Pediatr Surg Int (2010) 26:871–878
DOI 10.1007/s00383-010-2679-1

REVIEW ARTICLE

Gastroschisis: an update

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Accepted: 21 July 2010 / Published online: 5 August 2010

Abstract Gastroschisis (GS) continues to increase in frequency, with several studies now reported an incidence of between 4 and 5 per 10,000 live births. The main risk factor would seem to be young maternal age, and it is in this group that the greatest increase has occurred. Whilst various geographical regions confer a higher risk, the impact of several other putative risk factors, including smoking and illicit drug use, may be less important than when first identified in early epidemiological studies. Over 90% of cases of GS will now be diagnosed on antenatal ultrasound, but its value in determining the need for early delivery remains unclear. There would appear no clear evidence for either routine early delivery or elective caesarean section for infants with antenatally diagnosed GS. Delivery at a centre with paediatric surgical facilities reduces the risk of subsequent morbidity and should represent the standard of care. The relative roles of primary closure, staged closure and ward reduction, with or without general anaesthesia, appear less clear with considerable variation between centres in both the use of these techniques and subsequent surgical outcomes. Survival rates continue to improve, with rates well in excess of 90% now routine. The limited long-term developmental data available would suggest that normal or near-normal outcomes may be expected although there remains a need for further studies.

Keywords Gastroschisis · Incidence · Risk factors · Antenatal diagnosis · Treatment strategies · Neurodevelopmental outcomes

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Introduction

The term gastroschisis (GS) derives from the Greek for stomach cleft or fissure, leading others to suggest the technically more correct term of laparoschisis [1]. It appears to have been used in the English language literature by Calder in 1733, but the first case may have been described as early as 1557 by Lycosthenes [2]. Typically reviewed in conjunction with other abdominal wall defects (AWD), including exomphalos (EXO) or omphalocoele and Prune Belly syndrome, GS remains uniquely different in its aetiology, predisposing risk factors, clinical management and associated malformations [3–7]. Whereas GS differs from other AWD in that the bowel has prolapsed without a covering through a defect adjacent to (and nearly always to the right of) an otherwise normal umbilicus, there remain rare cases that escape ready classification or in which similarities between EXO and GS exist [8–11]. Without doubt, however, the incidence of this important congenital AWD has increased dramatically over the last century: the case reports of the 1940s and 1950s have given way to large series in the 1980s and 1990s [1, 2, 4, 5, 12]. In parallel with this increase, there have been occasionally controversial innovations in both the surgical approach to management of these infants and increasing application of novel forms of silo to facilitate staged reduction of the abdominal viscera [13, 14]. Whilst these have impacted on

immediate outcomes, there remains limited data on the long-term outlook for these infants in relation to gastrointestinal function, cardiopulmonary and neurodevelopmental outcomes [15, 16].

Incidence

In 1963, Moore [17], whilst describing a single case of GS in the United States of America (USA), identified further 31 cases reported in the literature between 1943 and 1962. Subsequently, Mann et al. [18] reviewed infants with AWD delivered in the West of Scotland between 1978 and 1981. They identified an incidence of AWD of one in 3,659 live births over this 4-year period, with GS accounting for just 18% of cases. In contrast, Lafferty et al. [19] assessed the outcome of infants between 1981 and 1986 with AWD referred to a regional centre in the South West of England. They found that GS now represented 56% of cases, supporting another review by Moore [19, 20] which had already suggested a rising incidence of GS in the USA.

A detailed review of the incidence of both GS and EXO reported to the National Congenital Malformation Notification Scheme in England and Wales between 1987 and 1993 found a doubling in the incidence of GS over the first 5 years of the study, with the highest incidence of 1.35 per 10,000 births in 1991 [21]. Interestingly, the authors observed a geographical gradient in the frequency of AWD, both GS and EXO occurring more frequently in the North of England but with other clusters also identified in the United Kingdom (UK) [21–24].

This increase in incidence has continued and clearly cannot be solely explained by a fall in the rate of terminations for GS over time [21]. Rankin et al. [22] investigated the prevalence of GS in the North of England between 1986 and 1996, and reported this as rising to 4.72 per 10,000 births in 1996. A similar study in North Carolina, USA, identified a peak prevalence of 4.49 per 10,000 births in 2000 [25]. One European study identified a near fourfold increase, irrespective of maternal age, in the risk of GS over time from 1980–1984 to 1995–2002 [24]. Geographical variation was again noted, with a peak of 4.48 per 10,000 live births in Mainz, Germany compared with 0.31 in Tuscany, Italy [24]. Generally the incidence was higher in Northern European countries compared to those bordering the Mediterranean [24].

Aetiology

Whilst there remains considerable speculation about the reasons for the changing incidence of GS compared to EXO, the most recognised risk factors remains young maternal age [1, 21, 22, 26–28]. Loane et al. [24] found a sevenfold increase in the relative risk of GS in mothers under 20 years of age compared to other age groups. The contribution of young maternal age has been linked to a number of potential cofactors, including cigarette smoking, use of recreational drugs, low socio-economic status, poor nutritional status, young age at time of first pregnancy and previous terminations [1, 3, 29–33]. Part of the complexity in unravelling the relative risk factors remains the bias inherent in any study attempting to retrospectively correlate peri-conceptual diet and behavioural factors, including exposure to putative environmental hazards and toxins, with a subsequently identified congenital abnormality. In addition, different risk factors may exert a greater influence in a specific subgroup; thus, smoking, for example, appears to be more important predisposing factor in mothers over 25 years of age [34].

Although previous studies have identified links between GS and use of vasoactive medications and recreational drugs, more recent data suggest that the relative contributions of these agents appears low [34, 35]. Other environmental factors, including toxins such as hydrogen sulphide and benzene, have been suggested to explain specific local clusters in the incidence of GS [24, 36]. Perhaps of more interest, despite the relatively low incidence of associated anomalies in infants with GS, appears increasing evidence for a genetic contribution with the recent identification of specific homozygous gene polymorphisms [32]. Familial cases of birth defects have been reported in <4% of cases, and there is an increased prevalence of dizygotic twinning [37].

Increasing evidence, from twin studies, animal models and epidemiological data, suggests that GS represents a true malformation rather than a disruption which has occurred following normal development [26, 38]. Feldkamp et al. [26], having discredited traditional explanations, suggest that GS may result from herniation of the bowel into the amniotic cavity through a lateral ventral wall defect resulting from a failure in development of a body wall fold. The classical right-sided location of the defect may be explained by the relative positions of the yolk sac and umbilical stalks, with the former generally to the right, supporting their hypothesis [4, 5, 26]. Perhaps of more importance clinically, however, remains the implication that the development of the GS malformation occurs very early in gestation, between the third and fifth post-conceptual weeks [26]. Many women at this time, especially a young primigravida, would be unaware of their pregnancy with limited or no opportunity for optimal pre- and peri-conceptual care [26, 31, 33].

Antenatal diagnosis

Over the last few decades there have been considerable improvements in the antenatal detection of GS, enabling

appropriate perinatal counselling [39–41]. Antenatal diagnosis is important for planning transfer of the mother to a tertiary perinatal centre for delivery, preferably one co-located with a paediatric surgical unit [39, 40]. In 2005, a population-based study reported antenatal diagnosis rates of over 90% [42]. This was in keeping with a study from NSW which demonstrated that between 2001 and 2004 the rate of delivery at co-located hospitals was 88% for gastroschisis [43]. More recently, two studies have suggested that more than 97% of isolated cases of GS are now being detected prenatally [44, 45]. It is unclear, however, whether antenatal diagnosis improves actual neonatal outcome, and a study by Murphy et al. [39] found no impact of antenatal diagnosis on the outcome of neonates with AWD.

An elevated maternal serum α-fetoprotein (MSAFP), the foetal analogue of albumin, has been found to be suggestive of GS [46]. This test was originally designed to detect neural tube defects and chromosomal abnormalities, but remains markedly elevated with GS and other AWD. In general, however, it is now only measured in women who, having missed first semester screening, undergo second trimester MSAFP [46].

More typically GS will now be diagnosed on routine prenatal ultrasound (US), in some cases as early as 10 weeks' gestation [47]. Multiple, round, thick-walled, anechoic tubular structures lying external to the anterior abdominal wall are seen with no covering sac [48]. Echogenic areas inside the bowel lumen represent meconium. Intrauterine growth restriction, often associated with GS, may be accompanied by oligo or anhydramnios [47, 49, 50].

Antenatal care

The diagnosis of a foetus with GS necessitates increased prenatal surveillance and delivery in a co-located tertiary obstetric hospital. Whilst many centres around the world are now reporting that the incidence of GS is highest in younger mothers [1, 28, 44, 50, 51], an Australian study found the incidence to be even higher in indigenous mothers [52]. Teenage mothers in general experience poorer pregnancy outcomes due both to socioeconomic hardship and biologic immaturity [24].

Whereas exact protocols vary, all concur that serial US and other assessments of foetal well-being remain indicated in view of the increased risk of intrauterine growth restriction (IUGR), stillbirth and premature delivery [3, 47, 53]. A Western Australian study of 122 cases of GS over a 22-year period recommended instigating a uniform antepartum approach to treatment comprising: serial US evaluation, amniotic fluid volume assessment from initial diagnosis and electronic foetal heart rate monitoring biweekly from 32 weeks gestation [50]. Towers et al. [54] suggested that antenatal screening should begin earlier, around 28 weeks gestation, while David et al. [3] advocated foetal US monitoring every 2 weeks from diagnosis.

Prematurity occurs in up to 60%, with between 10 and 31% having an associated birth defect [47, 55]. Relatively common associations include gastrointestinal (GI) atresia, in one small series occurring in 25% of cases [56] and undescended testis [3, 57, 58]. In a retrospective study by Nicholas et al. [47] aiming to determine the predictive value of prenatal factors on outcome in 80 infants with GS, IUGR was identified as the only significant (RR 1.9, $p = 0.04$) predictor of adverse neonatal outcome. The diagnosis of IUGR itself can be problematic (because of difficulty measuring the torso), but has been reported to affect between 30 and 70% of foetuses [53, 59]. Although the cause of foetal growth failure in gastroschisis remains unknown, it has been hypothesised to be due to either an inadequate supply of nutrients or secondary to protein loss from the exposed viscera [60].

This exposed bowel is vulnerable to injury which can range in severity from volvulus with loss of the entire midgut to a more localised intestinal atresia or stenosis, to widespread inflammatory peel or serositis that can make the bowel loops indistinguishable from one another [56, 58]. The inflammatory peel, difficult to quantify pre- and post-natally, develops after 30 weeks gestation. Aetiological factors include bowel wall exposure to amniotic fluid and intestinal lymphatic obstruction [60]. Recent experimental studies to evaluate the roles of amnioexchange and fetoscopy to reduce either peel, perhaps as a result of reduced matrix metalloproteinase (MMP) levels in the amniotic fluid, or GI complications as a result of a narrow defect, whilst interesting, remain unproven in a clinical setting [49, 61–63].

The most devastating prenatal complication with GS has been the uncommon but apparently unpredictable foetal death, which usually occurs in the third trimester [60, 64]. It may be caused by an in utero midgut volvulus or probably more commonly by an acute compromise of umbilical blood flow by the eviscerated bowel [62, 65, 66]. Recent evidence suggests a generalised cytokine-mediated inflammatory response ensues, and this may help explain the failure of conventional foetal surveillance techniques to reduce stillbirth [49, 50, 66, 67]. Whilst overall stillbirth rates of 10% have been reported, there appears to be an association between stillbirth and abnormal amniotic fluid volume [3, 50]. Reid et al. [50] reported a 50% stillbirth rate in oligohydramnios compared to 16.7% with high amniotic fluid volume. Furthermore, 70% of the pregnancies with an abnormal amniotic fluid volume were delivered preterm compared with just 30% of cases in which the volume was normal [50].

Timing and mode of delivery

There continues to be controversy regarding the timing and mode of delivery of a foetus with GS. Typically spontaneous onset of labour in a mother of a foetus with GS will occur by 36 weeks of gestation, with the route of delivery largely determined by obstetric indications [68, 69].

Several studies have advocated earlier delivery, based either on the development of bowel ischaemia, complicated GS or upon reaching a gestational age of 38 weeks [40, 50, 54, 64, 70, 71]. Moir et al. [71] prospectively evaluated a small cohort of 16 women with antenatally diagnosed GS who were evaluated weekly by US from 26 weeks of gestation and compared them with a historical control group. Early delivery was offered after 30 weeks of gestation in those with US evidence of bowel compromise. Those enrolled in the trial were delivered earlier (34.2 vs. 37.7 weeks), has no bowel compromise, earlier establishment of full enteral feeding and shorter length of stay (LOS).

Whilst biased with an inadequate control group, this American study prompted a later randomised controlled trial in the UK, in which 42 women with prenatally diagnosed GS were randomly assigned to either induction of labour at 36 weeks or allowed to labour spontaneously [71, 72]. Both groups of women experienced high rates of caesarean delivery (39%), primarily for foetal distress. No statistically significant differences were observed between the two groups regarding time to full enteral or length of hospital stay. This failure to demonstrate clear benefit, coupled with in some cases greater morbidity associated with preterm delivery, has been echoed in a number of other, non-randomised studies [73, 74]. A systematic review of 34 full text articles similarly found insufficient evidence to support induction of labour in GS [75].

In part, these results may reflect a lack of agreement on the importance of a variety of US criteria used to identify high-risk patients. These have variously included a bowel diameter ranging from >6 to 18 mm, bowel wall thickening of >2 to 3 mm and subjective assessments on bowel wall peristalsis and the degree of matting of bowel loops [45, 64, 70, 71, 76–79]. Evaluation and refinement of objective, standardised antenatal criteria would seem to be required, but at present early delivery would seem proven for obstetric indications only [73, 74].

In Australasia, there has been an increasing trend for delivery via caesarean section for infants with GS, from 41.1% in 1997 to 69% in 2005 [68, 80]. In contrast, an American study by Payne et al. [55] of 155 infants diagnosed between 1990 and December 2007 found that 61% were born by vaginal delivery, similar to the 59% rate reported by Skarsgard et al. [78] in Canada. Davis et al. [45] in their study of 46 neonates with GS born between 1998 and 2007 found no significant difference in outcome between vaginal and caesarean birth, with 56.5% of their cohort delivered by caesarean section. A systematic review by Segel et al. [81] in 2001 had made a similar recommendation, finding no data to support the use of caesarean section in GS.

Initial management

The traditional approach to the management of a newborn with GS has been a temporary sterile covering, nasogastric decompression, resuscitation with intravenous fluids whilst maintaining normothermia [82]. Heat loss continues to be an important issue as do high fluid losses from evaporation and extravasation [1, 3, 83]. Serum glucose levels would seem especially important because of the associated prematurity and IUGR.

As the uterus remains the ideal and most economical transportation unit, and as some form of surgical intervention will be required for all infants with GS, a planned delivery at a facility with both neonatal and paediatric surgical support would seem both logical and optimal [39, 84]. Robilio et al. [85] retrospectively reviewed 515 infants with GS delivered after 34 weeks of gestation between 1992 and 1997 in California, USA. At their tertiary care facility, outborn patients who were statistically significant more likely to suffer respiratory distress syndrome, meconium aspiration and sepsis compared to inborn neonates. Similar adverse outcomes, including longer LOS, greater duration of total parenteral nutrition (TPN) and slower introduction of full enteral feeds, were also identified in outborns by Kitchanan et al. [83] in a review of 21 patients with AWD admitted to their unit in Queensland, Australia.

Irrespective of the site of delivery, for those patients with uncomplicated GS, the surgeon has the choice of either primary closure (PC) or some form of delayed or secondary closure, usually under general anaesthesia (GA) in the operating theatre (OT). Those infants with either complicated GS or in whom the loss of abdominal domain obviated complete reduction have generally been treated by use of a silo, initially sutured to the rim of the defect, with reduction subsequently staged over several days followed by formal closure [1, 4, 82]. With the advent of pre-formed, spring-loaded silos inserted under the abdominal fascia, several authors have suggested improved outcomes with reduced morbidity, including reductions in duration of ventilation, time to first and full feeds, using this approach [14, 86–88]. The use of pre-formed silos inserted on the ward, as the first step in a staged reduction with delayed closure in the OT or even on the ward, was initially reported in 1995 by Fischer et al. [89]. Several later studies

have advocated this approach with reported reductions in the incidence of complications and LOS when compared with both PC and ward reduction (WR) [14, 87, 90, 91].

Infants with GS have been generally supported by mechanical ventilation following surgery, which, as a result the disparity between the volume of the bowel and abdominal cavity, will generally be associated with an increase in intra-abdominal pressure [92]. During this time, appropriate pain management and sedation have been regarded as the standard of care [93]. Most will also require central lines for TPN until full enteral feeding has been established [83, 93].

Ward reduction

Bianchi and Dickson's [13] pilot study of 'delayed' or WR of the bowel in neonates without GA or sedation in 14 patients on the neonatal nursery was published in 1988. Whilst the authors concluded that the procedure was safe, there were two late deaths from a volvulus and perforated ileal atresia that complicated the WR [13]. Following this report, the benefits of analgesia and selective use of sedation have been identified, together with other technical modifications to enhance the likelihood of successful reduction [84, 94]. In addition, several exclusion criteria were developed, including associated atresia, intestinal perforation or atresia and cardiorespiratory instability [94, 95].

Despite these modifications and the undoubted benefits of WR, concerns have remained over the risk of mortality and potential associated short-term complications [95, 96]. A non-randomised, retrospective study of 27 neonates with GS from Western Australia between 2004 and 2008 compared the results of GA reduction in the OT with WR. Although the results did not reach statistical significance, there was a higher incidence of bowel ischaemia, the need for prolonged TPN and unscheduled return to theatre in the WR group [97]. These concerns, together with variations in case selection and technique, have let a number of authors to recommend a randomised control trail (RCT) as suggested by a systematic review in 2002 [90, 97, 98].

Survival and nutritional outcomes

The survival of infants with GS continues to improve, with survival rates of greater than 90% following live birth now routinely reported [44, 68, 83, 99, 100]. There remains significant associated morbidity, which would appear to be dependent on the condition and length of the preserved bowel, complications associated with surgical care and nutrition, associated anomalies and the consequences of prematurity and IUGR [11, 64, 74, 101, 102]. Cholestasis and related hepatic dysfunction remain important sequelae of prolonged TPN although obstructive jaundice related to mechanical obstruction of the biliary tree has been reported [53, 103, 104].

Infants often have ongoing nutritional issues, with feeding complicated by gastro-oesophageal reflux and dysmotility [3, 82]. Whilst a well-conducted, multicentre, randomised, blinded, placebo controlled trial found no benefit in the value of oral erythromycin on enteral feeding in infants with GS at a dose of 12 mg/kg/day, a later systemic review found some evidence that higher doses may be of some benefit in neonates of greater than 32 weeks of gestation [105, 106]. Early trophic feeding has been associated with reduced LOS and shorter duration of TPN, but the evidence for this approach, whilst logical, remains weak with a need for further studies [3, 100, 107].

There remain few reviews of the long-term outcomes in GS survivors. Berseth et al. [108] found that at 3 years of age, most has poor weight gain despite no apparent objective or functional evidence of either GI or metabolic consequences from GS. Similarly, a study of 24 infants at 16–24 months following their repair of GS at a centre in North America between 2003 and 2005 found that one-third of infants suffered growth delay [109]. In contrast, in a review of 22 out of 40 children originally treated for GS in Germany between 1994 and 2004 at a mean 6.3 years later, Henrich et al. [110] found that only 9% were below the third centile for weight and 14% for height. Although some of these differences may reflect the expected general improvements in care that will have occurred between 1982 and 2008, there remains a clear need for further data.

Developmental status

The importance of developmental outcomes of infants who have undergone major surgery is becoming evident, with recommendations from one review that all infants who undergo surgery for congenital anomalies be enrolled in multi-disciplinary follow-up sessions [111].

To date, there have been few studies detailing the neurodevelopmental outcome specifically for infants with GS. The 1982 study by Berseth et al. [108] found that infants with GS and EXO had a lower intelligence quotient (IQ), with a third an IQ of less than 90. South et al. [109] identified 3 of 24 infants following GS repair that were assessed as less than 85 using the Bayley Scale of Infant Development although Henrich et al.'s [110] study suggested that such delays were easily recovered after treatment. Minimal adverse neurodevelopmental outcomes were also found in a West Australian study which assessed 43 infants with GS at 1 year of age using the Griffiths Developmental Assessment, reporting a normal median

general quotient (GQ) at 12 months of age [112]. Clearly, better evaluation would seem to be required, both to facilitate optimal medical care and ensure accurate advice may be given to prospective parents [3, 110].

Summary

The GS has increased in frequency up to 4.72 per 10,000 live births. It represents a major congenital malformation that occurs very early in gestation. Despite several early studies claiming evidence of association with a variety of agents, the additional risks attributed to tobacco consumption and illicit drug use appear low. GS particularly affects young, teenage mothers who will often be both unaware of their early pregnancy and unlikely to always comply with optimal antenatal care. Whilst readily diagnosed on antenatal US, the role and frequency of subsequent monitoring appears unclear. Although there remains no convincing evidence to support either routine early delivery of elective caesarean section in the absence of obstetric indications, delivery should optimally occur at a centre with paediatric surgical facilities. The relative advantages and complications of WR, staged reduction using a silo or PC would be better defined through a multicentre, prospective RCT. As survival rates following live birth of an infant with GS continue to improve, the focus should move to improved evaluation of long-term nutritional and neurodevelopmental outcomes.

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