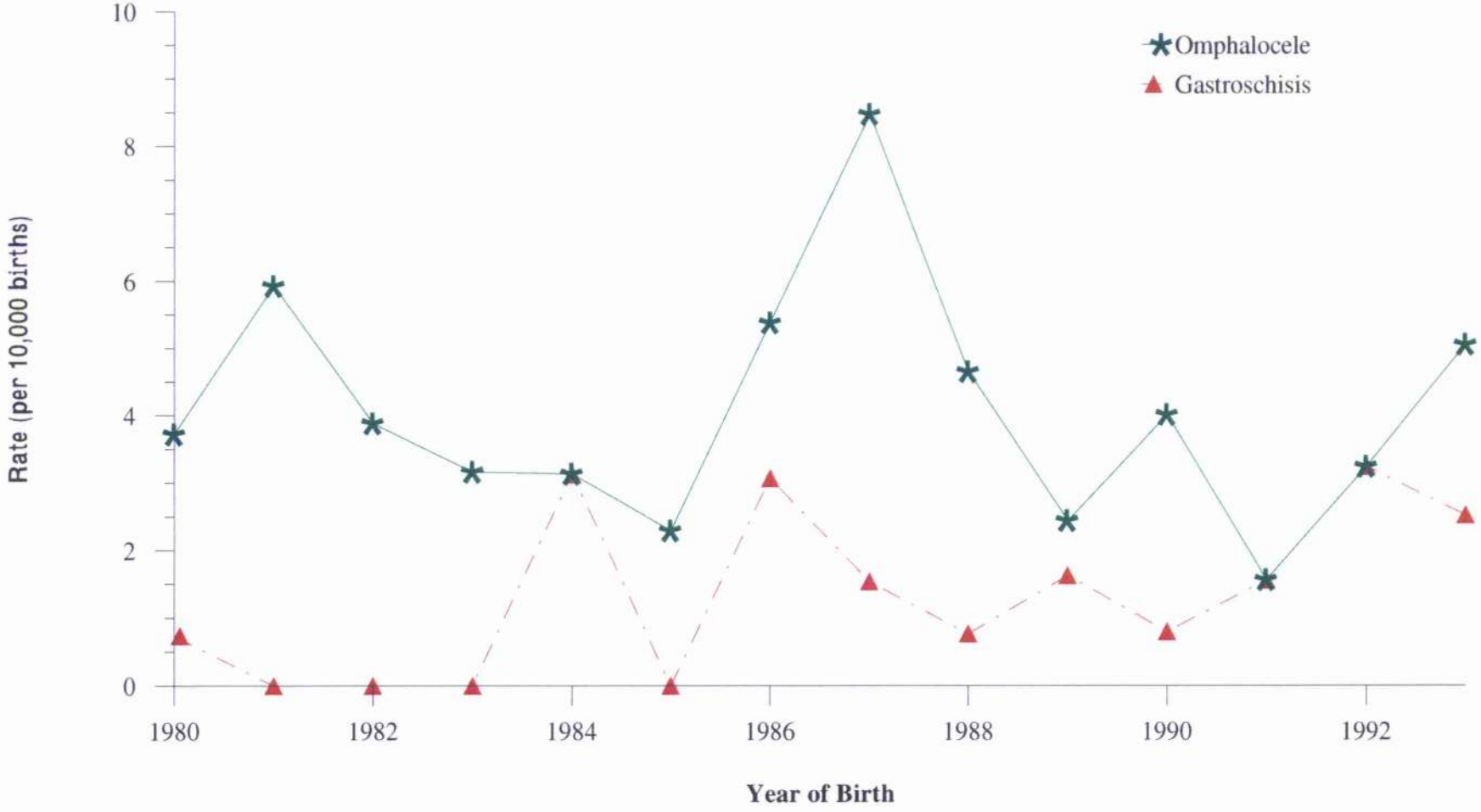



**Figure 4.1.** Pregnancy prevalence of omphalocele and gastroschisis in Glasgow during 1980-1993

**Table 4.2**. Numbers and rates (per 10,000 births) of O&G (births, terminations and pregnancies) in Glasgow, 1980 -1993

| Year of birth | Total births | Births (live+still) | | Terminations | | Pregnancies (births+termination) | | |
|---|---|---|---|---|---|---|---|---|
| | | No | Rate | No | % | No | Rate | 95% C.I |
| 1980 | 13438 | 4 | 3.0 | 2 | 33.3 | 6 | 4.5 | 0.89 to 8.04 |
| 1981 | 13491 | 6 | 4.5 | 2 | 25.0 | 8 | 5.9 | 1.82 to 10.04 |
| 1982 | 12884 | 2 | 1.6 | 3 | 60.0 | 5 | 3.9 | 0.48 to 7.28 |
| 1983 | 12661 | 2 | 1.6 | 2 | 50.0 | 4 | 3.2 | 0.06 to 6.25 |
| 1984 | 12783 | 5 | 3.9 | 3 | 37.5 | 8 | 6.3 | 1.92 to 10.5 |
| 1985 | 13089 | 3 | 2.3 | 0 | 0.0 | 3 | 2.3 | -0.3 to 4.88 |
| 1986 | 13013 | 6 | 4.6 | 5 | 45.5 | 11 | 8.5 | 3.46 to 13.45 |
| 1987 | 12987 | 7 | 5.4 | 6 | 46.2 | 13 | 10.0 | 7.57 to 15.45 |
| 1988 | 12908 | 4 | 3.1 | 3 | 42.9 | 7 | 5.4 | 1.41 to 9.44 |
| 1989 | 12289 | 3 | 2.4 | 2 | 40.0 | 5 | 4.1 | 0.51 to 7.63 |
| 1990 | 12471 | 2 | 1.6 | 4 | 66.7 | 6 | 4.8 | 0.96 to 8.66 |
| 1991 | 12831 | 3 | 2.3 | 1 | 25.0 | 4 | 3.1 | 0.06 to 6.17 |
| 1992 | 12339 | 7 | 5.7 | 1 | 12.5 | 8 | 6.5 | 1.99 to 10.97 |
| 1993 | 11883 | 4 | 3.4 | 5 | 55.6 | 9 | 7.6 | 2.63 to 12.52 |
| Total | 179067 | 58 | 3.2 | 39 | 40.2 | 97 | 5.4 | 4.32 to 6.48 |

Mantel-Haenszel test for pregnancies= 0.64; (p= 0.42) for total (NS) and for birth prevalence M.H= 0.26; (p=0.61) for live+still births (NS)

**Table 4.3**. Numbers and rates (per 10,000 births) of omphalocele, (births, terminations and pregnancies) in Glasgow, 1980 -1993

| Year of birth | Total births | Births (live+still) | | Terminations | | Pregnancies (births+termination) | | |
|---|---|---|---|---|---|---|---|---|
| | | No | Rate | No | % | No | Rate | 95% C.I |
| 1980 | 13438 | 3 | 2.2 | 2 | 40.0 | 5 | 3.7 | 0.46 to 6.48 |
| 1981 | 13491 | 6 | 4.4 | 2 | 0.25 | 8 | 5.9 | 1.82 to 10.04 |
| 1982 | 12884 | 2 | 1.6 | 3 | 60.0 | 5 | 3.9 | 0.48 to 7.28 |
| 1983 | 12661 | 2 | 1.6 | 2 | 50.0 | 4 | 3.2 | 0.06 to 6.25 |
| 1984 | 12783 | 1 | 0.8 | 3 | 75.0 | 4 | 3.1 | 0.08 to 6.18 |
| 1985 | 13089 | 3 | 2.3 | 0 | 0.0 | 3 | 2.3 | -0.3 to 4.88 |
| 1986 | 13013 | 3 | 2.3 | 4 | 57.1 | 7 | 5.4 | 1.41 to 9.39 |
| 1987 | 12987 | 6 | 4.6 | 5 | 45.4 | 11 | 8.5 | 3.47 to 13.47 |
| 1988 | 12908 | 4 | 3.1 | 2 | 33.3 | 6 | 4.6 | 0.93 to 8.37 |
| 1989 | 12289 | 1 | 0.8 | 2 | 66.7 | 3 | 2.4 | -0.32 to 5.20 |
| 1990 | 12471 | 2 | 1.6 | 3 | 60.0 | 5 | 4.0 | 0.50 to 7.52 |
| 1991 | 12831 | 1 | 0.8 | 1 | 50.0 | 2 | 1.6 | -0.6 to 3.71 |
| 1992 | 12339 | 3 | 2.4 | 1 | 25.0 | 4 | 3.2 | 0.07 to 6.42 |
| 1993 | 11883 | 2 | 1.7 | 4 | 66.7 | 6 | 5.0 | 2.07 to 11.39 |
| Total | 179067 | 39 | 2.2 | 34 | 46.6 | 73 | 4.1 | 3.16 to 5.04 |

Mantel-Haenszel test for pregnancies =0.16; p=0.69 (NS)

**Table 4.4**. Numbers and rates (per 10,000 births) of gastroschisis (births, terminations and pregnancies) in Glasgow, 1980 -1993

| Year of birth | Total births | Births (live+still) | | Terminations | | Pregnancies (births+termination) | | |
|---|---|---|---|---|---|---|---|---|
| | | No | Rate | No | % | No | Rate | 95% C.I |
| 1980 | 13438 | 1 | 0.7 | 0 | 0 | 1 | 0.7 | 0.07 to 0.22 |
| 1981 | 13491 | 0 | 0.0 | 0 | 0 | 0 | 0 | ------- |
| 1982 | 12884 | 0 | 0.0 | 0 | 0 | 0 | 0 | ------- |
| 1983 | 12661 | 0 | 0.0 | 0 | 0 | 0 | 0 | ------- |
| 1984 | 12783 | 4 | 3.1 | 0 | 0 | 4 | 3.1 | 0.01 to 0.61 |
| 1985 | 13089 | 0 | 0.0 | 0 | 0 | 0 | 0 | ------- |
| 1986 | 13013 | 3 | 2.3 | 1 | 25.0 | 4 | 3.1 | 0.01 to 0.61 |
| 1987 | 12987 | 1 | 0.8 | 1 | 50.0 | 2 | 1.5 | -0.06 to 0.36 |
| 1988 | 12908 | 0 | 0.0 | 1 | 100 | 1 | 0.8 | -0.08 to 0.24 |
| 1989 | 12289 | 2 | 1.6 | 0 | 0.0 | 2 | 1.7 | -0.06 to 0.39 |
| 1990 | 12471 | 0 | 0.0 | 1 | 100 | 1 | 0.8 | -0.08 to 0.24 |
| 1991 | 12831 | 2 | 1.6 | 0 | 0.0 | 2 | 1.6 | -0.06 to 0.37 |
| 1992 | 12339 | 4 | 3.2 | 0 | 0.0 | 4 | 3.2 | 0.01 to 0.64 |
| 1993 | 11883 | 2 | 1.7 | 1 | 33.3 | 3 | 2.5 | -0.03 to 0.54 |
| Total | 179067 | 19 | 1.1 | 5 | 20.8 | 24 | 1.34 | 0.77 to 1.83 |

Mantel-Haenszel test for pregnancies =5.46; df=2; p=0.02, and birth prevalence =2.76; df=2; p=0.25 for L+S (NS) (1980-84, 1985-88, 1989-1993)

**Table 4.5**. Numbers and rates (per 10,000 births) of gastroschisis (GAS) (births, terminations and pregnancies) in Glasgow, 1980 -1984, 1985-1988, and 1989-1993

| Year of birth | Total births | Births[2] | | Termination | | Pregnancies[3] | | |
|---|---|---|---|---|---|---|---|---|
| | | No | Rate[4] | No | (%) | No (%) | Rate | 95% CI |
| 1980-84 | 65257 | 5 | 0.77 | 0 | (0.0) | 5 (100) | 0.8 | 0.10 to 1.44 |
| 1985-88 | 51997 | 4 | 0.77 | 3 | (42.9) | 7 (100) | 1.4 | 0.35 to 2.34 |
| 1989-93 | 61813 | 10 | 1.62 | 2 | (16.7) | 12 (100) | 2.0 | 0.84 to 3.04 |
| Total | 179067 | 19 | 1.1 | 5 | (20.8) | 24 (100) | 1.3 | |

Gastroschisis
Mantel-Haenszel test for pregnancies = 5.46; df=2; p=0.02, and birth prevalence =2.76; df=2; p=0.25 for L+S (NS)

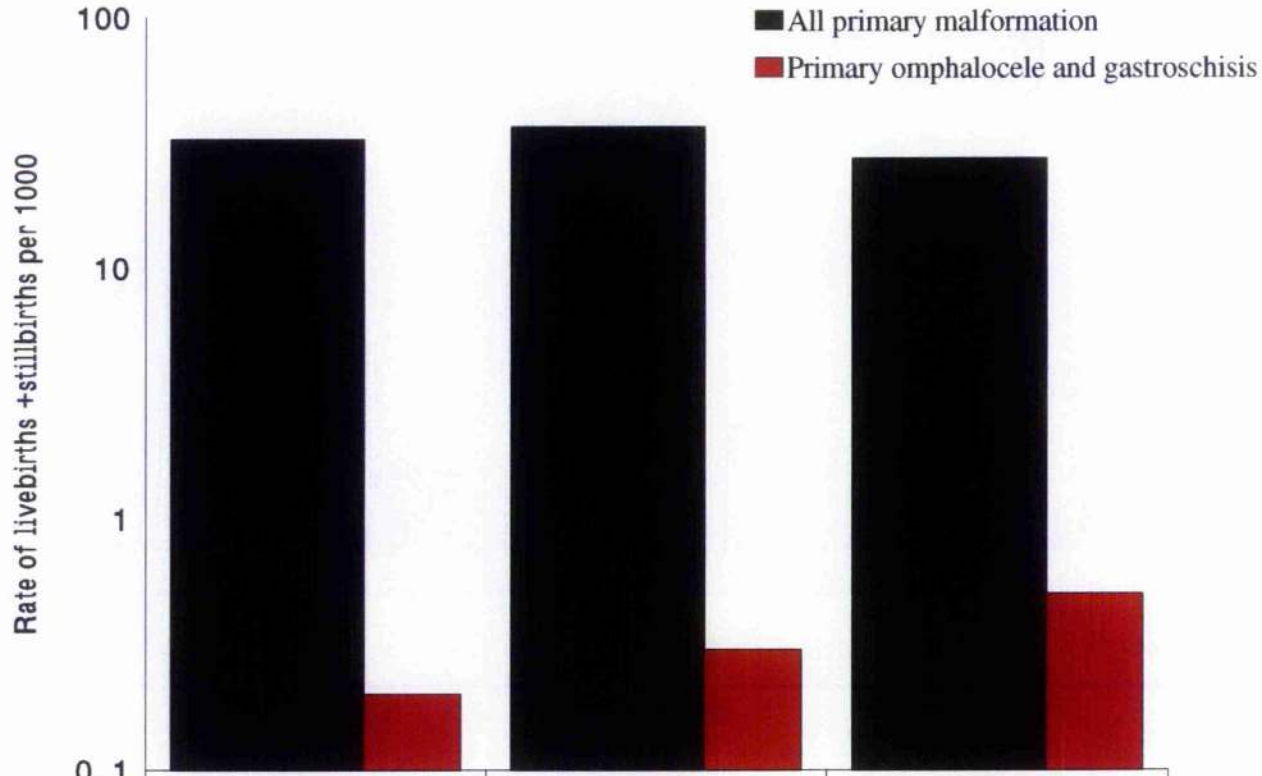
[2] Births (live+still).
[3] Pregnancies (births+termination).
[4] Rates are expressed per 10,000 total births.

**Table 4.6**. Numbers and rates (per 10,000 births) of omphalocele (OM) (births, terminations and pregnancies) in Glasgow, 1980 -1984, 1985-1988, and 1989-1993

| Year of birth | Total births | Births | | Termination | | Pregnancies | | |
|---|---|---|---|---|---|---|---|---|
| | | No | Rate | No | (%) | No (%) | Rate | 95% CI |
| 1980-84 | 65257 | 14 | 2.2 | 12 | (46.2) | 26 (100) | 4.0 | 2.47 to 5.53 |
| 1985-88 | 51997 | 16 | 3.1 | 11 | (40.7) | 27 (100) | 5.2 | 3.23 to 7.15 |
| 1989-93 | 61813 | 9 | 1.5 | 11 | (55.0) | 20 (100) | 3.2 | 1.83 to 4.65 |
| Total | 179067 | 39 | 2.2 | 34 | (46.6) | 73 (100) | 4.1 | |

**Table 4.7**. Numbers and rates (per 10,000 births) of O&G (births, terminations and pregnancies) in Glasgow, 1980 -1984, 1985-1988, and 1989-1993

| Year of birth | Total births | Births | | Termination | | Pregnancies | | |
|---|---|---|---|---|---|---|---|---|
| | | No | Rate | No | (%) | No (%) | Rate | 95% CI |
| 1980-84 | 65257 | 19 | 2.9 | 12 | (38.7) | 31 (100) | 4.8 | 2.66 to 6.84 |
| 1985-88 | 51997 | 20 | 3.8 | 14 | (41.2) | 34 (100) | 6.5 | 4.35 to 8.73 |
| 1989-93 | 61813 | 19) | 3.1 | 13 | (40.6) | 32 (100) | 5.2 | 3.38 to 6.98 |
| Total | 179067 | 58 | 3.2 | 39 | (40.2) | 97 (100) | 5.4 | |




| | 1973-79 | 1980-86 | 1987-93 |
|---|---|---|---|
| All primary malformation | 32.6 | 36.6 | 27.4 |
| Primary omphalocele and gastroschisis | 0.2 | 0.3 | 0.5 |

**Figure 4. 2 .** Comparison of rates of all primary malformation with rates of omphalocele and gastroschisis (O&G) in Glasgow (excluding induced abortions), 1973-1993

**Table 4.8 a**. Prevalence (per 10,000) of abdominal wall defects in UK

| Geographical coverage | Year | Total births | Induced abortions included? | Omphalocele | | Gastroschisis | | O/G ratio (95% CI) | Total O+G | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | No | Rate (95% CI) | No | Rate (95% CI) | | No | Rate (95% CI) |
| Glasgow | 1980-93 | 179,067 | yes | 73 | 4.1 (3.1 to 5.0) | 24 | 1.3 (0.8 to 1.9) | 3.0 (1.9 to 4.8) | 97 | 5.4 (4.3 to 6.5) |
| Northern Region | 1988-92 | 201,973 | yes | 43 | 2.1 (1.5 to 2.8) | 56 | 2.8 (2.1 to 3.5) | 0.8 (0.5 to 1.1) | 99 | 4.9 (3.9 to 5.9) |
| Liverpool | 1980-88 | 184,530 | yes | 60 | 3.3 (2.4 to 4.1) | 28 | 1.5 (1.0 to 2.1) | 2.1 (1.4 to 3.4) | 88 | 4.8 (3.8 to 5.8) |
| Belfast | 1980-92 | 355,875 | yes | 105 | 3.0 (2.4 to 3.5) | 29 | 0.8 (0.5 to 1.0) | 3.6 (2.4 to 5.5) | 134 | 3.8 (3.1 to 4.4) |
| Scotland | 1988-95 | 515,759 | No | 63 | 1.2 (0.9 to 1.5) | 97 | 1.9 (1.5 to 2.3) | 0.6 (0.5 to 0.9) | 160 | 3.1 (2.6 to 3.6) |
| England and Wales* | 1987-93 | 4,859,221 | No | 448 | 0.9 (0.8 to 1.0) | 539 | 1.1 (1.0 to 1.2) | 0.8 (0.7 to 0.9) | 987 | 2.0 (1.9 to 2.2) |

* Prevalence of all abdominal wall defects ranges from S.W. Thames region (1.23 /10,000 births) to Northern region (3.11 / 10,000 births)

**Table 4.8 b**. Prevalence of abdominal wall defects per 10,000 births in regions of England and Wales, 1987-93. Estimate of denominator is based on total births 1987-93 in region

| Region | All abdominal wall defects | Gastroschisis | Omphalocele |
|---|---|---|---|
| Northern | 3.11 | 1.55 | 1.38 |
| Yorkshire | 2.24 | 1.11 | 0.96 |
| North West | 2.86 | 1.60 | 1.13 |
| Mersey | 2.09 | 1.32 | 0.64 |
| Trent | 3.09 | 1.62 | 1.23 |
| West Midlands | 1.84 | 0.87 | 0.89 |
| Oxford | 1.59 | 0.76 | 0.76 |
| East Anglia | 2.00 | 0.98 | 0.98 |
| North West Thames | 1.80 | 0.65 | 1.01 |
| North East Thames | 1.72 | 0.87 | 0.74 |
| South East Thames | 1.47 | 0.72 | 0.64 |
| South West Thames | 1.23 | 0.58 | 0.62 |
| Wessex | 2.56 | 1.58 | 0.90 |
| South West | 2.28 | 1.40 | 0.77 |
| Wales | 1.97 | 0.96 | 0.96 |

Adapted fromTan et al., 1996

### 4.1.2. Gender

Table 4.9 demonstrates the gender distribution of cases of omphalocele and gastroschisis. The male to female ratio for omphalocele was 0.8, and for gastroschisis 2.0 (isolated and associated). A non-significant female excess was observed in omphalocele associated with neural tube defects, but if NTD are excluded, there was an equal gender ratio. There was a non-significant male excess among gastroschisis cases compared to the omphalocele cases (chi-square test =3.39, df=1, p=0.07). There was a non-significant male excess among omphalocele cases associated with syndromes.

### 4.1.3. Maternal Age

The maternal-age specific frequencies and rates of omphalocele and gastroschisis (births and terminations) are shown in Table 4.10. There was no trend with maternal age.

Table 4.11 and 4.12 present the maternal-age specific frequencies and rates of omphalocele and gastroschisis (births and terminations) respectively. The prevalence of gastroschisis was inversely correlated with maternal age (Mantel-Haenszel test=8.78, p=0.003). The highest rate was found for maternal age under 20. The maternal age group under 20 was 4.0 (95% CI= 1.38 to 11.43) times more at risk than 20-24 years old, and the maternal age group under 20 was 4.9 times more at risk than in over 20 years old (RR= 4.9; 95% CI=2.09 to 11.41). There was no tendency to maternal age for omphalocele and there was no increased risk for omphalocele when <20 compared with >20 years old.

Table 4.13 shows the effect of maternal age on risk of gastroschisis and omphalocele. There was a greatly increased risk for young mothers of isolated gastroschisis (under 20 years) compared to those aged >20 years (Mantel-Haenszel test= 26.4, p<0.0001). These young mothers were 7.8 times more at risk than those over 20 years old (RR=7.8; 95% CI=3.08 to 19.79). There was increased risk of gastroschisis when the under 20 were compared with age group 25-29 (RR=4.0; 95% CI= 1.38 to 11.43) in total, and 7.9 (95% CI= 2.10 to 29.91) in isolated cases. There was no maternal age related increased risk for omphalocele.

**Table 4.9**. Sex distribution of cases with omphalocele and gastroschisis by isolated, multiple malformed, and syndrome

| | Male | Female | Indeterminate | Sex ratio | chi-square test |
|---|---|---|---|---|---|
| **Omphalocele** | | | | | |
| Isolated[1] | 9 | 10 | - | 0.90 | |
| Multiple malformed | 21 | 27 | 5 | 0.77 | |
| Without NTD[2] | 25 | 26 | 2 | 0.96 | |
| With NTD[3] | 5 | 11 | 3 | 0.45 | NS |
| Syndrome | 9 | 6 | 5 | 1.5 | |
| Total[4] | 30 | 37 | 5 | 0.81 | |
| **Gastroschisis** | | | | | |
| Isolated [5] | 12 | 6 | - | 2.0 | NS |
| Multiple malformed | 4 | 2 | - | 2.0 | |
| Total[6] | 16 | 8 | - | 2.0 | NS |

1 versus 5; chi-square test =1.40; df= 1, p=0.24

2 versus 3; chi-square test =1.55; df= 1, p=0.21

4 versus 6; chi-square test =3.39; df= 1, p=0.07

**Table 4.10**. Maternal age-specific frequencies and rates (per 10,000 total births) of O&G pregnancies (births + termination), Glasgow, 1980-1993

| Maternal Age (year) | Total births No (%) | O&G No (%) | Rate/1,000 births 95% CI | |
|---|---|---|---|---|
| <20 | 14848 (9.3) | 15 (15.5) | 1.01 | (0.76 to 1.26) |
| 20-24 | 44193 (27.6) | 26 (26.8) | 0.59 | (0.36 to 0.81) |
| 25-29 | 55342 (34.6) | 31 (32.0) | 0.56 | (0.36 to 0.76) |
| 30-34 | 32570 (20.3) | 19 (19.6) | 0.58 | (0.32 to 0.85) |
| 35+ | 12905 (8.1) | 6 (6.2) | 0.46 | (0.09 to 0.84) |
| Total | 159858 (100) | 97 (100) | 0.61 | (0.47 to 0.81) |

Mantel-Haenszel test= 2.15; P= 0.14 (NS)

**Table 4.11**. Maternal age-specific frequencies and rates (per 10,000 total births) of omphalocele pregnancies (births + termination), Glasgow, 1980-1993

| Maternal Age (year) | Total births No (%) | Omphalocele No (%) | Rate /1,000 births (95% CI) |
|---|---|---|---|
| <20 | 14848 (9.3) | 7 (9.6) | 0.47 (0.12 to 0.82) |
| 20-24 | 44193 (27.6) | 20 (27.4) | 0.45 (0.25 to 0.65) |
| 25-29 | 55342 (34.6) | 24 (32.9) | 0.43 (0.26 to 0.61) |
| 30-34 | 32570 (20.3) | 17 (23.3) | 0.52 (0.27 to 0.77) |
| 35 + | 12905 (8.1) | 5 (6.9) | 0.39 (0.05 to 0.73) |
| Total | 159858 (100) | 73 (100) | 0.46 (0.33 to 0.58) |

MH=0.00008; P=0.99 (NS)

chi-square test=0.008 , p=0.93 (<20 with >20)

**Table 4.12**. Maternal age-specific frequencies and rates (per 10,000 total births) of gastroschisis pregnancies (births + termination), Glasgow, 1980-1993

| Maternal Age (year) | Total births No (%) | Gastroschisis No (%) | Rate/1,000 births (95% CI)[5] | |
|---|---|---|---|---|
| < 20 | 14848 (9.3) | 8 (33.3) | 0.54 | (0.17 to 0.91) |
| 20-24 | 44193 (27.6) | 6 (25.0) | 0.14 | (0.03 to 0.24) |
| 25-29 | 55342 (34.6) | 7 (29.2) | 0.13 | (0.03 to 0.22) |
| 30-34 | 32570 (20.3) | 2 (8.3) | 0.06 | ---------- |
| 35 + | 12905 (8.1) | 1 (4.2) | 0.08 | ---------- |
| Total | 159858 (100) | 24 (100) | 0.15 | (0.08 to 0.22) |

Mantel-Haenszel test = 8.78; (p=0.003)

<20 with >20 (chi-square test=16.47; p<0.0001), RR= 4.9; 95% CI = 2.09 to 11.41

<20 with 20-24 (chi-square test= 7.61;p=0.006), RR= 4.0 ; 95% CI = 1.38 to 11.43

[5] Confidence interval for age 30-34 and >35 of gastroschisis cases are not shown because the lower limit was negative.

**Table 4.13** . Effect of maternal age on risk of omphalocele and gastroschisis

| Maternal Age | Gastroschisis | | | | | | Omphalocele | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | | | Isolated | | | Total | | | Isolated | | | Total* | | |
| | No | RR | 95%CI | No | RR | 95%CI | No | RR | 95%CI | No | RR | 95%CI | No | RR | 95%CI |
| 25-29 | 6 | 1.0 | R | 3 | ---- | R | 20 | 1.0 | R | 8 | ---- | R | 17 | --- | R |
| <20 | 8 | 4.0 | 1.38 to 11.43 | 8 | 7.9 | 2.10 to 29.91 | 7 | 1.0 | 0.44 to 2.46 | 1 | 0.4 | 0.05 to 2.97 | 6 | 1.2 | 0.41 to 2.66 |
| 20-24 | 7 | 0.9 | 0.31 to 2.77 | 7 | 1.9 | 0.48 to 7.20 | 24 | 1.0 | 0.53 to 1.73 | 6 | 0.6 | 0.21 to 1.72 | 17 | 0.8 | 0.41 to 1.56 |
| 30-34 | 2 | 0.5 | 0.09 to 2.24 | 0 | - | - | 17 | 1.2 | 0.60 to 2.20 | 2 | 0.3 | 0.07 to 1.60 | 15 | 1.2 | 0.60 to 2.40 |
| 35+ | 1 | 0.6 | 0.07 to 4.74 | 0 | - | - | 5 | 0.9 | 0.32 to 2.28 | 3 | 1.3 | 0.34 to 4.84 | 3 | 0.6 | 0.18 to 2.06 |
| Total | 24 | | | 18 | | | 73 | | | 20 | | | 58 | | |

<20 with >20 in isolated gastroschisis (RR= 7.8; 95% CI = 3.08 to 19.79)

<20 with >20 in isolated omphalocele (RR=0.5; 95% CI = 0.07 to 3.84)

<20 with >20 in omphalocele [RR=1.1; 95% CI = 0.48 to 2.62 (excluding chromosomal cases)]

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* excluding chromosomal cases

R= Reference

### 4.1.4. Neighbourhood Type

Table 4.14, 4.15 and 4.16 shows that the crude prevalence rate of O&G, omphalocele and gastroschisis was highest in neighbourhood types 7-8 (most deprived). There appeared to be a trend of increasing risk with deprivation. However, after direct age standardisation, no significant association with deprivation was found. There were no significant differences between neighbourhood types except between 3-6 and 7-8 among O&G cases.

### 5.1.5. Birth weight and Gestational Age

Table 4.17 demonstrates the length of gestational age in livebirths and stillbirths with omphalocele and gastroschisis. Both defects were associated with premature birth, an effect that was more pronounced for multiply malformed than for isolated cases. The mean gestational age (isolated, multiple malformed) in cases of gastroschisis was earlier (but non-significantly) than cases of omphalocele (p = 0.60, p=0.41 respectively).

Table 4.18 shows the birthweight in livebirths and stillbirths with omphalocele and gastroschisis. Both omphalocele and gastroschisis were associated with low birth weight. This effect was greater for multiple malformed cases than for isolated cases particularly for gastroschisis. Isolated cases of gastroschisis had significantly lower mean birth weight than omphalocele ($p<0.03$) and non significantly for total ($p<0.09$) and multiple malformed ($p=0.14$).

### 4.1.6. Associated Anomalies

Associated anomalies, excluding those thought to be a consequence of the condition (mainly lung hypoplasia), occurred more frequently among cases of omphalocele (53/73 or 72.6%) than gastroschisis (6/24 or 25.0%) (chi-square test = 17.18, df=1, $p<0.0001$) (Table 4.19). There were 16 cases of omphalocele associated with syndromes (nine cases of trisomy 18, two of trisomy 13, three of Wiedemann-Beckwith syndrome, one of Trisomy 4P, and one of Asplenia). Omphalocele had a higher frequency of association with syndromes and chromosomal anomalies (16 versus one of gastroschisis cases).

In the group of infants with multiple malformations (multi- malformed infants) (Table

4.20) the most common abnormalities were musculoskeletal anomalies (26%), genital and urinary anomalies (15%), NTD (13%), and GI in the upper alimentary tract (13%). Only one case of gastroschisis was associated with a neural tube defect.

The most frequent abnormalities among musculoskeletal anomalies were (kyphosis=14), NTD (anencephaly=12 and spina bifida without hydrocephalus=3), and bulbus cordis anomalies and anomalies of cardiac septal closure (V.S.D[6]=8).

### 4.1.7. Seasonality

Table 4.21 shows the omphalocele, gastroschisis and O&G by expected season of birth. There were no seasonal trends in the dates of birth ( actual or expected) for O&G (chi-square test= 3.54; df=3; p=0.32) or for either omphalocele (chi-square test = 3.70; d=3; p=0.30) or gastroschisis (chi-square test = 0.87; df=3; p=0.83). The peak prevalence of O&G and omphalocele appeared highest for children born in Autumn, while that of gastroschisis was highest in Spring.

### 4.1.8. Smoking

Table 4.22 shows the proportion of smokers in the mothers of isolated and associated and total of omphalocele, gastroschisis and O&G in Glasgow, 1980-1993. The percentage of smokers in the mothers of isolated cases of gastroschisis was significantly higher than for associated cases (Fisher's exact test, two tailed = 0.01) and also O&G (chi-square test = 6.51, p<0.01).

The percentage of smokers in the mothers of isolated cases of omphalocele was non-significantly higher than for associated cases. Among associated and total cases, the percentage of smokers was lower than non-smokers.

The percentage of smokers in the mothers of gastroschisis was higher than for omphalocele but non-significantly (chi-square test=1.88, p= 0.17).

[6] Ventricle Septal Defects

**Table 4.14**. Prevalence of O&G pregnancies by neighbourhood type (1-2, 3-6, 7-8) in Glasgow, 1980-1993

| Neighbourhood type | Total births No | O&G No | Crude rate/ 10,000 births | Age standardised rate (95% confidence limits) |
|---|---|---|---|---|
| 1-2 | 36149 | 19 | 5.26 | 6.74 5.47 to 8.02 |
| 3-6 | 78885 | 39 | 4.94 | 5.70 4.71 to 7.09 |
| 7-8 | 49974 | 39 | 7.80 | 8.82 7.37 to 10.28 |
| Total | 165,008 | 97 | 5.88 | |

**Table 4.15**. Prevalence of omphalocele pregnancies by neighbourhood type (1-2, 3-6, 7-8) in Glasgow, 1980-1993

| Neighbourhood type | Total births No | Omphalocele No | Crude rate/ 10,000 births | Age standardised rate (95% confidence limits) |
|---|---|---|---|---|
| 1-2 | 36149 | 17 | 4.70 | 5.80 4.62 to 6.98 |
| 3-6 | 78885 | 27 | 3.42 | 4.24 3.23 to 5.24 |
| 7-8 | 49974 | 29 | 5.80 | 6.82 5.54 to 8.10 |
| Total | 165,008 | 73 | 4.42 | |

**Table 4.16**. Prevalence of gastroschisis pregnancies by neighbourhood type (1-2, 3-6, 7-8) in Glasgow, 1980-1990

| Neighbourhood type | Total births No | Gastroschisis No | Crude rate /10,000 births | Age standardised (95% confidence limits) | |
|---|---|---|---|---|---|
| 1-2 | 36149 | 2 | 0.55 | 0.94 | 0.47 to 1.41 |
| 3-6 | 78885 | 12 | 1.52 | 1.80 | 1.14 to 2.45 |
| 7-8 | 49974 | 10 | 2.0 | 2.00 | 1.31 to 2.70 |
| Total | 165,008 | 24 | 1.45 | | |

**Table 4.17**. Length of gestation age in livebirths and stillbirths with omphalocele and gastroschisis (Isolated and multiple malformed)

| | Gestational age (wks) | | |
|---|---|---|---|
| | Mean | SE | No of cases |
| **Omphalocele** | | | |
| *Total* | 35.8 | 0.66 | 39 |
| Isolated[1] | 37.2 | 0.97 | 13 |
| Multiple malformed[3] | 35.5 | 0.98 | 14 |
| Syndrome | 34. 8 | 1.5 | 12 |
| **Gastroschisis*** | | | |
| *Total* | 35.8 | 0.65 | 19 |
| Isolated[2] | 36.6 | 0.34 | 15 |
| Multiple Malformed[4] | 31.3 | 2.85 | 3 |

T test = 1 versus 2 (p= 0.60 ); 3 versus 4 (p= 0.41).

* Only one syndrome associated with gastroschisis.

**Table 4.18** . Birthweight in livebirths and stillbirths with omphalocele and gastroschisis (Isolated and multiple malformed)

| | Birthweight (grams) | | |
|---|---|---|---|
| | Mean | SE | No of cases |
| **Omphalocele** | | | |
| *Total*[1] | 2,66 | 182,7 | 38 |
| Isolated[3] | 2,885 | 278,9 | 12 |
| Multiple malformed[5] | 2,172 | 263,79 | 14 |
| Syndrome | 2,072 | 381,4 | 12 |
| **Gastroschisis** * | | | |
| *Total*[2] | 1,991 | 122,3 | 19 |
| Isolated[4] | 2,155 | 86,0 | 15 |
| Multiple malformed[6] | 1,400 | 521,7 | 3 |

T test = 1 versus 2 ($p< 0.09$); 5 versus 6 ($p= 0.14$); 3 versus 4; ( $p< 0.03$; 95% CI= -1361.23 to -99.76))

* Only one syndrome associated with gastroschisis.

**Table 4.19**. Proportions of cases of omphalocele (OM) and gastroschisis (GAS) associated with other congenital malformations ,1980-1993

| Group | Isolated No (%) | Associated No (%) | Total | 95% CI |
|---|---|---|---|---|
| OM | 20 (27.4) | 53*(72.6) | 73 (100) | 0.73 0.64 - 0.82 |
| GAS | 18 (75.0) | 6* (25.0) | 24 (100) | 0.25 0.17 - 0.34 |
| Total | 38 (39.2) | 59 (60.8) | 97 (100) | |

*chi-square test=17.18, p=0.0001

**Table 4.20**. The percentage of cases of omphalocele (OM), gastroschisis (GAS) and O&G associated with other non-syndromic congenital malformations

| Group of congenital malformation | OM | | GAS | | O&G | |
|---|---|---|---|---|---|---|
| | No | % | No | % | No | % |
| Musculoskeletal anomalies (Kyphosis=14) | 34 | 25.8 | 3 | 30.0 | 37 | 26.1 |
| Genital organs and Urinary system | 20 | 15.2 | 1 | 10.0 | 21 | 14.8 |
| NTD (Anencephaly=12, Spina bifida without hydrocephalus=3) | 17 | 12.9 | 1 | 10.0 | 18 | 12.7 |
| GI in the Upper alimentary tract | 17 | 12.9 | 1 | 10.0 | 18 | 12.7 |
| Limb | 10 | 7.6 | 3 | 30.0 | 13 | 9.2 |
| Bulbus cordis anomalies and anomalies of Cardiac septal closure (V.S.D=8), Heart and Circulatory system | 9 | 6.8 | 1 | 10.0 | 10 | 7.0 |
| Ear ,face and neck | 7 | 5.3 | 0 | 0 | 7 | 4.9 |
| Cleft palate and cleft lip | 4 | 3.0 | 0 | 0 | 4 | 2.8 |
| Respiratory system | 4 | 3.0 | 0 | 0 | 4 | 2.8 |
| Integument | 3 | 2.3 | 0 | 0 | 3 | 2.1 |
| Other specified anomalies of brain and Microcephalus | 3 | 2.3 | 0 | 0 | 3 | 2.1 |
| Eye | 2 | 1.5 | 0 | 0 | 2 | 1.4 |
| Adrenal gland | 1 | 0.8 | 0 | 0 | 1 | 0.7 |
| Conjoined twins | 1 | 0.8 | 0 | 0 | 1 | 0.7 |
| Total | 132 | 100 | 10 | 100 | 142 | 100 |

**Table 4.21**[7]. Numbers and rates (per 10,000 total births) of omphalocele, gastroschisis and O&G, by seasons (expected or actual) of births, Glasgow, 1980-1993

| Seasons | | Omphalocele | | Gastroschisis | | O&G | |
|---|---|---|---|---|---|---|---|
| | Total births | No of cases | Rate /10,000 births | No of cases | Rate /10,000 births | No of cases | Rate /10,000 births |
| Winter | 33494 | 14 | 4.18 | 4 | 1.19 | 18 | 5.37 |
| Spring | 33993 | 20 | 5.88 | 7 | 2.06 | 27 | 7.94 |
| Summer | 35680 | 15 | 4.20 | 7 | 1.96 | 22 | 6.17 |
| Autumn | 34232 | 24 | 7.01 | 6 | 1.75 | 30 | 8.76 |
| Total | 137,399 | 73 | 5.31 | 24 | 1.74 | 97 | 7.06 |

chi-square test=3.54; df=3; p=0.32 (O&G)

chi-square test=3.70; df=3; p=0.30 (omphalocele)

chi-square test=0.87; df=3; p=0.83 (gastroschisis)

[7] Total births are calculated from 1983 because there is not information before 1983.

**Table 4.22**. Proportion of smokers in isolated and associated of omphalocele (OM), gastroschisis (GAS) and O&G in Glasgow, 1980-1993

| | GAS | | | OM | | | O& G | | |
|---|---|---|---|---|---|---|---|---|---|
| | Isolated | Associated | Total | Isolated | Associated | Total | Isolated | Associated | Total |
| | No (%) | No (%) | No (%) | No (%) | No (%) | No (%) | No (%) | No (%) | No (%) |
| Smoker | 14 (77.8)a | 1 (16.2)b | 15 (62.5) | 9 (56.3) | 20 (42.6) | 29 (46.0) | 23 (67.6) | 21 (39.6) | 44 (50.6) |
| Non-smoker | 4 (22.2) | 5 (83.3) | 9 (37.5) | 7 (43.8) | 27 (57.5) | 34 (54.0) | 11 (32.4) | 32 (60.4) | 43 (49.4) |
| Total | 18 | 6 | 24 | 16 | 47 | 63 | 34 | 53 | 87 |

(a *versus* b) Fisher exact' test two tailed= 0.01

## 4.2. *THE CASE - CONTROL STUDY*

### 4.2.1. Univariate Analysis

Univariate correlation analyses were carried out first in order to explore the relationship between maternal risk factors (maternal age, neighbourhood type, illness before and after pregnancy, drugs and smoking) and maternal reproductive factors (total pregnancy, parity, history of spontaneous abortion, history of induced abortion and history of stillbirth) among omphalocele, gastroschisis and O&G with malformed, non-malformed and malformed+non-malformed controls (all the analyses are in appendix $A_1$, $A_2$).

The maternal risk factors significantly related to gastroschisis were maternal age and smoking. For O&G only smoking was significant. This was not found for omphalocele cases alone (all analyses are in appendix $A_1$, $A_2$).

#### 4.2.1.1. *Maternal Age*[8]

The proportion (35%) of mothers of gastroschisis cases (less than 20 years old) was significantly different from malformed (11%) and malformed + non-malformed controls (6%). Relative to women 30 years or older, there was an excess risk (RR=7.5, 95%CI = 1.3 to 43.0), (RR= 10, 95% CI = 1.9 to 58.4) of malformed and malformed + non-malformed respectively in the univariate analysis (Table 4.23).

#### 4.2.1.2. **Smoking**

A significantly higher proportion (62%) of the mothers of gastroschisis cases smoked during pregnancy than those of non-malformed controls (27%) and malformed + non-malformed controls (32%). Mothers who smoked cigarettes were at 4.3 (95% CI = 1.3 to 14.0) and 3.40 (95% CI= 1.3 to 9.1) times greater risk than non-smokers of having infant with gastroschisis than mothers of non-malformed and malformed+non-malformed respectively controls (Table 4.23).

Mothers who smoked cigarettes among O&G cases were at 2.53 (95% CI = 1.34 to 479) and 2.01 (95% CI = 1.17 to 3.46) times greater risk than non-smokers (non-malformed and malformed+non-malformed respectively) (Table 4.24).

[8] There were no mothers under 20 years old among non-malformed controls.

**Table 4.23**. Univariate analysis of gastroschisis with maternal age and smoking among malformed controls, non-malformed controls and malformed + non-malformed controls

| Factor | Malformed controls | | | Non-malformed controls | | Malformed and Non-malformed controls | |
|---|---|---|---|---|---|---|---|
| | Cases | Control | Odds ratio(95%CI) | Control | Odds ratio(95%CI) | Control | Odds ratio(95%CI) |
| | No (%) | No (%) | | No (%) | | No (%) | |
| Maternal age | | | | | | | |
| <20 | 9 (34.6) | 3 (10.7) | 7.5 (1.3 to 43.0) | | | 3 (5.8) | 10 (1.9 to 58.4) |
| 20-24 | 6 (23.1) | 7 (25.0) | 2.3 (0.5 to 10.9) | ---------- | | 14 (26.9) | 1.5 (0.3 to 6.5) |
| 25-29 | 7 (26.9) | 9 (32.1) | 1.8 (0.4 to 8.1) | | | 21 (40.4) | 1.2 (0.3 to 4.7) |
| 30+ | 4 (15.4) | 9 (32.2) | R* | | | 14 (26.9) | R |
| Smoking | | | | | | | |
| Yes | | --------- | | 7 (26.9) | 4.3 (1.3 to14.0) | 16 (32.0) | 3.4 (1.3 to 9.1) |
| No | | | | 19 (73.1) | R | 34 (68.0) | R |
| U/k | | | | | | 2 | |

* R= Reference

**Table 4.24**. Univariate analysis of O&G with smoking among non-malformed controls and malformed + non-malformed controls

| Factor | Non-malformed controls | | | Malformed and non-malformed controls | | |
|---|---|---|---|---|---|---|
| | Cases | Control | Odds ratio (95%CI) | Cases | Control | Odds ratio (95%CI) |
| | No (%) | No (%) | | No (%) | No (%) | |
| Smoking | | | | | | |
| Yes | 41 (51.9) | 26 (29.9) | 2.53 (1.34 to 4.79) | 41 (51.9) | 59 (34.9) | 2.01 (1.17 to 3.46) |
| No | 38 (48.9) | 61 (70.1) | R | 38 (48.9) | 110 (65.1) | R |
| U/k | 8 | | | 8 | 5 | |

### 4.2.2. Multivariate Analysis

The results of the univariate correlations indicated which factors should be considered as predictors in the multiple regression models.

#### 4.2.2.1. *Maternal Age*

To investigate the relative importance of the various risk factors, a multivariate model (logistic regression) was developed for age (continuous), smoking, illness during and after pregnancy, and drugs. Age remained significant in the multivariate analysis for malformed (RR= 0.9, 95%CI = 0.79 to 0.99) and malformed + non-malformed (RR= 0.9, 95%CI = 0.80 to 0.99) respectively (Table 4.25).

#### 4.2.2.2. *Smoking*

After logistic regression, smoking remained a significant risk among gastroschisis cases relative to non-malformed controls factor (RR= 3.8, 95% CI = 1.16 to 12.45) and malformed + non-malformed (RR= 2, 95% CI= 1.12 to 3.4) (Table 4.25).

After logistic regression, there was no significant association of smoking among O&G compared to non-malformed, and malformed+non-malformed controls (RR= 2.48, 95% CI = 0.26 to 1.55) (RR= 1.95, 95% CI = 0.11-1.22).

#### 4.2.2.3. *Parity and neighbourhood type*

After conditional logistic regression (for parity and cluster group), only parity among gastroschisis compared to malformed + non-malformed controls remained significant ($p < 0.01$) ( Table 4.26). Parity remained significant after including maternal age in the regression; the same result was found in the univariate analysis.

**Table 4.25**. Multivariate regression analysis of the maternal age and smoking among gastroschisis cases and malformed, non-malformed and malformed+ non-malformed controls

| Factor | Malformed controls | | | Non-malformed controls | | Malformed and Non-malformed controls | |
|---|---|---|---|---|---|---|---|
| | Cases | Control | Logistic regression (95%CI) | Control | Logistic regression (95%CI) | Control | Logistic regression (95%CI |
| | No (%) | No (%) | | No (%) | | No (%) | |
| Maternal age | | | | | | | |
| <20 | 9 (34.6) | 3 (10.7) | 0.9 (0.79 to 0.99) | ---------- | | 3 (5.8) | 0.9 (0.80 to 0.99) |
| 20-24 | 6 (23.1) | 7 (25.0) | | | | 14 (26.9) | |
| 25-29 | 7 (26.9) | 9 (32.1) | | | | 21 (40.4) | |
| 30+ | 4 (15.4) | 9 (32.2) | | | | 14 (26.9) | |
| Smoking | | | | | | | |
| Yes | | --------- | | 7 (26.9) | 3.8 (1.16 to 12.45) | 16 (32.0) | 2 (1.12 to 3.4) |
| No | | | | 19 (73.1) | | 34 (68.0) | |
| U/k | | | | | | 2 | |

**Table 4.26**. Conditional logistic regression [parity and neighbourhood type (NT)] of omphalocele (OM), gastroschisis (GAS) and O&G with malformed, non-malformed, and malformed + non-malformed controls

| | OM | | GAS | | O&G | |
|---|---|---|---|---|---|---|
| | Parity<br><br>P value | NT<br><br>P value | Parity<br><br>P value | NT<br><br>P value | Parity<br><br>P value | NT<br><br>P value |
| Malformed controls | NS | NS | NS | NS | NS | NS |
| Non-malformed controls | NS | NS | NS | NS | NS | NS |
| Malformed + non-malformed controls | NS | NS | **0.01** | NS | NS<br>(0.05) | NS |

N= Non significant

## 4.3. *PRENATAL DIAGNOSIS*

Table 4.27 shows proportion of isolated and associated cases of omphalocele (OM), gastroschisis (GAS) and O&G prenatally diagnosed according to outcome of pregnancy (births or induced abortion (IA) in Glasgow, 1980-1993. The percentages of induced abortions following prenatal diagnosis were 67% (34/51) for omphalocele (58% isolated, 69% associated) and 28% (5/24) for gastroschisis (21% isolated and 50% associated). About half of the O&G cases had induced abortions following prenatal diagnosis (57%). More than half of associated cases of O&G had induced abortions following prenatal diagnosis (67%). Less than three-quarters of O&G cases had prenatal diagnosis (71%). Although more omphalocele cases were associated with other anomalities than gastroschisis. The percentage of induced abortions following prenatal diagnosis was 69% and 50% respectively.

The proportion of induced abortions following prenatal diagnosis of associated O&G was significantly more than for isolated defects (chi-square test =5.54, p=0.02). The proportion of associated cases prenatally diagnosed was non-significantly higher than for isolated defects (chi-square test=0.22, p=0.64). The proportion of isolated gastroschisis prenatally diagnosed was more than omphalocele (chi-square test=1.38, p=0.24), but the proportion of induced abortions following prenatal diagnosis of isolated and associated cases of omphalocele was higher than for gastroschisis (Fisher's exact test= 0.10, 0.58 respectively). In table 4.27 the proportion of isolated gastroschisis prenatally diagnosed was significantly higher than omphalocele among live and stillbirths cases (Fisher's exact test two tailed= 0.03).

More than half 56% (19/34) of these induced abortions of omphalocele were associated with NTD (16 cases) and syndromes (three cases), as were more than the half (55%) (28/51) of the percentage of omphalocele cases which were prenatally diagnosed; of these 19 cases were NTD and nine were syndromes.

The proportion of gastroschisis prenatally diagnosed increased significantly from 1980-1986 to 1987-1993 (Fisher's exact test=0.01) (Table 4.28) but non-significantly in the cases of omphalocele (Table 4.28) and O&G (Table 4.30). There was a non-significant increase in the proportion of induced abortions following prenatal diagnosis from 1980-

86 to 1987-93 for gastroschisis (Fisher's exact test=0.10) while it decreased non-significantly for omphalocele (chi-square test =0.64, p=0.42) and O&G. The proportion of gastroschisis prenatally diagnosed significantly increased from 1980-86 to 1988-93 (Fisher's exact test two tails= 0.04) and O&G (chi-square test =7.66, p< 0.006) but not omphalocele (chi-square test =2.7, p=0.10) among live and stillbirths.

Figure 4.3 shows the percentage of prenatal diagnoses according to gestational age. The majority of prenatal diagnoses of gastroschisis were performed after 32 weeks (12/18, 67%) while for omphalocele most were performed before 23 weeks (31/51, 61%) (one case of omphalocele among >32 is u/k).

Table 4.31 presents the proportion of omphalocele (OM), gastroschisis (GAS) and O&G cases prenatally diagnosed among live births who survived in Glasgow, 1980-1993. The proportion of gastroschisis was significantly higher than omphalocele among surviving cases who had been prenatally diagnosed (chi-square test =10.94; df=1; p=0.0009) (a, b). Ten cases of gastroschisis were live births after 1987, and all of them had been prenatally diagnosed, and just one died.

**Table 4.27** .Proportion of isolated and associated cases of omphalocele (OM), gastroschisis (GAS) and O&G prenatally diagnosed according to outcome of pregnancy (births or induced abortion (IA) in Glasgow, 1980-1993.

| | Isolated | | | | Associated | | | | Total | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total pregnancies No (%) | PND No (%) | Total IA No (%) | % IA / PND | Total pregnancies No (%) | PND No (%) | Total IA No (%) | % IA/ PND | Total pregnancies No (%) | PND No (%) | Total IA No (%) | % IA/ PND |
| OM | 20 (100) | 12 (60.0) | 7 (35.0) | 58.3 | 53 (100) | 39 (73.6) | 27 (50.9) | 69.2 | 73 (100) | 51 (69.9) | 34 (46.6) | 66.7 |
| GAS | 18 (100) | 14 (77.8) | 3 (16.7) | 21.4 | 6 (100) | 4 (66.7) | 2 (33.3) | 50.0 | 24 (100) | 18 (75) | 5 (20.8) | 27.8 |
| O&G | 38 (100) | 26 (68.4) | 10 (26.3) a | 38.5 b | 59 (100) | 43 (72.9) | 29 (49.2) c | 67.4 d | 97 (100) | 69 (71.1) | 39 (40.2) | 56.5 |

a *versus* c (chi-square test =5.70; p=0.02)

b *versus* d (chi-square test =5.54; p=0.02)

**Table 4.28**. Proportion of gastroschisis (GAS) cases prenatally diagnosed (PND) according to outcome of pregnancy [(births or induced abortion (IA)] in Glasgow, 1980-86, 1987-93

| Year of birth | Total pregnancies of GAS<br>No (%) | PND of total births<br>No (%) | Total live and still births | PND of total live and still births<br>No (%) | Total induced abortions<br>No (%) | % IA / PND |
|---|---|---|---|---|---|---|
| 1980-1986 | 9 (100) | 4 (44.4)[a] | 8 | 3 (37.5)[g] | 1 (11.1)[e] | 25.0e |
| 1987-1993 | 15 (100) | 14 (93.3)[b] | 11 | 10 (90.9)[h] | 4 (26.7)[f] | 28.6d |
| Total | 24 (100) | 18 (75.0) | 19 | 13 (68.4) | 5 (20.8) | 27.8 |

(a versus b) Fisher test, two tailed = 0.01

(c versus d) Fisher test two tailed = 1.0 (NS)

(e versus f), Fisher test two tailed = 0.61 (NS)

(g versus h) Fisher test two tailed= 0.04

**Table 4.29**. Proportion of omphalocele (OM) cases prenatally diagnosed (PND)according to outcome of pregnancy (births or induced abortion (IA) in Glasgow, 1980-86, 1987-93[9]

| Year of birth | Total pregnancies of OM<br>No (%) | PND of total births<br>No (%) | Total births and stillbirths | PND of total births and stillbirths<br>No % | Total induced abortions<br>No % | % IA / PND |
|---|---|---|---|---|---|---|
| 1980-1986 | 36 (100) | 22 (61.1)[a] | 19 | 6 (31.6) [c] | 16 (44.4) | 72.7c |
| 1987-1993 | 37 (100) | 29 (78.4)[b] | 19 | 11 (57.9) [f] | 18 (48.7) | 62.1d |
| Total | 73 (100) | 51 ( 69.9) | 38 | 17 (44.7) | 34 (46.6) | 66.7 |

(a versus b) chi-square = 2.58, (p= 0.11) NS

(c versus d) chi-square = 0.64, (p= 0.42) NS

(e versus f) chi-square = 2.7, (p= 0.10) NS

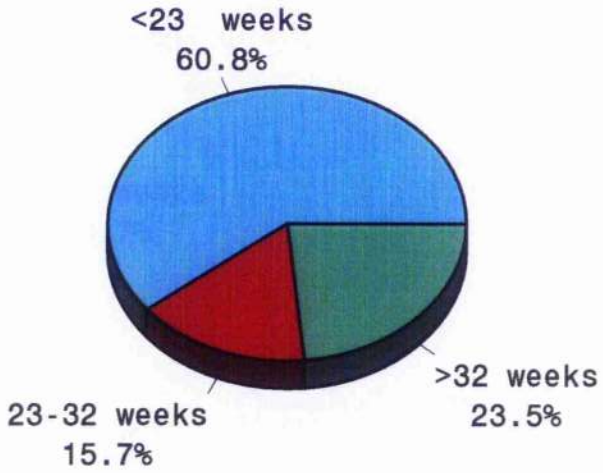
[9] One case of PND among omphalocele (livebirth) was unknown in 1981.

**Table 4.30**. Proportion of O&G cases prenatally diagnosed (PND) according to outcome of pregnancy [(births or induced abortion (IA)] in Glasgow, 1980-86, 1987-93

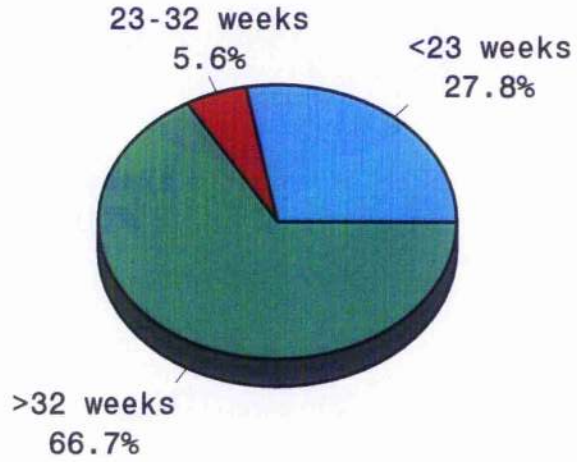
| Year of birth | Total pregnancies O&G births<br>No (%) | PND<br>No (%) | Total births and stillbirths | PND of total births and stillbirths<br>No (%) | Total induced abortions<br>No (%) | % IA / PND |
|---|---|---|---|---|---|---|
| 1980-1986 | 35 (100) | 26 (74.3)[a] | 27 | 9 (33.3) [e] | 17 (48.6) | 65.4[c] |
| 1987-1993 | 52 (100) | 43 (82.7)[b] | 30 | 21 (70.0) [f] | 22 (42.3) | 51.6[d] |
| Total | 97 (100) | 69 (71.1) | 57 | 30 (52.6) | 39 (40.2) | 56.5 |

(a versus b) chi-square = 0.90, df=1; p= 0.34

(e versus f) chi-square = 7.66, df=1; p= 0.006




**Omphalocele**




**Gastroschisis**

**Figure 4.3** . Precentage of omphalocele and gastroschisis cases prenatally diagnosed according to gestational age in Glasgow, 1980-1993

**Table 4.31**. Proportion of omphalocele (OM), gastroschisis (GAS) and O&G cases prenatally diagnosed (PND) among live births who survived in Glasgow, 1980-1993

| | Total live births | Survival | | |
|---|---|---|---|---|
| | | Live births | PND (Yes) | PND (No) |
| | No | No (100) | No (%) | No (%) |
| OM[10] | 27 | 19 (100) | 4 (21.1) a | 14 (73.7) |
| GAS[11] | 16* | 15 (100) | 12 (80.0) b | 3 (20) |
| O&G | 43 | 34 (100) | 16 (47.1) | 17 (50.0) |

(a versus b) chi-square = 10.94, ($p<0.0009$)

[10] PND of one case of omphalocele was unknown
[11] *PND of one case of gastroschisis was unknown

## 4.4. *PERINATAL MORTALITY AND SURVIVAL*

Table 4.32 shows the percentage of deaths from 1980-1993. Perinatal deaths were more frequent among omphalocele cases than gastroschisis (chi-square test =2.81; p=0.09). Most deaths in omphalocele cases during the first week were caused by syndromes (63%) (8 cases of omphalocele who died during first year, five had associated syndromes). Two-thirds (67%; 14/20) of perinatal deaths were caused by NTD and syndromes. The perinatal mortality rate was 0.9 (17/179067) for omphalocele and 0.2 (4/179067) per 10,000 for gastroschisis.

Table 4.33 presents the survival to one year of omphalocele (OM), gastroschisis (GAS) and O&G in Glasgow, 1980-1993. The survival rate during first year and first week was significantly higher among gastroschisis cases than omphalocele (chi-square test =10.6; p=0.001 one year) (chi-square test=8.02; p=0.005 first week).

The survival of isolated cases of O&G decreased by about 30% after birth followed by a plateau tail which showed a slight decrease after one week and no change in percentage of O&G in one year. However, for associated cases percentage of surviving was about 25% after births followed by a curve which showed a steady decreasing in surviving after week and one year respectively (Figure 4.4). There was a significant difference in survival between isolated cases and cases associated with other abnormalities (log rank test, p<0.001) (Table 4.33).

Isolated cases of omphalocele showed about 45% and 50% decrease in the percentage of omphalocele surviving after birth and one week respectively with no change at one year. Associated cases showed about 70% decrease in survival followed by a curve which showed a steady decrease in survival after one week and up to one year (Figure 4.5). There was a significant difference in survival between isolated cases and cases associated with other abnormalities (log rank test, p<0.007) (Table 4.33).

Isolated cases of gastroschisis showed about 15% decrease in survival followed by a curve which showed a slight decrease in survival at one week then no change until one year. However, associated cases of gastroschisis showed a sharp decrease in percentage

of surviving of about 85% followed by a plateau tail with no change at one week and up to one year respectively. The percentage of isolated of gastroschisis cases surviving was higher than associated cases (17% vs. 78%)[12] (Figure 4.6). There was a significant difference in survival between isolated cases of gastroschisis and associated with other abnormalities (log rank test, $p<0.005$) (Table 4.33).

[12] The number of isolated of gastroschisis was too smal, so it calculate a percentage.

**Table 4.32**. Perinatal deaths of isolated and associated cases of omphalocele (OM), gastroschisis (GAS) and O&G in Glasgow, 1980-1993

| | Isolated<br>No (%) | Associated<br>No (%) | Total<br>No (%) | Total<br>No (%) | Total live and still births of O&G<br>No (%) |
|---|---|---|---|---|---|
| OM | 3 (17.7) | 14 (82.4) | 17 (100) | 17 (43.6)a | 39 (100) |
| GAS | 1 (25.0) | 3 (75.0) | 4 (100) | 4 (21.1)b | 19 (100) |
| O&G | 4 (19.0) | 17 (81.0) | 21 (100) | 21 (36.2) | 58 (100) |

chi-square test=2.8, df=1, $p < 0.09$ (a versus b)

**Table 4.33**. Survival up to the one year of isolated (IS) and associated (AS) of omphalocele (OM), gastroschisis (GAS) and O&G in Glasgow, 1980-1993

| | Total cases | | Total live births | | Died during first week | | Died during first year | |
|---|---|---|---|---|---|---|---|---|
| | IS | AS | IS<br>No(%) | AS<br>No(%) | IS<br>No(%) | AS<br>No(%) | IS<br>No(%) | AS<br>No(%) |
| OM | 20 | 53 | 11 (55) | 14 (26) | 10 (50) | 12 (23) | 10 (50) | 9 (17) |
| GAS | 18 | 6 | 15 (83) | 1 (16) | 14 (78) | 1 (16) | 14 (78) | 1 (16) |
| O&G | 38 | 59 | 26 (68) | 15 (25) | 24 (63) | 12 (20) | 24 (63) | 9 (15) |

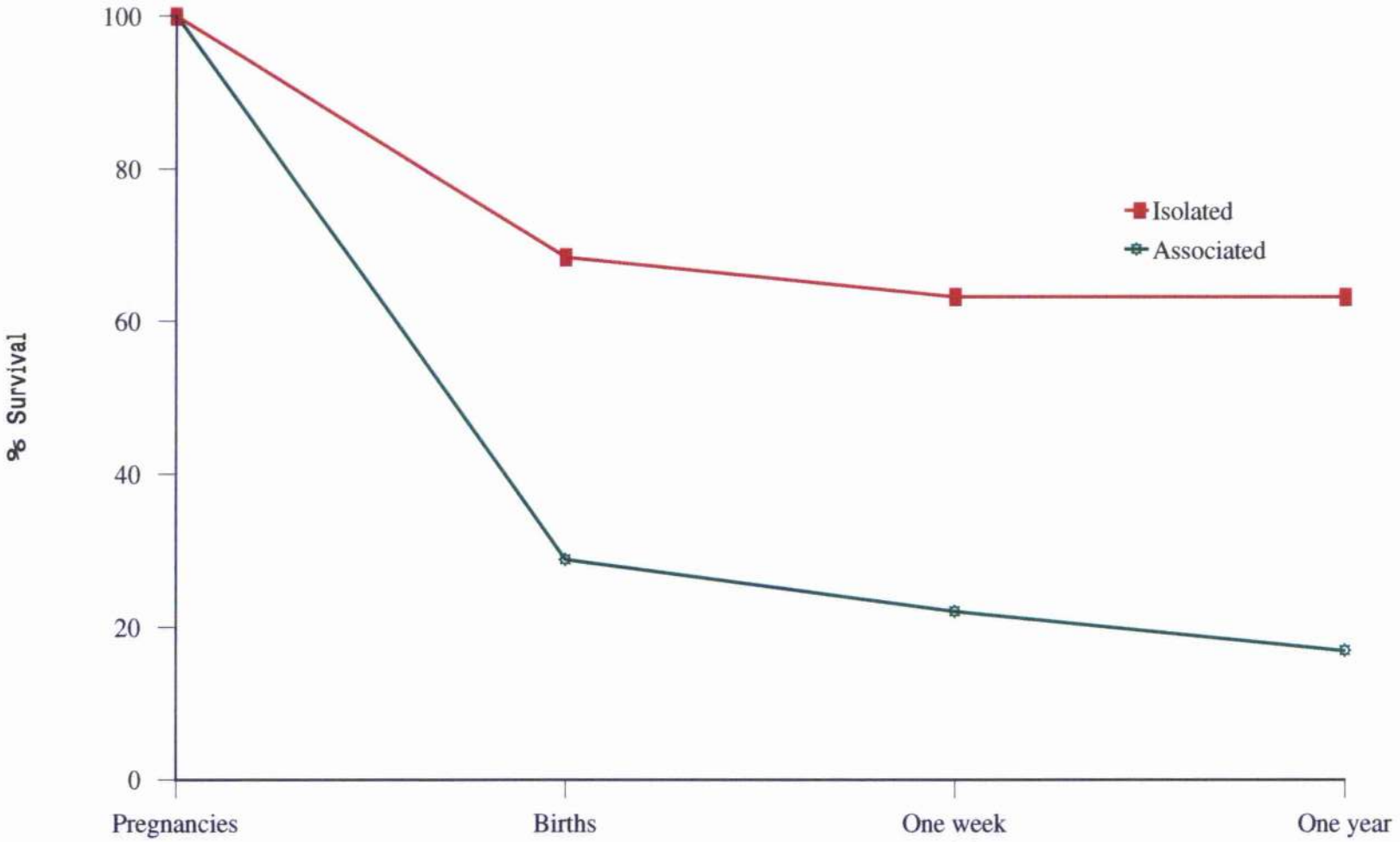



**Figure 4.4** . Survival to one year of isolated and associated cases of omphalocele and gastroschisis(O&G) in Glasgow, 1980-1993.

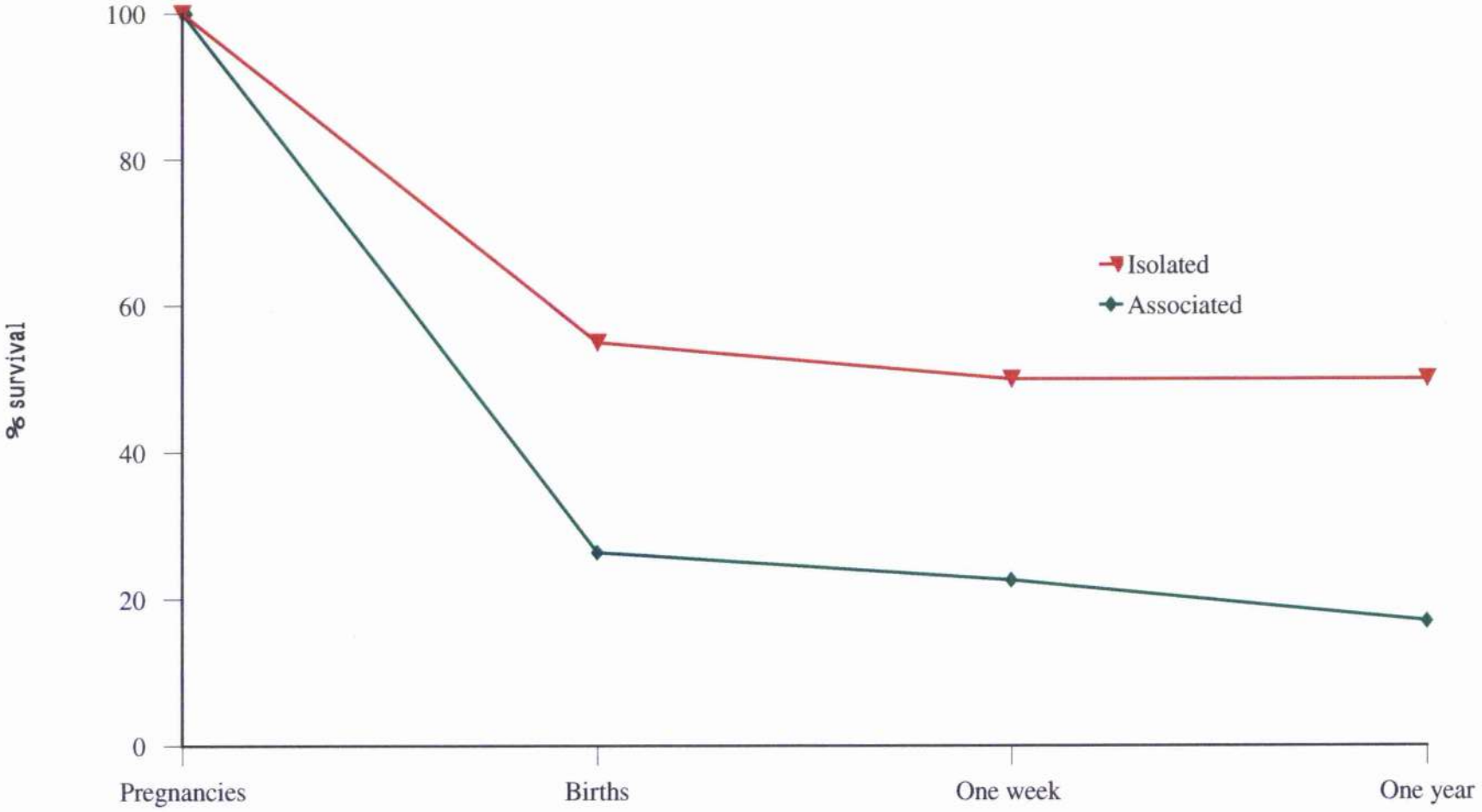



**Figure 4.5** . Survival to one year of isolated and associated cases of omphalocele in Glasgow, 1980-1993.

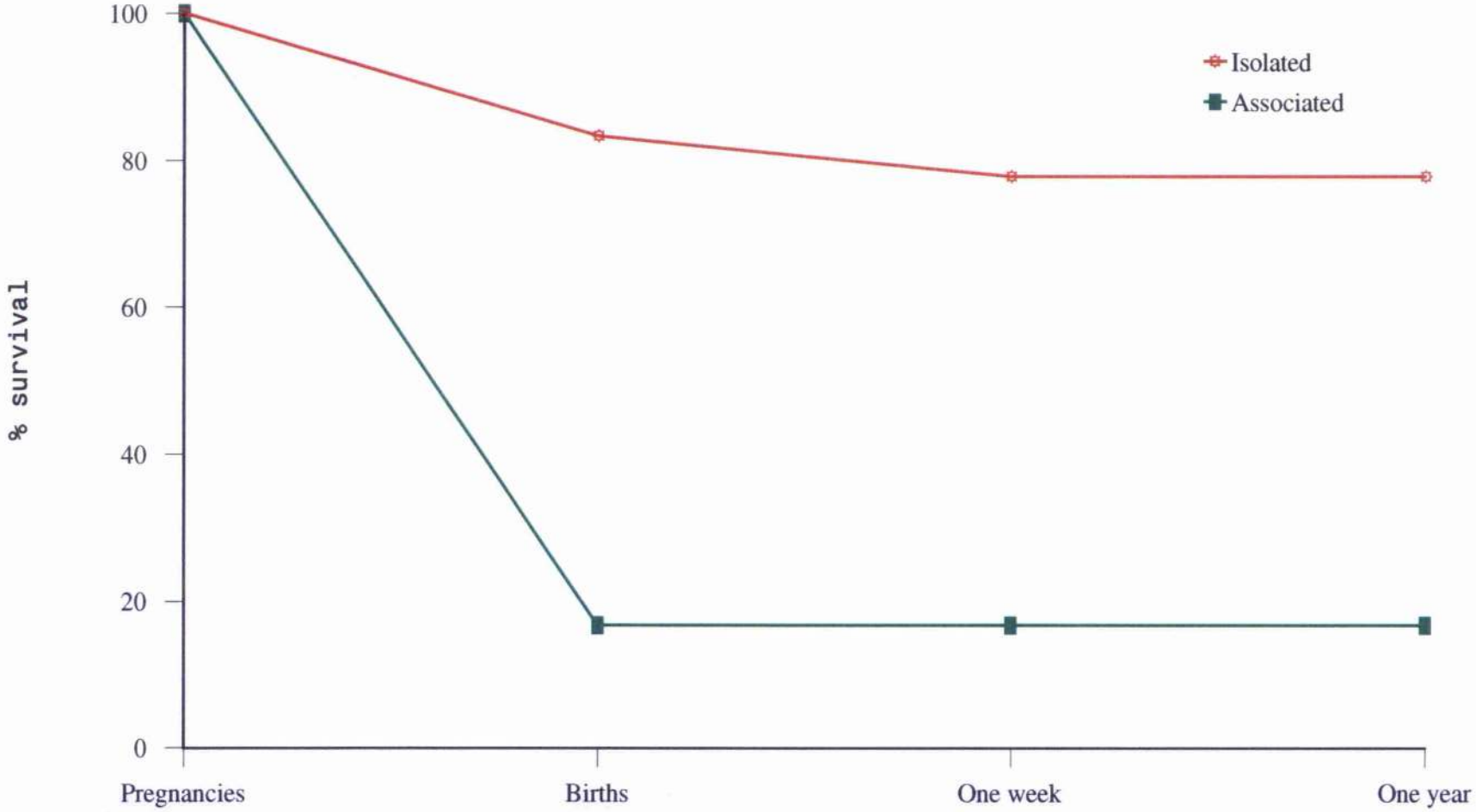



**Figure 4.6**. Survival to one year of isolated and associated cases of gastroschisis in Glasgow, 1980-1993.

In summary, the pregnancy prevalence of gastroschisis showed that a significantly increasing secular trend during 1980-93, but this was not seen for omphalocele. The prevalence rate of omphalocele in Glasgow is the highest reported in the UK.

The prevalence of gastroschisis was highest for mothers aged under 20, and the rate increasing significantly with decreasing of maternal age. Moreover, there was a greatly increased risk for young mothers of isolated gastroschisis cases.

Omphalocele and gastroschisis were associated with early gestational age and low birth weight. This was more pronounced for multiple malformations than for isolated cases.

Associated anomalies were more frequent among omphalocele cases than gastroschisis. Omphalocele cases associated with syndrome (trisomy 18, 13, Wiedemann-Beckwith syndrome). The common associated abnormalities in the group of multiple malformations were musculoskeletal anomalies, genital and urinary anomalies, NTD, GI in the upper alimentary tract.

Neither seasonal nor socio-economic status showed any significant association with either malformation.

The percentage of smokers among isolated cases of gastroschisis was significantly higher than associated cases.

In the case-control study, in univariate analysis, mothers of gastroschisis less than 20 years old were at a significant higher risk than mothers of malformed and malformed+non-malformed controls. The frequency of smoking among gastroschisis cases was higher than non-malformed and malformed+ non-malformed controls. In the multivariate analysis, young age and smoking among gastroschisis remained significant risk factors. In the conditional logistic regression, only parity remained significant.

Less than three-quarters of O&G had a prenatal diagnosis. About half of O&G had induced abortions following prenatal diagnosis. The proportion of isolated gastroschisis prenatal diagnosed among live and stillbirths was significantly higher than omphalocele cases. The proportion of prenatally diagnosis among gastroschisis cases rose

significantly from 1980-86 to 1987-93. Prenatal diagnosis was higher than among gastroschisis than omphalocele among surviving cases.

The majority of prenatal diagnosis of omphalocele were before 23 weeks while for gastroschisis most were at after 32 weeks.

The percentage of deaths among omphalocele cases was more than among gastroschisis cases. Two-thirds of perinatal deaths of omphalocele cases were caused by NTD and syndromes.

The percentage of surviving cases of gastroschisis was significantly higher than omphalocele cases (up to the one week and one year). The percentage of survival of isolated cases of (gastroschisis, omphalocele and O&G) was significantly higher than associated with other abnormalities.

# SECTION V: DISCUSSION

# SECTION V: DISCUSSION

## 5.1. *METHODOLOGICAL ASPECTS*

The quality of data is likely be high because it derived from the Glasgow Register of Congenital Anomalies (GRCA) which is population based, uses multiple sources of ascertainment, has no time limit after birth for notification, and has been systematically validated (Stone, 1986; Stone and Hamilton, 1987). While the denominator is relatively small (about 12,000 births per annum), ascertainment is likely to be high. Since 1980, GRCA has participated in the international EUROCAT network, which adds an additional level of quality control (EUROCAT report 5, 1993). Misclassification of gastroschisis as omphalocele (Baird and MacDonald, 1981; and Torfs *et al.*, 1990) is unlikely given the rigorous diagnostic validation to which all notified anomalies to the GRCA are subjected (see Methods, page 52). All cases of omphalocele and gastroschisis are selected. Induced abortions are included. According to some (Dillon *et al.*, 1997) it is preferable to register all abnormalities including those ending in miscarriage and terminations, since these account for most of apparent any change in birth prevalence. It is important in the present study because about 40% of abdominal wall defects, 47% of omphalocele and 21% of gastroschisis are induced abortions. While a high level of ascertainment may be a contributing factor, the similarity of this geographical pattern to that of NTD (EUROCAT report 6, Calzolari *et al.*, 1995) is strongly suggestive of a real variation in risk, either genetic or environmental. Part of the explanation may lie in the specific association between omphalocele and NTD in multiple malformed infants highlighted by Calzolari *et al.* (1995). This study in turn drew attention to the earlier suggestion of Dolk *et al.* (1991) that omphalocele and isolated NTD may be aetiologically related.

The possibility of error in the present study should be considered. In the descriptive study, this may be due to:

- Small sample size
- Inaccurate data
- Misclassification of defects
- Variation in ascertainment
- Missing data
- Bias

**Small sample size:**

Increasing the sample size might improve statistical power and transform a non-significant result into a significant one (e.g. in neighbourhood type analysis).

**Inaccurate records:**

Apart from missing data, inaccuracies can creep in during the process of data abstraction, recording, coding and analysis.

**Misclassification of defects**:

Although the records are presumed to be accurate there may be a possibility of misclassification; for example, in the early years of the study period there was no distinction between gastroschisis and omphalocele which led to inaccuracy in reporting the disease.

**Variation in ascertainment**:

New methodological approaches to the identification of the defects may lead to varying ascertainment of the defects. If ascertainment has improved over the study period, this could have resulted in a spurious increase in prevalence (e.g. of gastroschisis)

**Missing data**

Varying influence of a large number of unknown or missing factors (e.g. alcohol) on the investigation aetiology of the disease. In other words, the available data rather than a priori hypotheses may dictate the nature of the investigation.

**Bias**

Neighbourhood type analysis might have had possible bias because a mixture of poor and wealthy people who might live in the same neighbourhood type, thereby reducing the utility of this method as a proxy for social class (see below).

Case-control studies are notoriously problematic. One of them is observation bias, or errors in obtaining information from subjects once they have been entered into a study, relating to the reporting of information by the subject or the recording or interpretation of this information by the examiner. Another form of bias arises when the relationship

between the exposure and disease observed among those who participate in the study is different from that for individuals who would have been eligible to participate but were not selected by the investigator. Misclassification is another form of bias which refers to errors in the categorization of either exposure or disease status (Hennekens and Buring, 1987). The extent to which bias may have occurred in the present study is difficult to assess, but should have been minimised by the selection of two types of control. The selection of non-malformed controls may have resulted in the introduction of a degree of recall or observer bias. If there was a tendency for risk factors in non-malformed controls to have been overlooked.

The selection of malformed controls may have introduced a bias if the exposures at issue were associated with birth defects overall, or with any of the specific defects within the control series. It was also possible but unlikely that the controls were contaminated with omphalocele and gastroschisis that were not mentioned in the records.

## 5.2. *DESCRIPTIVE EPIDEMIOLOGY*

### 5.2.1. **Birth Prevalence**

Congenital abdominal wall defects appear to occur more frequently in Glasgow than elsewhere in the UK. The prevalence of omphalocele in Glasgow (4.1 per 10,000) is higher than most other areas in the UK (Dillon and Renwick, 1995; Tan *et al.*, 1996; Chalmers *et al.*, 1997) and Europe (second rate after Mainz) (EUROCAT Working Group, Report 6, 1995). The prevalence of gastroschisis is increasing significantly over time in Glasgow. It is widely accepted that an increase in the prevalence of gastroschisis has occurred in many other parts of the world (Lindham, 1981; Hemminki *et al.*, 1982; Martinez-Frias *et al.*, 1984; Moore and Nur, 1986 a; Roeper *et al.*, 1987; De Lorenzo *et al.*, 1987; Goldbaum *et al.*, 1990; Puffinbarger *et al.*, 1995; Lancaster and Pedisish, 1995; Tan *et al.*, 1996 but not others Calzolari *et al.*, 1993; Chalmers *et al.*, 1997; Dillon *et al.*, 1997.

Possible reasons for the changing prevalence of omphalocele and gastroschisis in Glasgow are as follows:

- This may relate to good ascertainment, increased risk, or both (Stone and Dolk, 1994).
- The increase in the total (pregnancy) prevalence of gastroschisis in this study strengthens the view, based on investigations from different parts of the world, that the true prevalence of gastroschisis has been rising over the past few decades. A possible explanation for this is that there has been a tend towards an increasing ascertainment of gastroschisis along with an enhanced ability to distinguish it from omphalocele as a result of advances in ultrasonographic and other diagnostic techniques. However, researchers from British Colombia and Italy have disputed this view (Calzolari *et al.*, 1993; Baird and MacDonald, 1981; Goldbaum, 1990; Dillon and Renwick, 1995).
- Increasing use of diagnostic technology such as ultrasound.
- Increasing emphasis on prevention.
- Association of omphalocele with chromosomal and neural tube defects and other lethal malformations that clinicians are increasing diagnosing.
- Consumer pressure on the part of parents wishing to receive more information on their fetus.

### 2.5.2. Gender

The predominance of males among gastroschisis cases observed in this study has also been reported elsewhere (Moore and Stokes, 1953; Moore, 1977; Berseth, 1982; Hemminki *et al.*, 1982; De Lorenzo *et al.*, 1987; Torfs *et al.*, 1990; Torfs *et al.*, 1994), but not others Lindham, 1981; Grosfeld *et al.*, 1981; Moore and Nur a, 1986; Goldbaum *et al.*, 1990). A female excess was observed significantly in omphalocele associated with neural tube defects in the study of Calzolari *et al.*, 1995 ($p<0.01$) but was not confirmed in Glasgow.

### 5.2.3. Maternal Age

The pattern of risk in relation to maternal age found in Glasgow is similar to that reported by other studies. Gastroschisis is generally more common in young prevalent mothers (Seashore, 1978; Lindham, 1981; Berseth, 1982; Hemminki *et al.*, 1982; Moore and Nur, 1986 a; Roeper *et al.*, 1987; De Lorenzo *et al.*, 1987; Novotny *et al.*, 1993; Calzolari *et al.*, 1995; Lancaster and Pedisish, 1995) (the highest teenage rate occurred 5.9 in Australia compared to 5.4 in Glasgow); Tan *et al.*, 1996. The rate of gastroschisis decreased significantly with increasing maternal age in Glasgow, a finding similar to that of Roeper *et al.*, 1987.

The finding that omphalocele is associated with older rather than younger mothers in Glasgow has been reported elsewhere (for example Hemminki *et al.*, 1982 in Finland; Martinez-Frias *et al.*, 1984 in pain; Roeper *et al.*, 1987 in California; in Australia (1995); Lindham, 1981; Berseth, 1982; Calzolari *et al.*, 1993).

Several possible explanations for the association between low maternal age and adverse pregnancy outcomes have been suggested. Compared with older mothers, teenage mothers are more likely to come from a poorer social environment, have inadequate prenatal care, and have poor health habits and diet (McAnarney, 1987; Ketterlinus *et al.*, 1990; Strobino *et al.*, 1995; Elster, 1984; Horon *et al.*, 1983; Gale *et al.*, 1989; Turner *et al.*, 1990). Teenage mothers may also differ from older mothers in terms of status, weight, and weight gain during pregnancy (Ketterlinus *et al.*, 1990; Horon *et al.*, 1983; Scholl *et al.*, 1987).

### 5.2.4. Social Factors

No striking difference in prevalence was found between socio-economic groups, as in neighbourhood types of maternal addresses in Glasgow, a finding similar to that of Drongowski *et al.*, 1991 (for gastroschisis) and Roeper *et al.*, 1987 (for gastroschisis or omphalocele). One statistically significant result did emerge (among O&G cases, neighbourhood type 7-8 significantly difference from neighbourhood type 3-6) but its epidemiological significance is unclear. In contrast, Torfs *et al.* (1994) found the highest frequency in the low or middle income and Iskaros *et al.*, 1996 in the case-control study found that the majority of cases were of low socio-economic status. The

absence of an association with socio-economic status, as assessed by place of maternal residence, casts doubt on the hypothesis that poor diet, or other teratogenic factors related to poverty, is causally important. Similarly, it suggests that the association of omphalocele with NTD is unlikely to be mediated through social or dietary factors. Alternatively, the use of maternal address as a proxy for socio-economic status may be inadequate or the numbers in the present study may be insufficient to achieve adequate statistical power (type II error).

### 5.2.5. Birthweight and Gestational Age

It is generally agreed that both omphalocele and gastroschisis are associated with early birth and low birth weight. This effect is greater for multiple malformed cases than for isolated cases (Martiinez-Friias *et al.*, 1984 (in the case-control study); De Lorenzo *et al.*, 1987; Calzolari *et al.*, 1993; Novotny *et al.*, 1993 (gastroschisis); Calzolari *et al.*, 1995; Lancaster and Pedisish (1995). The birthweight of gastroschisis cases was less than omphalocele in this study which is consistent with the data of Moore and Nur, 1986a; Irving, 1990; Drongowski *et al.*, 1991 (in the case-control study); Iskaros *et al.*, 1996).

### 5.2.6. Associated Anomalies

The proportion of cases in the two groups with associated anomalies was markedly different. As in other studies, omphalocele was frequently associated with other abnormalities (NTD, musculoskeletal). Omphalocele was most often associated with trisomies (of chromosomes 13 and 18) and Beckwith-Wiedemann syndrome (as Grosfeld *et al.*, 1981; Moore and Nur., 1986 b; Calzolari *et al.*, 1993; Calzolari *et al.*, 1995; and Dillon and Renwick, 1995.

On the other hand, some reports in the literature have suggested that chromosomal abnormalities are absent or rare in gastroschisis, and this accords with the Glasgow data. Some studies did not find an association with any chromosomal abnormalities (Mann *et al.*, 1984; Sermer *et al.*, 1987; and Roeper *et al.*, 1987). This suggests that omphalocele appears to be distinct from gastroschisis and its aetiology is likely be different.

### 5.2.7. Seasonality

Gastroschisis showed an insignificant peak in Spring in Glasgow in contrast to Goldbaum *et al.* (1990) who found that infants born during January, February, or March were at greater risk than infants born in any other months (OR= 2.2, 95% CI =1.1 to 4.1). Goldbaum *et al.* (1990) concluded that seasonal pattern may be due to an infectious aetiology, such as influenza. Hemminki *et al.* (1982) did not show any significant seasonality for omphalocele but Paulozzi and Milham (1986) observed a possible influence of seasonality for omphalocele in Washington. The lack of a seasonal trend in either omphalocele or gastroschisis in Glasgow is a consistent finding (Hemminki *et al.*, 1982 for omphalocele and Hemminki *et al.*, 1982; Roeper *et al.*, 1987; Werler *et al.*, 1992a for gastroschisis) which suggests that infection is unlikely to be an important aetiological factor.

## 5.3. *CASE - CONTROL STUDY*

### 5.3.1. Maternal Age

In the case-control study, young mothers appeared at significantly higher risk of gastroschisis than controls. Other case-control studies have shown a strong inverse association with maternal age (Drongowski *et al.*, 1991; Werler *et al.*, 1992 with malformed controls; Iskaros *et al.*, 1996), and in the case-control study by Martinez-Frias *et al.* (1984) young maternal age is significantly less than the mean of non-malformed controls, as found in Glasgow. Maternal age less than 20 years was associated with a tenfold increased risk of having an affected baby in Glasgow which was nearly twice the rate in the study reported by Goldbaum *et al.*, 1990. The proportion of gastroschisis cases with maternal age under 20 years old of gastroschisis is closer to the study of Tan *et al.*, 1996 (34.1% in England and Wales to 33.3% in Glasgow) and also for omphalocele (13.0% in England and Wales to 9.59% in Glasgow).

### 5.3.2. **Smoking**

According to some reports smoking has been increasing among young people in recent years. In a survey in European Community (EC) by Graham between 1950-1990, it was shown that smoking prevalence among women in UK, born before 1970, increased and there is fluctuation in the decade from 1970, but after that the prevalence decreased and in 1990 remained constant (Graham, 1996).

In the report of the Research Unit in Health and Behavioural Change by MacQueen and Campostrini (1991) in Glasgow from July 1987 to August 1990, that men are changing their smoking habits rapidly and women are not (females are changing, but very slowly), the female trend picture is less encouraging. The report of the Research Unit in Health and Behavioural Change and GGHB Health in Glasgow between 1988-1993 by Hay *et al.* (1994) indicated that smoking decreased in all age groups except the 18 to 21 year olds where it remained stable. The annual report of the director of public health in Glasgow gives the proportion of mothers who smoke in relation to neighbourhood type. Over the period 1986 to 1990 the proportion of mothers who smoked remained almost constant in neighbourhood types 1, 2 (about 9% and 20% respectively), but between 1986-1989 the proportion of mothers who smoked increased in neighbourhood type 7, 8, but in 1990 it decreased slightly (to 49% and 41% respectively) (GGHB, 1990).

Smoking appears to be associated with gastroschisis in Glasgow and in some other studies. Nicholls *et al.* (1996) concluded that smoking during pregnancy may be associated with an increased risk of gastroschisis. Goldbaum *et al.* (1990) in Washington State were the first to suggest this relationship in a case-control study. A 2.0 (95% CI= 1.03 to 3.8) times greater risk was observed, and 2.1 times (95% CI= 0.9 to 4.8) were found by Haddow *et al.* (1993) which compared to 3.40 (95% CI= 1.27 to 9.14) in Glasgow. This indicates that prevalence of smoking in Glasgow is higher than in these centres and consistent with only one study which showed a significantly higher risk associated with smoking

The harmful effect on the infant of cigarette smoking during pregnancy is well known. It is generally accepted that cigarette smoking during pregnancy increases the risk of

intrauterine growth retardation, prematurity, perinatal mortality, and spontaneous abortion (Landesman-Dwyer and Emanuel, 1979: Johnston, 1981. Smoking has been associated with a possible teratogenic effect on the developing embryo (Kelsey *et al.*, 1978; Himmelberger *et al.*, 1978; Christensen, 1980; Naeye, 1978 b). A prospective study by Naeye (1978 a) found an association between smoking and perinatal death due to congenital malformations, including anencephaly. Controversy still exists as to whether or not cigarette smoking increases the risk of congenital malformations but Nash and Persaud (1988) believe that smoking increases incidence of birth defects. Kelsey *et al.*, 1978, in a case-control study, based on interviews, that included 1,367 mothers of malformed infants and 2,963 mothers of normal infants, found a significant effect of heavy maternal smoking on malformation rates.

Some studies have suggested that the risk of certain specific congenital anomalies increases as a result of intrauterine exposure to tobacco smoke. Among these are NTD (Choi and Klaponski, 1970; Andrews and McGarry, 1972; Kelsey *et al.*, 1978; Hearey *et al.*, 1984); anencephaly (Naeye ,1978 a; Hearey *et al.*, 1984); cleft palate and lip (Andrews and McGarry, 1972; Saxen, 1974; Himmelberger *et al.*, 1978; Naeye, 1978 a; Ericson *et al.*, 1979; Aro, 1983; Khoury *et al.*, 1987; Khoury *et al.*, 1989); congenital heart defects (Fedrick *et al.*, 1971; Kelsey *et al.*,1978; Himmelberger *et al.*, 1978; limb reduction defects (Aro, 1983; Czeizel *et al.*, 1994, terminal transverse limb deficiencies (Källén, 1989). Recently, Källén (1997 a) found an association between maternal smoking during pregnancy, limb reduction and congenital urinary tract anomalies (Li *et al.*, 1996); Källén (1997 b) recently reported an association between maternal smoking during pregnancy and kidney malformations, as did Li *et al.* 1996.

There is evidence that smoking by pregnant women substantially raises the carboxyhaemoglobin level of the blood of the fetus (Cole *et al.*, 1972); and that in animals a high induced concentration of carboxyhaemoglobin in pregnant females is associated with an increased frequency of congenital malformations in offspring (Astrup *et al.*, 1972). Hoyme *et al.* (1983) have reported that abdominal wall disruption may follow interruption of the omphalomesenteric artery. DeVries (1980) has suggested that either premature atrophy or abnormal persistence of the right umbilical vein could lead to gastroschisis. Smoking clearly affects the vascular system. Barry *et al.* (1988) linked smoking to coronary artery spasm resulting in myocardial ischaemia. Lehtovirta

*et al.* (1984) demonstrated narrowing of coronary arteries among infants of smokers. Smoking clearly affects the placenta (Lehtovirta and Forss 1978; Naeye, 1978 b; Naeye, 1979; Van der Veen and Fox, 1982; Van der Velde *et al.*, 1983. Van Allen (1981) and Hoyme *et al.* (1983) believe that the aetiology of gastroschisis involves vascular disruption.

## 5.4. *PRENATAL DIAGNOSIS*

Omphalocele was prenatally diagnosed in 70% of cases in Glasgow, and in 77% of cases it was associated with another major abnormality. Gastroschisis was prenatally diagnosed in 75% of cases in Glasgow, less than that of Fisher *et al.* (1996) (98% of omphalocele, 95% of gastroschisis) but higher than an earlier study from the West of Scotland by Morrow *et al.* (1993) (66% of omphalocele, 70% of gastroschisis).

Haddock *et al.* (1996) suggested that the prenatal diagnosis of gastroschisis can, in theory, be made on the basis of raised maternal AFP and anomalous ultrasound scan in virtually 100% of cases. Prenatal diagnosis of gastroschisis increased in Glasgow in keeping with report in the West of Scotland by Haddock *et al.* (1996), that the take-up rate for maternal serum AFP scanning over the decade 1983-1993 has steadily increased to approximately 85%.

A high proportion of O&G cases were prenatally diagnosed. In this study omphalocele tended to be diagnosed earlier in pregnancy than gastroschisis, doubtless due to its more obvious anatomical configuration. The rising proportions of gastroschisis cases prenatally diagnosed in recent years is probably due to a combination of technological advances and increasing professional skill. There was, however, a striking divergence in the proportion proceeding to termination of pregnancy. Two-thirds of prenatally diagnosed omphalocele cases were terminated compared to just over a quarter of gastroschisis cases. The reason for this difference is unclear but presumably reflects, in part at least, parental (and professional) awareness of the poorer prognosis of omphalocele than that of gastroschisis. Whether improvements in prenatal diagnostic rates have led to more effective surgical intervention, in terms of post-operative survival and morbidity, cannot be determined from data of this study.

Early and accurate sonographic evaluation of anterior abdominal wall defects is important to allow for appropriate counselling and treatment, and to allow parents to decide about termination. Prenatal paediatric surgical consultation may have a significant impact on the perinatal management of the fetus with a surgically correctable congenital anomaly. Providing obstetric colleagues and families with valuable insight into the surgical management of anomalies allows fetal intervention when appropriate, and delivery in an appropriate setting by the safest mode of delivery, and at a gestational age which minimizes the effects of the anomaly.

The key to reducing mortality and morbidity further lies in extending the availability of prenatal diagnosis and in continuing to study gastroschisis *in utero* in order to detect and define those babies at greater risk of complications of the gastroschisis or of the delivery. It may be possible to identify more accurately an "at risk" group who should be closely monitored by serial ultrasound scans and biophysical assessment (Haddock *et al.*, 1996).

However, the complexity of the issues surrounding screening (see introduction) is such that they lie outwith the scope of the present study. Any attempt to increase the impact of PND will require to take account of the various scientific, ethical and economic factors involved.

Due to improved neonatal care, the mortality has fallen steadily and is now of the order of 4-10% for gastroschisis (Crabbe *et al.*, 1991; and Stringer *et al.*, 1991). Since the advent of antenatal diagnosis, controversy has arisen over the optimal timing and route of delivery. Stringer *et al.* (1991) suggested that delivery in a specialist obstetric centre with neonatal surgery on site, facilitating early operation, leads to a shorter postoperative course.

Haddock *et al.* (1996) reported that perinatal anaesthetic and surgical management now produce survival in approximately 90% of cases. It is important, however, for the paediatric surgeon to be involved as early as possible in the decision making since he (or she) is the person best able to give the parents an accurate account of the treatment which the infant will require and of the likely outcome. If the pregnancy proceeds there

should be a team approach to the management of delivery and perinatal care. It may be necessary to transfer the mother for delivery at special centre. (Irving, 1990).

Larsson and Kullendorff (1990) reported that in the new-born with an abdominal wall defect (omphalocele and gastroschisis) the mortality rate was high prior to the introduction of total parenteral nutrition, postoperative ventilatory support and improved surgical techniques. With modern intensive care the mortality rate is low and related to the presence of severe associated anomalies. More and more patients are accordingly reaching adult life. However, surgical intervention may influence the long term results regarding quality of life.

Clinical and subclinical folate deficiency during pregnancy has been frequently reported. Abdominal wall defects are reported in animal experiments and association between omphalocele and NTD has been found. Moreover, the prevalence of low folate levels has been measured in US and British populations, the prevalence of this deficiency is estimated to be about 25% in North America and Britain (Nutrition Recommendations: the report of the Scientific Review committee 1990, 1990). This study recommended that this primary preventive method has great public health significance, being a better alternative than prenatal diagnosis and selective abortion. In addition to the lessening of human suffering, supplementation would decrease medical costs.

In summary, clear epidemiological differences between omphalocele and gastroschisis were identified firstly, by higher mean age for mothers of infants with omphalocele than that of mothers of infants with gastroschisis, and a markedly higher risk of the latter in mothers under 20 years. Secondly, a higher association between omphalocele with other anomalies and chromosomal syndromes, than gastroschisis.

## 5.6. PERINATAL MORTALITY AND SURVIVAL

Perinatal mortality among omphalocele cases is usually higher than for gastroschisis, and that was the case in the present study. This also accords with the work of Roeper *et al.*, 1987; Lancaster and Pedisish, 1995; Calzolari *et al.*, 1995; Tan *et al.*, 1996. This may be due to the association of omphalocele with other anomalies and syndromes

which is a finding consistent with that of a study by Martinez-Frîet *et al.*, 1984; Yazbeck *et al.*, 1986; Chang *et al.*, 1992.

The percentage of survival during first year was significantly higher among gastroschisis cases in Glasgow than omphalocele, a finding consistent with that of Chang *et al.*, 1992

The percentage of survival among isolated gastroschisis cases was higher than associated with other anomalies. It may reflect the quality life of children as Swartz *et al.* (1986) found isolated cases of gastroschisis had normal growth and development and Davies and Stringer (1997) concluded most (96%) survivors can eventually expect normal growth and good health.

Because of the high rate of associated abnormalities, and chromosomal syndromes among omphalocele cases, the mortality rate is high, while gastroschisis has a high survival rate because of a low association with other anomalies. Moreover, Swartz *et al.* (1986) suggested that the survival of infants with gastroschisis has increased over the past 20 years due to improvements in parenteral nutrition, paediatric ventilators, surgical technique, and general neonatal intensive care.

## 5.7. IMPLICATIONS OF FINDINGS

The most notable finding of this study was the clear epidemiological difference between omphalocele and gastroschisis. In particular, a higher mean age for mothers of infants with omphalocele than that of mothers of infants with gastroschisis was found, and a markedly higher risk of the latter in mothers under 20 years. A higher frequency of association of omphalocele with other abnormalities than gastroschisis also suggests that omphalocele of gastroschisis are distinct entities. These findings are in close agrument with most other series.

The prevalence of gastroschisis is increasing significantly in Glasgow, and the prevalence of omphalocele is the highest in the UK. The prevalence in Glasgow was more than four times higher than that reported in England and Wales. However, the specific causes of

these defects are still unknown, but the high risk group in the population for gastroschisis are mothers under the age of 20 years and who smoke. For omphalocele, no specific factors are recognisable. Continuous epidemiological monitoring of both defects is clearly desirable in the light of this ignorance of aetiology.

Because of current medical advances, an increasing number of infants afflicted with abdominal wall defects are now surviving. For this reason it is important to identity prenatally those infants where a good prognosis can be anticipated. Where the prognosis is grave, because of the anomalies, a decision may have to be made about terminating the pregnancy. Survivors should be followed up to optimise their quality of life.

Genetic counselling is a form of primary prevention. Early and accurate diagnosis and prompt surgery are forms of secondary prevention. Preconception counselling should be offered to all women under 20 years due to their elevated risk of gastroschisis.

Folic acid supplementation might be effective forms of primary prevention. It is the duty of public health agencies to advise women to consume a good diet containing folic acid, not only in early pregnancy but also before pregnancy. This is especially important for women under 20 years old.

Long-term follow-up of children with gastroschisis is now possible due to increasing survival. This is particularly important for associated cases with other anomalies of gastroschisis because of the increased risk for long-term bowel problems and abdominal complaints. Children born with O&G, despite antenatal screening, should continue to receive the highest standard of social and medical care.

The proportion screened could be increased by health education designed to encourage mothers (particularly under 20) to attend for antenatal screening. The impact of antenatal screening and therapeutic termination of the affected fetuses requires continued research (particularly mothers under 20 years old for gastroschisis cases). However, improved prenatal diagnoses of isolated cases of omphalocele and gastroschisis are important.

Health care policy should be considered in relation to teenage pregnancy due to their high risk. The community should provide adequate prenatal care for them. The confirmed teratogenic effect of maternal smoking might be a further strong indication for public health interventions aimed at preventing smoking during pregnancy, particularly among those of young maternal age. Hence, the efficiency of anti-smoking for all young mothers remains to be improved by public health assessment.

## 5.8. *IMPLICATIONS FOR FUTURE RESEARCH*

Although the prevalence of gastroschisis is increasing and the rate of omphalocele is high in Glasgow, surprisingly few clinical, epidemiological, and laboratory studies have been done to investigate the cause of these defects. Therefore, continued research into aetiology is necessary.

Through this study, some factors were unknown or missing which truly may affect the O&G. On the other hand, some factors like social factors which may influence the conclusion were identified through the neighbourhood type. The postcode not mean necessarily that all the people in the same area have the socio-economic situation.

In the present study, we found that young mothers (less than 20 years) and smoking are risk factors among gastroschisis cases, as found in the other parts of the world. Therefore in future case-control study, cases should be matched with controls by mothers age (younger mothers, under 20 years).

Due to the small numbers of cases in this study, increasing the number of cases and, especially controls will improve power of the study.

It is necessary to investigate the effect of folic acid on the prevalence of omphalocele and gastroschisis because, firstly, it has been shown in some studies that folic acid can prevent some congenital malformations such as clip lip and palate, NTD. Secondly, omphalocele is associated with NTD. Thirdly, deficiency of abdominal wall defects may follow floate depletion in an animal experience. Fourthly, the prevalence of folate levels is low in U. K.

Antenatal screening in high risk populations may make a contribution to the future reduction of O&G prevalence. Therefore, further investigation into the efficiency of screening service and the effectiveness of antenatal service is essential. This study suggests that a comprehensive public health strategy, including screening, is likely to be required to prevent O&G.

It is important to undertake prospective studies of children after surgery to assess their disabilities, quality of life and long-term outcome.

# SECTION VI: CONCLUSIONS

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1. Omphalocele and gastroschisis are the commonest malformations of the abdominal wall. While these defects are rare, they present clinically as emergencies. The defects vary in their severity but most are potentially lethal if untreated surgically.

2. Glasgow appears to have experienced an unusually high prevalence of omphalocele, relative to other parts of the UK and Europe. The reported prevalence of omphalocele in Glasgow is the highest in the United Kingdom. Indeed, the prevalence found in the present study is more than four times that in England and Wales and twice in Scotland for omphalocele, and twice that in England and Wales for gastroschisis.

3. In recent years, there appears to have been a rising prevalence of gastroschisis but not omphalocele in Glasgow.

4. The epidemiological characteristics of omphalocele and gastroschisis are suggestive of a different aetiology for each of the two defects.

5. The present study has confirmed the strong association between gastroschisis but not omphalocele with young maternal age. The higher rate of occurrence of gastroschisis in younger women's pregnancies suggests that exposure to a potential teratogen may be related to maternal age. First pregnancies have a significantly increased risk for gastroschisis after correction for maternal age.

6. The percentage of smokers among mothers of isolated cases of gastroschisis was significantly higher than in mothers of cases associated with other anomalies but not omphalocele. This suggests either that cigarette smoking is a risk factor and or that a related behavioural or environmental factor may be important. Mothers who are socially disadvantaged during their youth and the time of pregnancy, and who report using cigarette smoking may be at increased risk for the birth of a child with gastroschisis. Because many of these mothers are unusually young, public health efforts should target this vulnerable population. However, even after controlling for maternal age and social class, smoking remained a risk factor for gastroschisis.

7. Both defects were associated with early birth and low birth weight, an effect that was more pronounced for multiple malformed than for isolated cases and for gastroschisis more than omphalocele.

8. The survival rate during first year and first week was significantly higher among gastroschisis cases than omphalocele because of the association of the latter with other anomalies, including chromosomal syndromes.

9. Of abdominal wall defects that were associated with other defects, most of the associated defects were musculoskeletal anomalies, genital and urinary abnormalities, NTD, and GI in the upper alimentary tract.

10. Prenatal diagnosis has been increasingly achieved, especially in cases of gastroschisis, but this has not been accompanied by a consequent rise in the frequency of terminations of pregnancy for the condition. Efforts to increase the impact of screening should be undertaken in the context a screening programme that fulfils conventional screening criteria.

# REFERENCES

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Allen, R.G. (1980) Omphalocele and gastroschisis. In: Holder, T.M and Ashcraft, K.W. Neonatal surgery .Chapter 47, Philadelphia: W.B Saunders Company. p 572-588.

Andrews, J and McGarry, J.M. (1972) A community study of smoking in pregnancy. Journal of Obstetrics and Gynaecology of the British Commonwealth, **79**, 1057-1073.

Angerpointner, T.b., Radtke, W., and Murken, J.D. (1981). Catamnestic Investigation in. children with malformation of the gastrointestinal tract and the abdominal wall. Zeitschrift Fur Kinderchirurgie, **32**, 129-144.

Aro, T. (1983) Maternal diseases, alcohol consumption, and smoking during pregnancy associated with limb reduction defects. Early Human Development, **9**, 49-57.

Astrup, P., Olsen, H.M., Trolle, D., and, Kjeldsen, K. (1972). Effect of moderate carbon monoxide exposure on fetal development. Lancet, **2**, 1220-1222.

Baird, P.A. and MacDonald, E.C. (1981) An epidemiological study of congenital malformation of the anterior abdominal wall in more than half a million consecutive live births. American Journal of Human Genetics, **33**, 470- 478.

Barry, J., Mead, K., Nabel, E.G., Rocco, M.B., Campbell, S., Fenton, T., Mudge, G.H., Jr., Selwyn, A.P. (1989) Effect of smoking on the activity of ischemic heart disease. Journal of the American Medical Association, **261**, 398-402.

Beaglehole, R., Bonita, R., and Kjellström, T. (1993) Epidemiology and prevention. Basic epidemiology. Chapter 6. Geneva, World Health Organization, p 83-96.

Bergsma, D. (1979) Birth defects compendium. (eds) National Foundation- March of Dimes by the Macmillan press (LTD), second edition.

Berseth, C.L., Malachowski, N., Cohn, R.B., and Sunshine, P. (1982) Longitudinal growth and late morbidity of survivors of gastroschisis and omphalocele. Journal of Paediatric Gastroenterology and Nutrition, **1**, 375-379.

Brun, M., Grignon, N., Guibaud, L.G., Laurent, G., Saint-Vil, D. (1996) Gastroschisis: are prenatal ultrasonographic findings useful for assessing the prognosis? Paediatric Radiology **26**, 723-726.

Bulut, M., Kalayoglu, M., and Hicsönmez, A. (1989) Pregastroschisis. Zeitschrift Fur Kinderchirugie, **44**, 58-59.

Canadian task force on the periodic health examination. (1994) Primary and secondary prevention of NTD. Canadian Medical Association Journal, **151**, 159- 166.

Calzolari, E., Bianchi, F., Dolk, H., Milan, M. and EUROCAT Working Group. (1995) Omphalocele and gastroschisis in Europe: A survey of 3 million births 1980-1993. American Journal of Medical Genetics, **58**, 187-194.

Calzolari, E., Volpato, S., Bianchi, F., Cianciulli, D., Tenconi, R., Clementi, M., Calabro, A., Lungarotti, S., *et al.* (1993) Omphalocele and gastroschisis: A collaborative study of five Italian congenital malformation registers. Teratology, **47**, 47-55.

Chalmers, J., Forrest, J., Cant, B., and Hollinsworth, M. (1997) Rate of abdominal wall defects is higher in Scotland than England and Wales. British Medical Journal, **314**, 371-372.

Chang, P.Y., Yeh, M.L., Sheu, J.C., and Chen, C.C. (1992) Experience with treatment of gastroschisis and omphalocele. Journal of the Formosan Medical Association, 91, 447-451.

Choi, M., and Klaponski, S (1970) On neural tube defects: an epidemiological elicitation of aetiological factors. Neurology, **20**, 399-400 (abstract).

Christianson, R.E. (1980). The relationship between maternal smoking and the incidence of congenital anomalies. American Journal of Epidemiology, **112**, 684-695.

Chun, K., Andrews, H.G., and White, J.J. (1993) Gastroschisis in successive siblings: Further evidence of an acquired aetiology. Journal of Paediatric Surgery, **28**, 838-839.

Cochrane, A.L., and Holland, W.W. (1971) Validation of screening procedures. British Medical Bulletin, **27**, 3-8.

Cole, P.V., Hawkins, L.H., and Roberts, D (1972) Smoking during pregnancy and its effects on the fetus. Journal of Obstetrics and Gynaecology of the British Commonwealth, **79**, 782-787.

Colombani, P.M., and Cunningham, M.D. (1977) Perinatal aspects of omphalocele and gastroschisis. American Journal of Disease of Childhood, **131**, 1386-1388.

Crabble, DC.G., Thomas, D.F.M., Beck, J.M., Spicer, R.D. (1991) Prenatally diagnosed gastroschisis: a case for preterm delivery? Paediatric Surgery International, **6**, 108-110.

Czeizel, A.E. (1996) Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplemenattion. American Journal of Medical Genetics, **62** 179-183.

Czeizel, A.E., and Dudas, I. (1992) Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation. New England Journal of Medicine **327**, 1832-1835.

Czeizel, A.E., Kodaj, I., and Lenz, W. (1994) Smoking during pregnancy and congenital limb deficiency. British Medical Journal, **308**, 1473-1476.

Czeizel, A.E., Toth, M., and Rockenbauer, M. (1996) Population-based case control study of folic acid supplemenation during pregnancy. Teratology, **53**, 345-351.

Davies, B.W., and Stringer, M.D. (1997) The survivors of gastroschisis. Archives of Disease in Childhood, 77, 158-160.

De Lorenzo, M.D., Yazbeck, S., and Ducharme, J.C. (1987) Gastroschisis: A 15-year experience. Journal of Paediatric Surgery, **22**, 710-712.

Department of National Health and Welfare. (1990) Nutrition recommendations. Ottawa 116-123.

De Vries, P.A. (1980) The pathogenesis of gastroschisis and omphalocele. Journal of Paediatric Surgery, **15**, 245.

Dillon, E., and Renwick, M. (1995) The antenatal diagnosis and management of abdominal wall defects: The Northern region experience. Clinical Radiology, **50**, 855-859.

Dillon, E., Renwick, M., Rankin, J. (1997) Authors' figure for Northern region are underestimates. British Medical Journal. **314**, 372.

Dixon, W.J. (1990) BMDP Statistical Software. Berkeley, University of California Press.

Dolk, H., De Wals, P., Lechat, M.F., Ayme, S., Beckers, R., Bianchi, F., Borlee, I., Calabro, A., *et al.* (1991) Prevalence of neural tube defects in 20 regions of Europe and the impact of prenatal diagnosis, 1980-1986. Journal of Epidemiology and Community of Health, **45**, 52-58.

Drongowki, R.A., Smith, R.K., Jr., Coran, A.G., Klein, M. (1991) Contribution of demographic and environmental factors to the gastroschisis: A hypothesis. Fetal Diagnosis and Therapy, **6**, 14-27.

Duhmel, B. (1963) Embryology of exomphalocele and allied malformations. Archives of Disease in Childhood, **38**, 142-147.

Elster, A.B. (1984) The effect of maternal age, parity, and prenatal care on perinatal outcome in adolescent mothers. American Journal of Obstetrics and Gynaecology, **149** 845-847.

Ericson, A., Källén, B and Westerholm, P. (1979) Cigarette smoking as an etiologic factor in cleft lip and palate. American Journal of Obstetrics and Gynaecology, **135**, 348-351.

EUROCAT Working Group. (1995) Surveillance of Congenital Anomalies in Europe, 1980-1992. Report 6. Brussels, Catholic University of Louvain.

Fedrick, J., Alberman, E,., Goldstein, H. (1971) Possible teratogenic effect of cigarette smoking. Nature, **231**, 529-530.

Fisher, R., Attah, A., Partington, A., and Dykes, E. (1996) Impact of antenatal diagnosis on incidence and prognosis in abdominal wall defects. Journal of Paediatric Surgery, **31**, 538-541.

Gaillard, D. (1980) Gastroschisis. American Journal of Disease of Childhood, **134**, 1179 (letter).

Gale, R., Seidman, D.S., Dollberg, S., Armon, Y., Stevenson, D.K. (1989) Is teenage pregnancy a neonatal risk factor? Paediatric Research, **25**, 99.

Gierup, J. and Lundkvist, K. (1979) Gastroschisis- A pilot study of its incidence and the possible influence of teratogenic factors. Zeitschrift Fur Kinderchirugie, **28**, 39-42.

Glick, P.L., Harrison, M.R., Adzick, N.S., Filly, R.A., deLorimier, A.A., and Callen, P.W. (1985) The missing link in the pathogenesis of gastroschisis. Journal of Paediatric Surgery **20**, 406-409.

Goldbaum, G., Daling, J. and Milham, S. (1990) Risk factors for gastroschisis. Teratology **42**, 397- 403.

Graham, H. (1996) Smoking prevalence among women in the European Community 1950-1990. Social Science and Medicine, **43**, 243-254.

Gray, S.W., Skandalakis, J.E. (1972) The diaphragm. In: Embryology for Surgeons. The embryological basis for the treatment of congenital defects. Philadelphia: W.B.Saunders & Co, 359-385.

Greater Glasgow Health Board. (1990) Annual Report of the Director of Public Health. Glasgow, GGHB.

Greater Glasgow Health Board. (1991) Annual Report of the Director of Public Health. Glasgow, GGHB.

Grosfeld, J.L., and Weber, T.R. (1982) Congenital abdominal wall defects: Gastroschisis and omphalocele. Current Problems in Surgery, **19**, 158-213.

Grosfeld, J.L., Dawes, L., and Weber, T.R. (1981) Congenital abdominal wall defects: Current management and survival. Surgical Clinics of North America. **61**, 1037-1049.

Gross, R.E. (1953) Omphalocele (umbilical eventration). In: The surgery of infancy and childhood. Philadelphia: W.B. Saunders Company, p 406-422.

Haddock, G., Davis, C.F., and Raine, P.A.M (1996) Gastroschisis in the decade of prenatal diagnosis: 1983-1993. European Journal of Paediatric Surgery, **6**, 18-22.

Haddow, J.E., Palomaki, G.E. and Holman, M.M. (1993) Young maternal age and smoking during pregnancy as risk factors for gastroschisis. Teratology; **47**, 225-228.

Haller, J.A. Jr., Kehrer, B.H., Shaker, I.J., Shermeta, D.W., and Wyllie, R.G. (1974) Studies of the pathophysiology of gastroschisis in fetal sheep. Journal of Paediatric Surgery, **9**, 627-632.

Hay, S., Uitenbroek, D., Robertson, B., Tannahill, C. (1994) Smoking in Glasgow. Factsheet No 1, The Research Unit in Health and Behavioural Change (RUHBC) and Greater Glasgow Health Board (GGHB).

Hearey, L.D., Haris, J.A., Usatin, M.S., Epstein, D.M., Ury, H.K., Neutra, R.R. (1984) Investigation of a cluster of anencephaly and spina bifida. American Journal of Epidemiology, **120**, 559-564.

Hemminki, K., Saloniemi, I., Kyyrönen, P., and Kekomäki, M. (1982) Gastroschisis and omphalocele in Finland in the 1970s: Prevalence at birth and its correlates. Journal of Epidemiology and Community Health, **36**, 289-293.

Hennekens, C.H., Buring, J.E. (1987) Case-control study. Epidemiology in Medicine. Boston/ Toronto; Litte, Brown and company, p 132-145.

Hershey, D.W., Haesslien, H.C, Marr, C.C., Adkins, J.C. (1989) Familial abdominal wall defects. American Journal of Medical Genetics, **34**, 174.

Himmelberger, D.U., Brown, B.W., and Cohen, E.N. (1978) Cigarette smoking during pregnancy and the occurrence of spontaneous abortion and congenital abnormality. American Journal of Epidemiology, **108**, 470-479.

Holland, W.W., and Stewart, S. (1990) Screening in health care. London, Nuffield Provincial Hospital Trust, P 1-72.

Horon, I.L., Strobino, D.M., MacDonald, H.M. (1983) Birth weights among infants born to adolescent and young adult women. American Journal of Obstetrics and Gynaecology, **146**, 444-9.

Hoyme, H.E., Higgingbottom, M.C., and Jones, K.L. (1981) The vascular pathogenesis of gastroschisis: intrauterine interruption of the omphalomesenteric artery. Journal of Paediatrics, **98**, 228-231.

Hoyme, H.E., Jones, M.C, and Jones, K.L. (1983) Gastroschisis: Abdominal wall disruption secondary to early gestational interruption of the omphalomesenteric artery. Seminars in Perinatology, 7, 294-302.

International Clearinghouse for Birth Defects Monitoring System. Annual report 1996 with data for 1994. Roma, Italy. International Centre for Birth Defects.

Irving, I.M. (1990). Umbilical abnormalities. In: Lister, J and Irving, I.M. Neonatal surgery. Chapter 27, Butterworths, third edition, p 376-402.

Iskaros, J., Morrison, J.J., Chitty, L.S., and Rodeck, C.H. (1995) Epidemiological and sonographic features of fetal gastroschisis and neonatal outcome. British Journal of Obstetrics and Gynaecology. **103**, 848.

Izant, R.J., Brown, F., and Rothmann, B.F. (1966) Current embryology and treatment of gastroschisis and omphalocele. Archives of Surgery, **93**, 49-53.

Jones, P.G. (1976) Exomphalocele and gastroschisis. In: By the staff of the Royal Children's Hospital, Melbourne (eds). Clinical Paediatric Surgery: Diagnosis and management. Second edition. Chapter 15. Oxford, Blackwell Scientific.

Jones, P.G and Woodward, A.A. (1986) Exomphalocele and gastroschisis. In: By the staff of the Royal Children's Hospital, Melbourne (eds). Clinical Paediatric Surgery: Diagnosis and management. Third edition. Chapter 15. Oxford, Blackwell Scientific, 127-140.

Johnston, C. (1981) Cigarette smoking and the outcome of human pregnancies: a state report on the consequences. Clinical Toxicology, **18**, 189-209.

Källán, B. ( 1989) A prospective study of some aetiological factors in limb reduction defects in Sweden. Journal of Epidemiology and Community Health, **43**, 186-191.

Källán, K. (1997a) Maternal smoking during pregnancy and limb reduction malformations in Sweden. American Journal of Public Health, **87**, 29-32.

Källán, K. (1997b) Maternal smoking and organ malformations. International Journal of Epidemiology, **26**, 571-574.

Kelsey, J.L., Dwyer, T., Holford, T.R., and Bracken, M.B. (1978) Maternal smoking and congenital malformations: An epidemiology study. Journal of Epidemiology and Community Health, **32**, 102-107.

Ketterlinus, R.D., Henderson, S.H., Lamb, M.E. (1990) Maternal age, sociodemographics, prenatal health and behaviour: Influences on neonatal risk status. Journal of Adolescence Health Care, **11**, 423-31.

Khoury, M.J., Gomez-Farias. M., and Mulinare, J. (1989) Does maternal cigarette smoking during pregnancy cause cleft lip and palate in offspring?. American Journal of Disease of Childhood, **143**, 333-337.

Khoury, M.J., Weinstein, A., Panny, S., Holtzman, N.A., Lindsay, P.K., Farrel, K., Eisenberg, M. (1987) Maternal cigarette smoking and oral clefts: a population-based study. American Journal of Public Health, 77, 623-625.

Kimmel, C.A., Wilson, J.G., and Schumacher, H.J. (1971) Studies on metabolism and identification of the causative agent in aspirin teratogenesis in rats. Teratology, **4**, 15-24.

King, D.R., Savrin, R.A and Boles, E.T., Jr. (1980) Gastroschisis update. Journal of Paediatric Surgery, **15**, 553.

Klück, P., Tibboel, D., Van der Kamp, A.W.M., and Molenaar, J.C. (1983) The effect of fetal urine on the development of the bowel in gastroschisis. Journal of Paediatric Surgery, **18**, 47-50.

La-Ha, C., Stone, D.H., Gilmour, W.H. (1995) Impact of prenatal screening and diagnosis on the epidemiology of structural congenital anomalies. Journal of Medical Screening, **2**, 67-70.

Lancaster, p., Pedisish, E. (1995) Congenital Malformations Australia, 1981-1992. Birth Defects Series. Number 1. Sydney, Australian Institute of Health and Welfare National Perinatal Statistic Unit.

Landesman-Dwyer, S., Emanuel, I. (1979) Smoking during pregnancy. Teratology **10**, 119-126.

Larsson, L.T., Kullendorff, C.M. (1990) Late surgical problems in children born with abdominal wall defects. Annals Chirurgiae et Gynaecologiae, **79**, 23-25.

Last, J.M. (1988) A dictionary of epidemiology. 2nd (ed). Oxford, Oxford University Press.

Leck, I. (1994). Structural birth defects. In: Pless, I.B (eds) The epidemiology of childhood disorders. Chapter 4. Oxford University Press, p 66-117.

Lehtovirta, P., and Forss, M. (1978) The acute effect of smoking on intervillous blood flow of the placenta. British Journal of Obstetrics and Gynaecology, **85**, 729-731.

Lehtovirta, P., Pesonen, E, and Sarna, S (1984) Effect of smoking on the fetal coronary arteries. Acta Pathologica Microbiologica Et Immunologica. Scandinavica Section [A], **92**, 189-193.

Li, De-kun., Mueller, B.A., Hickok, D.E., Daling, J.R., Fantel, A.G., Checkoway, H., Weiss, N.S. (1996) Maternal smoking during pregnancy and the risk of congenital urinary tract anomalies. American Journal of Public Health, **86**, 249-253.

Lindham, S. (1981) Omphalocele and gastroschisis in Sweden 1965-1976. Acta Paediatrica Scandinavica, **70**, 55-60 .

Lopez, P.M., Stone, H.D and Gilmour, H. (1995) Epidemiology of Down's syndrome in a Scottish city. Paediatric and Perinatal Epidemiology, **9**, 331-340.

Mann, L., Ferguson-Smith, M.A., Desai, M., Gibson, A.M., and Raine, P.A.M. (1984) Prenatal assessment of anterior abdominal wall defects and their prognosis. Prenatal Diagnosis, **4**, 427-435.

Margulies, L. (1945) Omphalocele (amniocele). American Journal of Obstetrics and Gynaecology, 49, 695-699.

Martínez-frías, M.L., Prieto, S.L., and Zaplana, J. (1984) Epidemiological study of gastroschisis and omphalocele in Spain. Teratology, **29**, 377-382.

Mayer, T.T., Black, R., Matlock, M., *et al.* (1980) Gastroschisis and omphalocele: An 8 year review. Annals of Surgery, **192**, 738.

McAnarney, E.R. (1987) Young maternal age and adverse neonatal outcome. American Journal of Disease of Childhood, **141**, 1053-1059.

McKeown, T., MacMahon, B., and Record, R.G. (1952) An investigation of 69 cases of exomphalos. Journal of Human Genetics, 5, 168-175.

McQueen, D., Campostrini, S. (1991) Smoking in Glasgow. A report. Edinburgh, The Research Unit in Health and Behavioural Change.

Milunsky, A., Jick, H., Jick, S.S., Bruell, C.L., Maclaughlin, D.S., Rothman, K.J and Willett, W. (1989) Multivitamin/ folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. Journal of the American Medical Association, **262** 2847-2852.

Moore, K.L and Persaud, T.V.N. (1993) The developing human: Clinically oriented embryology, 5th ed. Philadelphia, PA, Saunders, p 70-92, 251.

Moore, T., and Stokes, G.F. (1953) Gastroschisis. Surgery, **33**, 112-20.

Moore, T.C and Nur, K. (1986a) An international survey of gastroschisis and omphalocele (490 cases) II. Relative incidence, pregnancy and environmental factors. Paediatric Surgery International, **1**, 105-109.

Moore, T.C and Nur, K. (1986b) An international survey of gastroschisis and omphalocele (490 cases) I. Nature and distribution of additional malformations. Paediatric Surgery International, **1**, 46-50.

Moore, T.C. (1977) Gastroschisis and omphalocele: Clinical differences. Surgery, **82**, 561-568.

Morrow, R.J., Whittle, M.J., McNay, M.B., Raine, P.A.M., Gibson, A.A. M., and Crossley, J. (1993) Prenatal diagnosis and management of anterior abdominal wall defects in the West of Scotland. Prenatal Diagnosis, **13**, 111-115.

MRC Vitamin Study Research Group. (1991) Prevention of neural tube defects: Results of the Medical Research Council Vitamin Study. Lancet, **338**, 131-137.

Naeye, R. L. (1978a) Relationship of cigarette smoking to congenital anomalies and perinatal death: A prospective study. American Journal of Pathology. **90**, 289-293.

Naeye, R.L. (1978b) Effects of maternal cigarette smoking on the fetus and placenta. British Journal of Obstetrics and Gynaecology. **85**, 732-737.

Naeye, R.L. (1979) The duration of maternal cigarette smoking, fetal and placenta disorders. Early Human Development, **3**, 229-237.

Nash, J.E., and Persaud, T.V.N. (1988) Embryopathic risks of cigarette smoking. Experimental Pathology, **33**, 65-73.

Nelson, T.C and Toyama, W.M. (1995) Familial gastroschisis: A case of mother- and- son occurrence. Journal of Paediatric Surgery, **30**, 1706-1708.

Nicholls, E.A., Ford, W.D., Barnes, K.H., Furness, M.E., Hayward, C. (1996) A decade of gastroschisis in the era of antenatal ultrasound. Australian and New Zealand Journal of Surgery, **66**, 366-368.

Nilsen, N.O. (1986) Vascular factors in teratogenesis. Teratology, **34**, 409 (abstract).

Novotny, D.A., Klein, R.L., and Boeckman, C.R. (1993) Gastroschisis: An 18-year review. Journal of Paediatric Surgery, **28**, 650-652.

Nyberg, D.A and Mahony. (1993) Pretorius: Diagnostic ultrasound of fetal anomalies. Chapter 11, p 385-432.

Omran, M.I. (1991) Evaluation of antenatal screening for neural tube defects in Glasgow 1976-1986. Thesis submitted for the degree of Ph.D., University of Glasgow.

O'Neill, J.A., Jr., and Grosfeld, J.L. (1974) Intestinal malfunction following closure of abdominal wall defects in children. American Journal of Surgery, **127**, 129.

Paidas, M.J., Crombleholme, T.M., and Robertson, F.M. (1994) Prenatal diagnosis and management of the fetus with an abdominal wall defects. Seminars in Perinatology, **18**, 196-214.

Pampfer, S., and Streffer, C. (1988) Prenatal death and malformations after irradiation of mouse zygotes with neutrons or x-rays. Teratology, **37**, 599-607.

Paulozzi, L.J., and Milham, S. (1986) Seasonality of omphalocele in Washington State. Teratology, **33**, 133-134.

Puffinbarger, N.K., Taylor, D.V., Stevens, R.J., Tuggle, D.W., and Tunell, W.P. (1995) Gastroschisis: A birth defect seen in increasing numbers in Oklahoma? Journal Oklahoma State Medical Association, **88**, 291-294.

Randall, C.L., Salo, A.L., Becker, H.C., and Patrick, K.S. (1994) Cocaine does not influence the teratogenic effects of acute ethanol in mice. Reproductive Toxicology, **8**, 341-350.

Redford, D.H., MacNay, M.B., and Whittle, M.J. (1985) Gastroschisis and exomphalos: precise diagnosis by midpregnancy ultrasound. British Journal of Obstetrics and Gynaecology, **92**, 54-59.

Rickham P P. (1970). Exomphalocele and gastroschisis. In: Rickham P P. and Johnston, J.H. Neonatal surgery. Chapter 23. London, Butterworth, p 254-270.

Roeper, P.J., Harris, J., Lee, G., and Neutra, R. (1987) Secular rates and correlates for gastroschisis in California (1968-1977). Teratology , **35**, 203-210.

Romero, R., Pilu, G., *et al.* (1988) The abdominal wall. Prenatal diagnosis of congenital anomalies. Chapter 6. Norwalk CT Appleton and Lange, 209-232.

Salinas, C.F., Bartoshesky, L., Othersen, H.B., Leape, L., Feingold, M., and Jorgeenson, R.J. (1979) Familial occurrence of gastroschisis. American Journal of Disease of Childhood, **133** 514-517.

Sarda, P and Bard, H. (1984) Gastroschisis in a case of dizygotic twins: The possible role of maternal alcohol consumption. Paediatrics, **74**, 94-95.

Sasaki, J., Yamaguchi, A., Nabeshima, Y., Shigemitsu, S., Mesaki, N., and Kubo, T. (1995) Exercise at high temperature causes maternal hyperthermia and fetal anomalies in rats. Teratology, **51**, 233-236.

Saxen, I. (1974) Cleft lip and palate in Finland: prenatal histories, course of pregnancy and selected environmental factors. International Journal of Epidemiology, **3**, 263-270.

Scholl, T.O., Miller, L.K., Wexberg Salmon, R., Carr Cofsky, M., Shearer, J. (1987) Prenatal care adequacy and the outcome of adolescent pregnancy: Effect on weight gain, preterm delivery, and birthweight. Obstetrics and Gynaecology, **69**, 312-6.

Schuster, J.R. (1986) Omphalocele and gastroschisis. In: Welch, K.J., Randolph, J.G., Ravitch, M.M., O'Neill, J.A., Rave, M.I. (eds). Paediatric Surgery. London, Year Book Medical: p 740-763.

Seashor, J.H. (1978) Congenital Abdominal Wall Defects. Clinics in Perinatology, **5**, 61-77.

Sermer, M., Benzie, R.J., Pitson, L., Carr, M., and Skidmore, M. (1987) Prenatal diagnosis and management of congenital defects of the anterior abdominal wall. American Journal Obstetrics and Gynaecology, **156**, 308-312.

Shaw, A. (1975) The myth of gastroschisis. Journal of Paediatric Surgery, **10**, 235-244.

Sherman, N.J., Asch, M.J., Isaacs, H. Jr., and Rosenkrantz, J.G. (1973) Experimental gastroschisis in the fetal rabbit. Journal of Paediatric Surgery, **8**, 165-169.

Stone, D.H, and Dolk, H. (1994) High reported prevalence of congenital anomalies in a Scottish city. Scottish Medical Journal, **39**, 170-172.

Stone, D.H. (1986) A method for the validation of data in a register. Public Health, **100** 131-324.

Stone, D.H. (1989) The Glasgow Register of Congenital Anomalies 1972-1988: A critical review. Journal of Inherited Metabolic Disease, **12**, 4-12.

Stone, D.H., and Hamilton, F.M.W. (1986) Uses and limitations of register of congenital malformations: A case study. Public Health, **101**, 191-197.

Stringer, M.D., Brereton, R.J., Wright, V.M. (1991) Controversies in the management of gastroschisis: a study of 40 patients. Archives of Disease in Childhood, **66**, 34-36.

Strobino, D.M., Ensminger, M.E., Kim, Y.J., Nanda, J. (1995) Mechanism for maternal age differences in birth weight. American Journal of Epidemiology, **142**, 504-14.

Swartz, K.R., Harrison, M.W., Campbell, J.R., and Campbell, T.J. (1986) Long-term follow-up of patients with gastroschisis. American Journal of Surgery, 151, 546-549.

Swenson, O. (1969) Umbilical anomalies. Paediatric surgery. Edition III, vol. 1. London, Butterworth.

Tan, K.H., Kilby, M.D., Whittle, M.J., Beattie, B.R., Booth, I.W., and Botting, B.J. (1996) Congenital anterior abdominal wall defects in England and Wales 1987-1993: Retrospective analysis of OPCS data. British Medical Journal, **313**, 903-906.

Tibbocl, D., Raine, P., McNee, M., Azmy, A., Kück, P., Young, D. *et al* (1986) Development aspects of gastroschisis. Journal of Paediatric Surgery, **21**, 865-869.

Tolarova, M. (1982). Periconceptional supplementation with vitamins and folic acid to prevent recurrence of cleft lip. Lancet, **2**, 217.

Torfs, C., Curry, C., and Harris, J. (1991) Familial cases of gastroschisis in a large population-based registry. American Journal of Human Genetics, **49**, 884 A (Suppl).

Torfs, C., Curry, C., and Roeper, P. (1990) Gastroschisis. The Journal of Paediatrics, **16**, 6.

Torfs, C.P., Velie, E.M., Oechsli, F.W., Bateson, T.F., and Curry, C.J.R. (1994) A population -based study of gastroschisis: Demographic, pregnancy, and lifestyle risk factors. Teratology, **50**, 44-53.

Torfs, C.P., Katz, E.A., Bateson, T.F., Lam, P.K., Curry, C.J. (1996) Maternal medications and environmental exposures as risk factors for gastroschisis. Teratology, **54**, 84-92.

Touloukian, R. J., and Spackman, T.J. (1971) Gatrointestinal function and radiographic appearance following gastroschisis repair. Journal of Paediatric Surgery, **6**, 427.

Turner, J.R., Grindstaff, C.F., Phillips, N. (1990) Social support and outcome in teenage pregnancy. Journal of Health Social Behaviour, **31**, 43-57.

Van Allen, M.I. (1981) Fetal vascular disruption: Mechanisms and some resulting birth defect. Paediatric Annals, **10**, 31-50.

Van der Veen, F., and Fox, H (1982) The effects of cigarette smoking on human placenta: A light and electron microscopy study. Placenta, **3**, 243-256.

Van der Velde, W.J., Copius Peereboom-Stegeman, J.H.J., Treffers, P.E., and James, J. (1983) Structural changes in the placenta of smoking mothers: A quantitative study. Placenta, **4**, 231-240.

Warkany, J. (1971) Congenital malformations. Chicago, Year Book Medical Publishers.

Weatherall, J.A.C., De Wals, P and Lechat, M.F. (1984) Evaluation of information systems for the surveillance of congenital malformations. International Journal of Epidemiology, **13**, 193-196.

Werler, M.M., Mitchell, A.A., and Shapiro, S. (1992a) Demographic, reproductive, medical, environmental factors in relation to gastroschisis. Teratology, **45**, 353-360.

Werler, M.M., Mitchell, A.A., and Shapiro, S. (1992b) First trimester maternal medication use in relation to gastroschisis. Teratology, **45**, 361-367.

Wilson, J.M.G., and Jungner, G. (1968) Principles and practice of screening for disease. Geneva: World Health Organisation.

Wyburn, G.M. (1953) Congenital defects of the anterior abdominal wall. British Journal of Surgery, **40**, 553.

Yang, P., Beaty, T.H., Khoury, M.J., Chee, E., Stewart, W., and Gordis, L. (1992). Genetic-epidemiologic study of omphalocele and gastroschisis: Evidence for heterogeneity. American Journal of Medical Genetics, **44**: 668-675.

Yazbeck, S., Ndoye, M. and Khan, A.H. (1986) Omphalocele: A 25-year experience. Journal of Paediatric Surgery, **21**, 761-763.

# APPENDIX

# APPENDIX $A_1$: STUDY DATA SHEET

DATA SHEET

**General Information** — Box numbers

| | | |
|---|---|---|
| -Study number | ☐☐☐☐ | 1-4 |
| -Date of birth (day, month, year) | ☐☐☐☐☐☐ | 5-10 |
| Hospital of birth | ☐☐☐☐☐ | 11-15 |
| Sex (1=male, 2=female, 3=indeterminate, 4=notknown) | ☐ | 16 |
| -Number of babies, fetuses delivered (1=singleton, 2=twins, 3=triplets, etc., 9=not known) | ☐ | 17 |
| -Outcome of pregnancy (1=livebirth, 2=stillbirth, 3= spontaneous abortion, 4= induced abortion) | ☐ | 18 |
| -Birthweight (g) | ☐☐☐☐ | 19-22 |
| -Gestational age (completed weeks) | ☐☐ | 23 |
| -Date of death (day, month, year) | ☐☐☐☐☐☐ | 24-29 |
| -Date of discovery (day, month, year) | ☐☐☐☐☐☐ | 30-35 |
| -When discovered (1=at birth, 2=less than 1 week, 3=1-4 weeks, 4=1-12 months, 5=over 12 months, 6=pre-natal diagnosis, 7=at spontaneous or induced abortion, 8=at post mortem, 9=not known) | ☐ | 36 |
| -Gestational age at discovery (completed weeks) | ☐☐ | 37-38 |
| -Condition of fetus at discovery (1=alive, 2=dead, 3=unknown | ☐ | 39 |
| -Age of mother at delivery (years) | ☐☐ | 40-41 |
| -Age of father at delivery (years) | ☐☐ | 42-43 |
| -Racial type of mother (0=Scotish, 1=English, Welsh, 2=Irish, 3=other European, 4=other white, 5=Indian, Pakistani, 6=Asian, 7=African, 8= British, 9=other or not known) | ☐ | 44 |
| -Racial type of father (same codes and instructions as for box 44) | ☐ | 45 |

## Prenatal Diagnosis

-Amniocentesis
(1=performed (result positive), 2=performed (result unknown)
3 or 0=notknown, 4=performed, result negative, 8=failed
9=not known

☐ 46

-Ultrasound
(1=performed (result positive), 2=performed (result unknown)
3 or 0=notknown, 4=performed, result negative, 8=failed
9=not known)

☐ 47

-Other techniques
(1=performed (result positive), 2=performed (result unknown)
3 or 0=notknown, 4=performed, result negative, 8=failed
9=not known)

☐ 48

-Karyotype of infant, fetus
(1=performed (result known), 2=performed (result unknown)
3 or 0=not performed, 8=failed, 9=not known)

☐ 49

-Post-mortem examination
(1=performed (result known), 2=performed (result unknown)
3 or 0=not performed, 9=not known and 4=macerated fetus)

☐ 50

## Reproductive History

-Number of previous spontaneous abortions
(0=none, 1=one, 2=two, 3=three etc., 9=not known)

☐ 51

-Number of previous induced abortions
(0=none, 1=one, 2=two, 3=three etc., 9=not known)

☐ 52

-Number of previous livebirths
(0=none, 1=one, 2=two, 3=three etc., 9=not known)

☐ 53

-Number of previous stillbirths
(0=none, 1=one, 2=two, 3=three etc., 9=not known)

☐ 54

-Number of previous pregnancies
(0=none, 1=one, 2=two, 3=three etc., 9=not known)

☐ 55

-Association with syndrome
(coded B.P.A)

☐☐☐☐☐ 56-60

-Malformation (s) present
(coded B.P.A)

☐☐☐☐☐ 56-60
☐☐☐☐☐ 66-70
☐☐☐☐☐ 71-75
☐☐☐☐☐ 76-80
☐☐☐☐☐ 81-85
☐☐☐☐☐ 86-90
☐☐☐☐☐ 91-95
☐☐☐☐☐ 96-100

## Information on Poverty

-Post code and GGHB cluster type ☐☐☐☐☐☐☐ 101-107

-Occupation of mother
(ILO code, 999=not known) ☐☐☐☐☐ 108-112

-Occupation of father
(ILO code, 999=not known, 88999=single mother) ☐☐☐☐☐ 113-117

## Information on "risk factors"

-Illness before pregnancy
(ICD code, 0 or 2=No, 999=not known) ☐☐☐☐ 118-121

-Illness during pregnancy
(ICD code, 0 or 2=No, 999=not known) ☐☐☐☐ 122-125

-Drugs
(ICD code, 0 or 2=No, 999=not known) ☐ 126-127

-Unusual exposure
(ICD code) ☐☐☐☐ 128-131

-Smoking (yes=1, No=0, 9=not known) ☐ 132

-Number of cigarette. day ☐☐ 133-134

APPENDIX $A_2$: Maternal risk factors among omphalocele, gastroschisis and O&G compared to malformed, non-malformed, and malformed+ non-malformed controls (univariate analysis).

Maternal risk factors among 108 O&G and 108 malformed controls

| Factor | Case | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Maternal age | | | | | | |
| <20 | 17 | 15.7 | 11 | 10.2 | 2.06 | 0.83 to 5.11 |
| 20-24 | 31 | 28.7 | 32 | 29.6 | 1.29 | 0.64 to 2.61 |
| 25-29 | 33 | 30.6 | 29 | 26.9 | 1.52 | 0.75 to 3.07 |
| 30+ | 27 | 25.0 | 36 | 33.3 | R | |
| Neighbourhood Type | | | | | | |
| 1-2 | 21 | 19.4 | 23 | 21.3 | R | |
| 3-6 | 46 | 42.6 | 49 | 45.4 | 1.03 | 0.50 to 2.10 |
| 7-8 | 41 | 38.0 | 36 | 33.3 | 1.25 | 0.59 to 2.62 |
| Illness before pregnancy | | | | | | |
| Yes | 31 | 21.9 | 20 | 18.9 | 1.78 | 0.93 to 3.38 |
| No | 75 | 78.1 | 86 | 81.1 | R | |
| U/k | 2 | | 2 | | | |
| Illness during pregnancy | | | | | | |
| Yes | 24 | 22.6 | 29 | 27.1 | 0.79 | 0.42 to 1.47 |
| No | 82 | 77.4 | 78 | 72.9 | R | |
| U/K | 2 | | 1 | | | |
| Drugs | | | | | | |
| Yes | 29 | 31.2 | 31 | 29.8 | 1.07 | 0.58 to 1.96 |
| No | 64 | 68.8 | 73 | 70.2 | R | |
| U/K | 15 | | 4 | | | |
| Smoking | | | | | | |
| Yes | 50 | 51.5 | 40 | 40.8 | 1.54 | 0.88 to 2.18 |
| No | 47 | 48.5 | 58 | 59.2 | R | |
| U/k | 11 | | 10 | | | |

R= Reference

Maternal risk factors among 80 omphalocele cases and 80 malformed controls

| Factor | Case | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Maternal age | | | | | | |
| <20 | 7 | 8.75 | 8 | 10.0 | 1.03 | 0.32 to 3.27 |
| 20-24 | 24 | 30.0 | 25 | 31.3 | 1.13 | 0.51 to 2.48 |
| 25-29 | 26 | 32.5 | 20 | 25.0 | 1.53 | 0.68 to 3.41 |
| 30+ | 23 | 28.75 | 27 | 33.8 | R | |
| Neighbourhood Type | | | | | | |
| 1-2 | 18 | 22.5 | 15 | 18.75 | R | |
| 3-6 | 31 | 38.75 | 39 | 48.75 | 0.66 | 0.29 to 1.52 |
| 7-8 | 31 | 38.75 | 26 | 32.6 | 1.00 | 0.42 to 2.35 |
| Illness before pregnancy | | | | | | |
| Yes | 22 | 28.2 | 12 | 15.38 | 2.16 | 0.98 to 4.75 |
| No | 56 | 71.8 | 66 | 84.62 | R | |
| U/k | 2 | | 2 | | | |
| Illness during pregnancy | | | | | | |
| Yes | 21 | 26.9 | 22 | 27.85 | 0.95 | 0.47 to 1.92 |
| No | 57 | 73.1 | 57 | 72.15 | R | |
| U/K | 2 | | 1 | | | |
| Drugs | | | | | | |
| Yes | 19 | 28.4 | 26 | 34.21 | 0.76 | 0.37 to 1.55 |
| No | 48 | 71.6 | 50 | 65.79 | R | |
| U/K | 13 | | 4 | | | |
| Smoking | | | | | | |
| Yes | 34 | 49.3 | 30 | 41.7 | 1.36 | 0.70 to 2.64 |
| No | 35 | 50.7 | 42 | 58.3 | R | |
| U/k | 11 | | 8 | | | |

R= Reference

Maternal information on risk factors among 28 gastroschisis cases and 28 malformed controls

| Factor | Case | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Maternal age | | | | | | |
| <20 | 10 | 35.7 | 3 | 10.7 | 7.50 | 1.31 to 43.03 |
| 20-24 | 7 | 25.0 | 7 | 25.0 | 2.25 | 0.46 to 10.88 |
| 25-29 | 7 | 25.0 | 9 | 32.1 | 1.75 | 0.36 to 8.14 |
| 30+ | 4 | 14.9 | 9 | 32.2 | R | |
| Neighbourhood Type | | | | | | |
| 1-2 | 3 | 10.71 | 8 | 28.57 | R | |
| 3-6 | 15 | 53.57 | 10 | 35.71 | 4.0 | 0.85 to 18.84 |
| 7-8 | 10 | 35.71 | 10 | 35.71 | 2.67 | 0.54 to 13.08 |
| Illness before pregnancy | | | | | | |
| Yes | 9 | 32.1 | 8 | 28.6 | 1.18 | 0.38 to 3.70 |
| No | 19 | 67.9 | 20 | 71.4 | R | |
| Illness during pregnancy | | | | | | |
| Yes | 3 | 10.7 | 7 | 25.0 | 0.36 | 0.08 to 1.57 |
| No | 25 | 89.3 | 21 | 85.0 | R | |
| Drugs | | | | | | |
| Yes | 10 | 38.5 | 6 | 21.4 | 2.29 | 0.69 to 7.60 |
| No | 16 | 61.5 | 22 | 78.6 | R | |
| U/K | 2 | | | | | |
| Smoking | | | | | | |
| Yes | 16 | 57.1 | 10 | 38.46 | 2.31 | 0.72 to 6.33 |
| No | 12 | 42.9 | 16 | 61.54 | R | |
| U/k | 0 | | 2 | | | |

R= Reference

Maternal risk factors among 87 O&G and 87 non-malformed controls

| Factor | Case | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Maternal age | | | | | | |
| <20 | 12 | 13.8 | 4 | 4.6 | 3.0 | 0.83 to 10.9 |
| 20-24 | 27 | 31.0 | 29 | 33.3 | 0.93 | 0.41 to 2.10 |
| 25-29 | 28 | 32.2 | 34 | 39.1 | 0.82 | 0.37 to 1.83 |
| 30+ | 20 | 23.0 | 20 | 23.0 | R | |
| Neighbourhood Type | | | | | | |
| 1-2 | 16 | 18.4 | 16 | 18.4 | R | |
| 3-6 | 39 | 44.8 | 47 | 54.0 | 0.83 | 0.37 to 1.87 |
| 7-8 | 32 | 36.8 | 24 | 27.6 | 1.33 | 0.56 to 3.19 |
| Illness before pregnancy | | | | | | |
| Yes | 23 | 26.4 | 34 | 39.1 | 0.56 | 0.29 to 1.06 |
| No | 64 | 73.6 | 53 | 60.9 | R | |
| Illness during pregnancy | | | | | | |
| Yes | 16 | 18.4 | 11 | 12.6 | 1.56 | 0.68 to 3.58 |
| No | 71 | 81.6 | 76 | 87.4 | R | |
| Drugs | | | | | | |
| Yes | 18 | 22.2 | 37 | 42.5 | 0.39 | 0.20 to 0.76 |
| No | 63 | 77.8 | 50 | 57.5 | R | |
| U/K | 6 | | | | | |
| Smoking | | | | | | |
| Yes | 41 | 51.9 | 26 | 29.9 | 2.53 | 1.34 to 4.79 |
| No | 38 | 48.1 | 61 | 70.1 | R | |
| U/K | 8 | | | | | |

R= Reference

Maternal risk factors among 61 omphalocele cases and 61 non-malformed controls

| Factor | Cases | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Maternal age | | | | | | |
| <20 | 3 | 4.9 | 4 | 6.6 | 0.66 | 0.12 to 3.45 |
| 20-24 | 21 | 34.4 | 21 | 34.4 | 0.87 | 0.34 to 2.24 |
| 25-29 | 21 | 34.4 | 22 | 36.1 | 0.83 | 0.33 to 2.12 |
| 30+ | 16 | 26.2 | 14 | 23.0 | R | |
| Neighbourhood Type | | | | | | |
| 1-2 | 13 | 21.3 | 13 | 21.31 | R | |
| 3-6 | 26 | 42.6 | 30 | 49.18 | 0.87 | 0.34 to 2.20 |
| 7-8 | 22 | 36.1 | 18 | 29.51 | 1.22 | 0.45 to 3.29 |
| Illness before pregnancy | | | | | | |
| Yes | 15 | 24.6 | 27 | 44.3 | 0.41 | 0.19 to 0.89 |
| No | 46 | 75.4 | 34 | 55.7 | R | |
| Illness during pregnancy | | | | | | |
| Yes | 13 | 21.3 | 10 | 16.4 | 1.38 | 0.55 to 3.44 |
| No | 48 | 78.7 | 51 | 83.6 | R | |
| Drugs | | | | | | |
| Yes | 10 | 17.5 | 30 | 49.2 | 0.22 | 0.09 to 0.51 |
| No | 47 | 82.5 | 31 | 50.8 | R | |
| U/K | 4 | | | | | |
| Smoking | | | | | | |
| Yes | 25 | 47.2 | 19 | 31.1 | 1.97 | 0.92 to 4.24 |
| No | 28 | 52.8 | 42 | 68.9 | R | |
| U/k | 8 | | | | | |

R= Reference

Maternal risk factors among 26 gastroschisis cases and 26 non-malformed controls

| Factor | Case | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Maternal age[1] | | | | | | |
| <20 | 9 | 34.6 | 0.0 | 0.0 | | |
| 20-24 | 6 | 23.1 | 8 | 30.8 | | ---------- |
| 25-29 | 7 | 26.9 | 12 | 46.2 | | |
| 30+ | 4 | 15.4 | 6 | 23.1 | | |
| Maternal age | | | | | | |
| <24 | 15 | 57.7 | 8 | 30.8 | 2.81 | 0.61 to 12.97 |
| 25-29 | 7 | 26.9 | 12 | 46.2 | | |
| 30+ | 4 | 15.4 | 6 | 23.1 | R | |
| Neighbourhood Type | | | | | | |
| 1-2 | 3 | 11.5 | 3 | 11.5 | R | |
| 3-6 | 13 | 50.0 | 17 | 65.4 | 0.76 | 0.13 to 4.42 |
| 7-8 | 10 | 38.5 | 6 | 23.1 | 1.66 | 0.25 to 11.07 |
| Illness before pregnancy | | | | | | |
| Yes | 8 | 30.8 | 7 | 26.9 | 1.21 | 0.36 to 4.01 |
| No | 18 | 69.2 | 19 | 73.1 | R | |
| Illness during pregnancy | | | | | | |
| Yes | 3 | 11.5 | 1 | 3.8 | 3.26 | 0.32 to 33.61 |
| No | 23 | 88.5 | 25 | 96.2 | R | |
| Drugs | | | | | | |
| Yes | 8 | 33.3 | 7 | 26.9 | 1.36 | 0.40 to 4.56 |
| No | 16 | 66.7 | 19 | 73.1 | R | |
| U/K | 2 | | | | | |
| Smoking | | | | | | |
| Yes | 16 | 61.5 | 7 | 26.9 | 4.34 | 1.34 to 14.03 |
| No | 10 | 38.5 | 19 | 73.1 | R | |

R= Reference

[1] Among non-malformed controls were not any mothers under 20 years old.

Maternal risk factors among 87 O&G and 174 non-malformed+malformed controls

| Factor | Cases | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Maternal age | | | | | | |
| <20 | 12 | 13.8 | 13 | 7.5 | 2.26 | 0.88 to 5.80 |
| 20-24 | 27 | 31.0 | 56 | 32.2 | 1.18 | 0.59 to 2.36 |
| 25-29 | 28 | 32.2 | 56 | 32.2 | 1.22 | 0.61 to 2.44 |
| 30+ | 20 | 23.0 | 49 | 28.2 | R | |
| Neighbourhood Type | | | | | | |
| 1-2 | 16 | 18.4 | 34 | 19.5 | R | |
| 3-6 | 39 | 44.8 | 86 | 49.4 | 0.96 | 0.78 to 1.95 |
| 7-8 | 32 | 36.8 | 54 | 31.0 | 1.26 | 0.60 to 2.63 |
| Illness before pregnancy | | | | | | |
| Yes | 23 | 26.4 | 50 | 28.9 | 0.88 | 0.50 to 1.58 |
| No | 64 | 73.6 | 123 | 71.1 | R | |
| U/K | | | 1 | | | |
| Illness during pregnancy | | | | | | |
| Yes | 16 | 18.4 | 32 | 18.5 | 0.99 | 0.51 to 1.93 |
| No | 71 | 81.6 | 141 | 81.5 | R | |
| U/K | | | 1 | | | |
| Drugs | | | | | | |
| Yes | 18 | 22.2 | 54 | 31.4 | 0.62 | 0.34 to 1.15 |
| No | 63 | 77.8 | 118 | 68.6 | R | |
| U/K | 6 | | 2 | | | |
| Smoking | | | | | | |
| Yes | 41 | 51.9 | 59 | 34.9 | 2.01 | 1.17 to 3.46 |
| No | 38 | 48.1 | 110 | 65.1 | R | |
| U/K | 8 | | 5 | | | |

R= Reference

Maternal risk factors among 61 omphalocele cases and 122 non-malformed +malformed controls

| Factor | Case | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Maternal age | | | | | | |
| <20 | 3 | 4.9 | 10 | 8.2 | R | |
| 20-24 | 21 | 34.4 | 42 | 34.4 | 1.67 | 0.41 to 6.71 |
| 25-29 | 21 | 34.4 | 35 | 28.7 | 2.0 | 0.49 to 8.10 |
| 30+ | 16 | 26.2 | 35 | 19.1 | 1.52 | 0.37 to 6.30 |
| Neighbourhood Type | | | | | | |
| 1-2 | 13 | 21.3 | 24 | 19.7 | R | |
| 3-6 | 26 | 42.6 | 59 | 48.4 | 0.81 | 0.36 to 1.84 |
| 7-8 | 22 | 36.1 | 39 | 32.0 | 1.04 | 0.44 to 2.44 |
| Illness before pregnancy | | | | | | |
| Yes | 15 | 24.6 | 35 | 28.9 | 0.80 | 0.40 to 1.62 |
| No | 46 | 75.4 | 86 | 71.1 | R | |
| U/K | | | 1 | | | |
| Illness during pregnancy | | | | | | |
| Yes | 13 | 21.3 | 24 | 19.8 | 1.09 | 0.51 to 2.34 |
| No | 48 | 78.7 | 97 | 80.2 | R | |
| U/K | | | 1 | | | |
| Drugs | | | | | | |
| Yes | 10 | 17.5 | 43 | 35.8 | 0.38 | 0.17 to 0.83 |
| No | 47 | 82.5 | 77 | 64.2 | R | |
| U/K | 4 | | 2 | | | |
| Smoking | | | | | | |
| Yes | 25 | 47.2 | 43 | 36.1 | 1.59 | 0.81 to 3.04 |
| No | 28 | 52.8 | 76 | 63.1 | R | |
| U/K | 8 | | 3 | | | |

R= Reference

Maternal risk factors among 26 gastroschisis cases and 52 non-malformed + malformed controls

| Factor | | | | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Maternal age | | | | | | |
| <20 | 9 | 34.6 | 3 | 5.8 | 10.0 | 1.89 to 58.36 |
| 20-24 | 6 | 23.1 | 14 | 26.9 | 1.50 | 0.35 to 6.50 |
| 25-29 | 7 | 26.9 | 21 | 40.4 | 1.17 | 0.29 to 4.74 |
| 30+ | 4 | 15.4 | 14 | 26.9 | R | |
| Neighbourhood Type | | | | | | |
| 1-2 | 3 | 11.5 | 10 | 19.2 | R | |
| 3-6 | 13 | 50.0 | 27 | 51.9 | 1.60 | 0.38 to 6.84 |
| 7-8 | 10 | 38.5 | 15 | 28.8 | 2.22 | 0.49 to 10.14 |
| Illness before pregnancy | | | | | | |
| Yes | 8 | 30.8 | 15 | 28.8 | 1.10 | 0.39 to 3.06 |
| No | 18 | 69.2 | 37 | 71.2 | R | |
| Illness during pregnancy | | | | | | |
| Yes | 3 | 11.5 | 8 | 15.4 | 0.72 | 0.17 to 2.97 |
| No | 23 | 88.5 | 44 | 84.6 | R | |
| Drugs | | | | | | |
| Yes | 8 | 33.3 | 11 | 21.2 | 1.86 | 0.63 to 5.48 |
| No | 16 | 66.7 | 41 | 78.8 | R | |
| U/K | 2 | | | | | |
| Smoking | | | | | | |
| Yes | 16 | 61.5 | 16 | 32.0 | 3.40 | 1.27 to 9.14 |
| No | 10 | 38.5 | 34 | 68.0 | R | |
| U/K | | | 2 | | | |

R= Reference

APPENDIX $A_3$: Maternal reproductive factors among omphalocele, gastroschisis and O&G compared to malformed, non-malformed, and malformed+ non-malformed controls (univariate analysis).

Maternal reproductive factors among 87 O&G cases and 87 non-malformed controls

| Factor | Cases | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Total pregnancy | | | | | | |
| 0 | 36 | 41.4 | 26 | 29.9 | 1.96 | 0.80 to 4.80 |
| 1 | 23 | 26.4 | 21 | 24.1 | 1.55 | 0.60 to 4.0 |
| 2 | 16 | 18.4 | 23 | 26.4 | 0.99 | 0.37 to 2.62 |
| 3 | 12 | 13.8 | 17 | 19.5 | R | |
| Parity | | | | | | |
| 0 | 50 | 57.5 | 32 | 36.8 | 2.81 | 0.86 to 9.15 |
| 1 | 18 | 20.7 | 28 | 32.2 | 1.16 | 0.33 to 4.01 |
| 2 | 14 | 16.1 | 18 | 20.7 | 1.40 | 0.38 to 5.12 |
| 3 | 5 | 2.9 | 9 | 10.3 | R | |
| History of spontaneous abortion | | | | | | |
| Yes | 21 | 24.1 | 21 | 24.1 | - | ---------- |
| No | 66 | 75.9 | 66 | 75.9 | | |
| History of spontaneous abortion* | | | | | | |
| 0 | 66 | 75.9 | 66 | 75.9 | R | |
| 1 | 17 | 19.5 | 16 | 18.4 | 1.03 | 0.50 to 2.28 |
| 1+ | 4 | 4.6 | 5 | 5.7 | 0.80 | 0.21 to 3.11 |
| History of induced abortion | | | | | | |
| Yes | 8 | 9.2 | 6 | 6.8 | 1.37 | 0.45 to 4.12 |
| No | 79 | 90.8 | 81 | 93.1 | R | |
| History of stillbirth | | | | | | |
| Yes | 1 | 1.1 | 2 | 2.3 | 0.49 | 0.04 to 5.55 |
| No | 86 | 98.9 | 85 | 97.7 | R | |

R= Reference

Maternal reproductive factors among 61 omphalocele cases and 61 non- malformed controls

| Factor | Cases | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Total pregnancy | | | | | | |
| 0 | 20 | 32.8 | 19 | 31.1 | 1.52 | 0.53 to 4.37 |
| 1 | 18 | 29.5 | 11 | 18.0 | 2.36 | 0.76 to 7.34 |
| 2 | 14 | 23.0 | 18 | 29.5 | 1.12 | 0.37 to 3.37 |
| 3 | 9 | 14.7 | 13 | 21.31 | R | |
| Parity | | | | | | |
| 0 | 32 | 52.5 | 24 | 39.3 | 1.60 | 0.44 to 5.87 |
| 1 | 12 | 19.7 | 17 | 27.9 | 0.85 | 0.21 to 3.43 |
| 2 | 12 | 19.7 | 14 | 23.0 | 1.03 | 0.25 to 4.23 |
| 3 | 5 | 8.2 | 6 | 9.84 | R | |
| History of spontaneous abortion | | | | | | |
| Yes | 17 | 27.8 | 16 | 8.02 | 1.09 | 0.49 to 2.42 |
| No | 44 | 72.1 | 45 | 73.8 | R | |
| History of spontaneous abortion* | | | | | | |
| 0 | 44 | 72.1 | 45 | 73.8 | R | |
| 1 | 15 | 24.6 | 12 | 19.7 | 1.24 | 0.54 to 3.04 |
| 1+ | 2 | 3.2 | 4 | 6.5 | 0.51 | 0.09 to 2.93 |
| History of induced abortion | | | | | | |
| Yes | 5 | 8.2 | 5 | 8.2 | - | |
| No | 56 | 91.8 | 56 | 91.8 | | |
| History of stillbirth | | | | | | |
| Yes | 1 | 1.5 | 1 | 1.6 | ---- | ---------- |
| No | 60 | 98.4 | 60 | 98.4 | | |

R= Reference

Maternal reproductive factors among 26 gastroschisis cases and 26 non- malformed controls

| Factor | Cases | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Total pregnancy | | | | | | |
| 0 | 16 | 61.5 | 7 | 26.9 | 3.05 | 0.53 to 17.37 |
| 1 | 5 | 19.2 | 10 | 38.5 | 0.67 | 0.11 to 4.21 |
| 2 | 2 | 7.7 | 5 | 19.2 | 0.53 | 0.06 to 4.91 |
| ≥3 | 3 | 11.5 | 4 | 15.38 | R | |
| Parity | | | | | | |
| 0 | 18 | 69.2 | 8 | 30.8 | R | 1.56 to 16.44 |
| ≥1 | 8 | 30.8 | 18 | 69.2 | 5.06 | |
| History of spontaneous abortion | | | | | | |
| Yes | 4 | 15.4 | 5 | 19.23 | 0.76 | 0.18 to 3.24 |
| No | 22 | 84.6 | 21 | 80.77 | R | |
| History of spontaneous abortion* | | | | | | |
| 0 | 22 | 84.6 | 21 | 80.8 | R | |
| 1 | 2 | 7.7 | 4 | 15.4 | 0.48 | 0.09 to 2.89 |
| 1+ | 2 | 7.7 | 1 | 3.8 | 1.91 | 0.16 to 22.66 |
| History of induced abortion | | | | | | |
| Yes | 3 | 11.5 | 1 | 3.8 | 3.26 | 0.32 to 33.61 |
| No | 23 | 88.5 | 25 | 96.2 | R | |

R= Reference

Maternal reproductive factors among 87 O&G cases and 174 malformed + non-malformed controls

| Factor | Cases | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Total pregnancy | | | | | | |
| 0 | 36 | 41.4 | 63 | 36.2 | 1.52 | 0.70 to 3.32 |
| 1 | 23 | 26.4 | 43 | 24.7 | 1.43 | 0.62 to 3.29 |
| 2 | 16 | 18.4 | 36 | 20.7 | 1.19 | 0.49 to 2.88 |
| 3 | 12 | 13.8 | 32 | 18.4 | R | |
| Parity | | | | | | |
| 0 | 50 | 57.5 | 74 | 42.5 | 2.16 | 0.74 to 6.28 |
| 1 | 18 | 20.7 | 52 | 29.9 | 1.1 | 0.35 to 3.46 |
| 2 | 14 | 16.1 | 32 | 18.4 | 1.40 | 0.43 to 4.58 |
| 3 | 5 | 5.7 | 16 | 9.2 | R | |
| History of spontaneous abortion | | | | | | |
| Yes | 21 | 24.1 | 38 | 21.8 | 1.14 | 0.62 to 2.09 |
| No | 66 | 75.9 | 136 | 78.2 | R | |
| History of spontaneous abortion* | | | | | | |
| 0 | 66 | 75.9 | 136 | 78.2 | R | |
| 1 | 17 | 19.5 | 26 | 14.9 | 1.35 | 0.68 to 2.66 |
| 1+ | 4 | 4.5 | 12 | 6.9 | 0.69 | 0.21 to 2.21 |
| History of induced abortion | | | | | | |
| Yes | 8 | 9.2 | 13 | 7.5 | 1.25 | 0.50 to 3.15 |
| No | 79 | 90.8 | 161 | 92.5 | R | |
| History of stillbirth | | | | | | |
| Yes | 1 | 1.1 | 3 | 1.7 | 0.66 | 0.07 to 6.47 |
| No | 86 | 98.9 | 171 | 98.3 | R | |

R= Reference

Maternal reproductive factors among 61 omphalocele cases and 122 malformed + nonmalformed controls

| Factor | Cases | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Total pregnancy | | | | | | |
| 0 | 20 | 32.8 | 44 | 36.1 | 1.41 | 0.56 to 3.54 |
| 1 | 18 | 29.5 | 23 | 18.9 | 2.43 | 0.92 to 6.43 |
| 2 | 14 | 23.0114 | 29 | 23.8 | 1.50 | 0.56 to 4.02 |
| 3 | 9 | .7 | 28 | 22.9 | R | |
| Parity | | | | | | |
| 0 | 32 | 52.5 | 53 | 43.4 | 1.57 | 0.51 to 4.81 |
| 1 | 12 | 19.7 | 30 | 24.6 | 1.04 | 0.30 to 3.56 |
| 2 | 12 | 19.7 | 26 | 21.3 | 1.2 | 0.35 to 4.14 |
| 3 | 5 | 8.2 | 13 | 10.6 | R | |
| History of spontaneous abortion | | | | | | |
| Yes | 17 | 27.9 | 30 | 24.6 | 1.18 | 0.59 to 2.37 |
| No | 44 | 72.1 | 92 | 75.4 | R | |
| History of spontaneous abortion* | | | | | | |
| 0 | 44 | 72.1 | 92 | 75.4 | R | |
| 1 | 15 | 24.6 | 21 | 17.2 | 1.49 | 0.70 to 3.17 |
| 1+ | 2 | 3.2 | 9 | 7.4 | 0.46 | 0.10 to 2.24 |
| History of induced abortion | | | | | | |
| Yes | 5 | 8.2 | 11 | 9.0 | 0.90 | 0.30 to 2.72 |
| No | 56 | 91.8 | 111 | 91.0 | R | |
| History of stillbirth | | | | | | |
| Yes | 1 | 1.6 | 2 | 1.6 | 1.0 | 0.09 to 11.25 |
| No | 60 | 98.4 | 120 | 98.4 | R | |

R= Reference

Maternal reproductive factors among 26 gastroschisis cases and 52 malformed +nonmalformed controls

| Factor | Cases | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Total pregnancy | 16 | 61.5 | 19 | 36.5 | 2.19 | 0.64 to 7.47 |
| 0 | 5 | 19.2 | 20 | 38.5 | 0.65 | 0.16 to 2.70 |
| 1 | 5 | 19.2 | 13 | 25.0 | R | |
| 2 | | | | | | |
| Parity | | | | | | |
| 0 | 18 | 69.2 | 21 | 40.4 | 3.32 | 1.22 to 9.03 |
| >1 | 8 | 30.8 | 31 | 59.6 | R | |
| History of spontaneous abortion | | | | | | |
| Yes | 4 | 15.4 | 8 | 15.4 | 1.0 | 0.27 to 3.39 |
| No | 22 | 84.6 | 44 | 84.6 | R | |
| History of spontaneous abortion* | | | | | | |
| 0 | 22 | 84.6 | 44 | 84.6 | R | |
| 1 | 2 | 7.7 | 5 | 9.6 | 0.80 | 0.14 to 4.46 |
| 1+ | 2 | 7.7 | 3 | 5.8 | 1.33 | 0.21 to 8.57 |
| History of induced abortion | | | | | | |
| Yes | 3 | 11.5 | 2 | 3.8 | 3.26 | 0.51 to 20.87 |
| No | 23 | 88.5 | 50 | 96.2 | R | |

R= Reference

Maternal reproductive factors among 108 O&G cases and 108 malformed controls

| Factor | Cases | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Total pregnancy | | | | | | |
| 0 | 42 | 39.3 | 46 | 42.6 | R | |
| 1 | 32 | 29.9 | 26 | 24.1 | 1.35 | 0.69 to 2.62 |
| 2 | 19 | 17.8 | 19 | 17.6 | 1.10 | 0.51 to 2.34 |
| 3 | 10 | 9.3 | 8 | 7.4 | 1.37 | 0.49 to 3.79 |
| 3+ | 4 | 3.7 | 9 | 8.3 | 0.49 | 0.14 to 1.70 |
| U/K | 1 | | | | | |
| Parity | | | | | | |
| 0 | 60 | 56.1 | 52 | 48.1 | 1.54 | 0.50 to 4.72 |
| 1 | 24 | 22.4 | 29 | 26.9 | 1.10 | 0.34 to 3.62 |
| 2 | 17 | 15.9 | 19 | 17.6 | 1.19 | 0.34 to 4.14 |
| 3 | 6 | 5.6 | 8 | 7.4 | R | |
| U/K | 1 | | | | | |
| Historyof spontaneous abortion | | | | | | |
| Yes | 26 | 24.3 | 20 | 18.5 | 1.41 | 0.73 to 2.72 |
| No | 81 | 75.7 | 88 | 81.5 | R | |
| U/K | 1 | | | | | |
| History of spontaneous abortion* | | | | | | |
| 0 | 81 | 75.7 | 88 | 81.5 | R | |
| 1 | 22 | 20.6 | 13 | 12.0 | 1.84 | 0.87 to 3.89 |
| 1+ | 4 | 3.7 | 7 | 6.5 | 0.62 | 0.17 to 2.20 |
| U/K | 1 | | | | | |
| History of induced abortion | | | | | | |
| Yes | 9 | 8.3 | 9 | 8.3 | 1.0 | 0.38 to 2.65 |
| No | 98 | 90.7 | 99 | 91.7 | R | |
| U/K | 1 | | | | | |
| History of stillbirth | | | | | | |
| Yes | 3 | 2.8 | 1 | 0.9 | 3.09 | 0.32 to 30.15 |
| No | 104 | 97.2 | 107 | 99.1 | R | |
| U/K | 1 | | | | | |

R= Reference

Maternal reproductive factors among 80 omphalocele cases and 80 malformed controls

| Factor | Cases | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Total pregnancy | | | | | | |
| 0 | 25 | 31.6 | 33 | 41.3 | R | |
| 1 | 26 | 32.9 | 16 | 20.0 | 2.14 | 0.95 to 4.83 |
| 2 | 17 | 21.5 | 17 | 21.3 | 1.32 | 0.56 to 3.09 |
| 3 | 11 | 13.9 | 14 | 17.5 | 1.04 | 0.40 to 2.67 |
| U/K | 1 | | | | | |
| Parity | | | | | | |
| 0 | 40 | 50.63 | 38 | 47.5 | 1.40 | 0.44 to 4.42 |
| 1 | 18 | 22.78 | 18 | 22.5 | 1.33 | 0.38 to 4.62 |
| 2 | 15 | 19.00 | 16 | 20.0 | 1.25 | 0.35 to 4.46 |
| 3 | 6 | 7.59 | 8 | 10.0 | R | |
| U/K | 1 | | | | | |
| History of spontaneous abortion | | | | | | |
| Yes | 21 | 26.6 | 17 | 21.8 | 1.34 | 0.64 to 2.79 |
| No | 58 | 73.4 | 63 | 78.8 | R | |
| History of spontaneous abortion* | | | | | | |
| 0 | 58 | 82.9 | 63 | 78.8 | R | |
| 1 | 19 | 24.1 | 12 | 15.0 | 1.72 | 0.77 to 3.85 |
| 1+ | 2 | 2.5 | 5 | 6.8 | 0.43 | 0.08 to 2.33 |
| U/K | 1 | | | | | |
| History of induced abortion | | | | | | |
| Yes | 6 | 7.6 | 7 | 8.8 | 0.89 | 0.27 to 2.67 |
| No | 73 | 92.4 | 73 | 91.2 | R | |
| U/K | 1 | | | | | |
| History of stillbirth | | | | | | |
| Yes | 3 | 3.8 | 1 | 1.3 | 3.12 | 0.32 to 30.64 |
| No | 76 | 96.2 | 79 | 98.8 | R | |
| U/K | 1 | | | | | |

R= Reference

Maternal reproductive factors among 28 gastroschisis cases and 28 malformed controls

| Factor | Cases | | Control | | Univariate analysis | |
|---|---|---|---|---|---|---|
| | No | % | No | % | Crude | Odds ratio (95% CI) |
| Total pregnancy | | | | | | |
| 0 | 17 | 60.7 | 13 | 46.4 | 1.31 | 0.22 to 7.57 |
| 1 | 6 | 21.4 | 10 | 35.7 | 0.60 | 0.09 to 3.99 |
| 2 | 2 | 7.1 | 2 | 7.1 | 1.0 | 0.08 to 12.56 |
| 3 | 3 | 10.71 | 3 | 10.71 | R | |
| Parity | | | | | | |
| 0 | 20 | 71.43 | 14 | 50.0 | 2.5 | 0.83 to 7.55 |
| ≥1 | 8 | 28.57 | 14 | 50.0 | R | |
| History of spontaneous abortion | | | | | | |
| Yes | 5 | 17.9 | 3 | 1.07 | 1.81 | 0.39 to 8.44 |
| No | 23 | 82.1 | 25 | 89.28 | R | |
| History of spontaneous abortion* | | | | | | |
| 0 | 23 | 82.1 | 25 | 89.28 | R | |
| 1 | 3 | 10.7 | 1 | 3.67 | 3.26 | 0.32 to 33.61 |
| 1+ | 2 | 7.1 | 2 | 7.14 | 1.09 | 0.14 to 8.36 |
| History of induced abortion | | | | | | |
| Yes | 3 | 10.7 | 2 | 7.2 | 1.56 | 0.24 to 10.14 |
| No | 25 | 89.3 | 26 | 92.9 | R | |
| History of stillbirth | | | ---- | ----- | --- | ---------- |
| Yes | 0 | 0.0 | | | | |
| No | 28 | 100 | | | | |

R= Reference

# APPENDIX $A_4$: RANGE OF SAMPLE SIZE

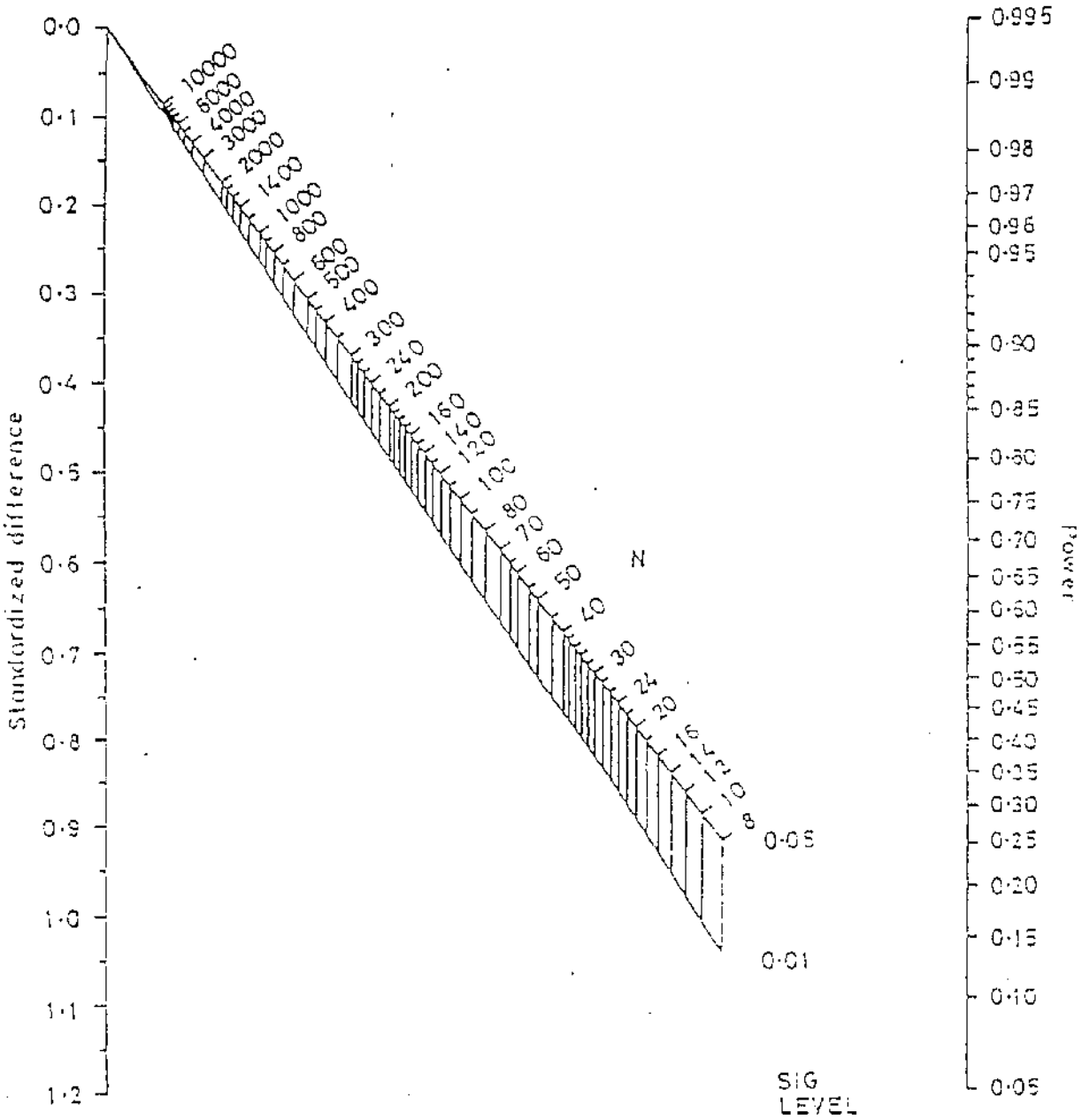


FIG 2—Nomogram for a two-sample comparison of a continuous variable, relating power, total study size, the standardised difference, and significance level.

From D.G. Altman, "How Large a Sample?"
B.M.J. 281, 1336-1338 (1980).