

Congenital Abdominal Wall Defects: An Update

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Key Words

Gastroschisis · Omphalocele · Abdominal wall defects · Prenatal evaluation · Postnatal outcome

Abstract

Objective: To review published peer-reviewed literature regarding abdominal wall defects including gastroschisis and omphalocele. **Methods:** Review of published peer-reviewed literature using Med Line 1985–2003 and textbooks. **Results:** Gastroschisis and omphalocele literature is reviewed using pathology, incidence and epidemiology, prenatal evaluation, pregnancy and delivery management, postnatal outcome and fetal therapy. **Conclusion:** Gastroschisis and omphalocele are common abdominal wall defects and have significant morbidity and mortality.

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Introduction

Routine pregnancy screening by maternal serum testing and ultrasound in the second trimester allows identification of the majority of congenital abdominal wall defects (omphalocele, gastroschisis). The etiology, incidence, and pathology of these abdominal wall defects dif-

fer greatly and require specific prenatal evaluation and pregnancy management for each condition. Accurate evaluation of these congenital abdominal wall defects will allow the identification of isolated defects compared to multiple anomalies with chromosomal, genetic syndromes, or anomaly associations.

Gastroschisis (Laproschisis)

Pathology

The term gastroschisis is derived from Greek roots meaning 'stomach cleft', but the correct term may be laproschisis (belly cleft) [1]. Gastroschisis is a common, prenatally diagnosed birth defect with an increasing incidence worldwide and generally affects fetuses of mothers less than 20 years of age. Routine ultrasound has allowed this birth defect to be identified in utero with high specificity and sensitivity. The abdominal wall defect in the fetus permits the small and large bowel to herniate through the defect and be exposed to the amniotic fluid environment. The size of the abdominal wall defect and the exposure to the amniotic fluid has effects on the condition and function of the bowel after birth and carries significant morbidity and mortality risks to the fetus and newborn.

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Table 1. Proposed etiologies of gastroschisis

<i>Malformation</i>	
Vascular	Abnormal involution of the right umbilical vein which occurs around 28–32 days gestation Disruption of the right terminal branch of the superior mesenteric artery within the extra-embryonic coelum of the body stalk In utero rupture of umbilical cord hernia before complete closure of the umbilical ring
Genetic	Familial clusters with autosomal inheritance pattern with variable expression [7–9]
<i>Disruption</i>	
Teratogens	Radiation damage at the pre-implantation stage Aspirin (OR 2.7, 95% CI 1.2–5.9) Pseudoephedrine (OR 1.8, 95% CI 1.0–3.2) Acetaminophen (OR 1.5, 95% CI 1.1–2.2) Pseudoephedrine combined with acetaminophen (OR 4.2, 95% CI 1.9–9.2) [11] Smoking (OR 1.6)

The categorization of gastroschisis within the congenital anomaly classification is not clear, as the specific etiology for this birth defect is unknown. Gastroschisis may be a malformation, disruption, or deformation (primary or secondary). Gastroschisis is a para-umbilical defect of the abdominal wall almost always right-sided resulting in herniation of the abdominal contents into the amniotic cavity [1–3]. The defect is usually small, less than 4 cm in diameter through which various segments of bowel and other abdominal organs (fallopian tubes or stomach) may be herniated. Gastroschisis can produce intrauterine and neonatal complications, which may include postnatal bowel dysfunction, bowel atresia, bowel necrosis and subsequent short bowel syndrome.

Gastroschisis may present as a primary malformation or secondary to disruption due to teratogens. A summary of the possible primary etiologies for gastroschisis are listed in table 1 [4–12].

Additional secondary deformation effects on gastroschisis indicate that the cause of bowel damage is not entirely understood. Much of the damage is caused by constriction at the site of the abdominal wall defect and this occurs primarily late in gestation [13, 14]. Langer et al. [15] suggested that the mechanism of constriction-induced damage is related mainly to venous and lymphatic obstruction not ischemia based on experimental findings in fetal lambs.

As the pregnancy progresses with gastroschisis, the bowel usually becomes coated in an inflammatory fibrotic

peel resulting in thickening of the bowel wall, matting of the intestines, decreased bowel motility and potentially luminal obstruction. Morrison et al. [16] demonstrated that the amniotic fluid from gastroschisis cases contained inflammatory cells and significantly elevated levels of the proinflammatory cytokine interleukin-8 compared to controls. Other intra-amniotic factors that have been reported to be associated with damaging bowel in gastroschisis are meconium, amniotic fluid pH and amniotic fluid β -endorphin [17–20]. Intestinal damage in gastroschisis has been shown to be independent of the size of the abdominal wall defect. Histology did not show venous stasis, ischemic lesions, or differences in the degree of edema between groups with a 2.6-mm ring compared to a 4.8-mm abdominal ring in a rabbit model. The conclusion was that intestinal changes in the length, weight, diameter, wall thickness, and histology in gastroschisis should not be attributed to the diameter of the abdominal wall defect [21]. In the rat and chicken model, meconium within the amniotic fluid has been associated with bowel damage. In the rat model, bowel damage parameters were affected by meconium contamination of the amniotic fluid supporting the hypothesis that bowel damage in gastroschisis is at least partially dependent on inflammatory meconium exposure [17]. In the chick model, different intra-amniotic concentrations of meconium were used, and it was demonstrated that there may be a threshold level of meconium to induce intestinal damage [19]. In the chick model, alkalization of the amnio-allantoic fluid prevented intestinal damage compared with normal amniotic fluid [18].

In the human fetus, more severe cases of gastroschisis were associated with high levels of amniotic fluid β -endorphin which led to the hypothesis that this fetal hormonal response could result from stress or pain caused by prenatal bowel damage [20].

Incidence and Epidemiology

The incidence of gastroschisis is 0.5–1.0 case per 10,000 births. Information from various geographic areas shows an increasing incidence [22–27] (table 2). The most common epidemiological association with gastroschisis is young maternal age, especially less than 20 years of age. Associated factors considered in this young maternal age population have been environmental teratogens such as cigarette smoking and drug abuse. There are significant associations with poor maternal education, low social economic status, more than one elective termination of pregnancy and a short interval between menarche and first pregnancy [7, 28]. There have been conflicting reports

looking at the incidence of gastroschisis and its seasonal variation. Studies have found an increased risk of gastroschisis in deliveries occurring in the winter months in the northern hemisphere [29–31]. Other studies have not found a seasonal variation [12, 32, 33].

Reports in the literature have shown a spectrum of defects associated with gastroschisis. These range from a description of gastroschisis minor [34] through typical gastroschisis with or without intestinal atresia [35–37] to closed gastroschisis [38] with increased morbidity and mortality.

Postnatal evaluation has classified gastroschisis into 2 groups, simple (2/3) and complex (1/3). Complex cases have bowel pathology with malrotation, volvulus, infarction, atresia, perforation, or stenosis. This bowel pathology may contribute to short bowel syndrome and increased risk of mortality. In a retrospective chart review of 103 infants with gastroschisis over a 5-year period, 71 infants had a simple defect and 32 were complex [36]. Separation of the population into simple and complex has not been possible prenatally. The postnatal complex designation has a mortality rate of 28% compared to a survival rate of 100% in the simple category. Table 3 summarizes comparison of gastroschisis with and without atresia [36, 37].

Gastroschisis minor [34] is described as small abdominal wall defect to the right of and adjacent to the umbilical cord with a small omental protrusion only. This minor variant of gastroschisis is described in a gastroschisis population of 21 patients with 6 having gastroschisis minor. All 6 gastroschisis minor patients survived while only 2 of the other 15 with normal gastroschisis survived. At the other end of gastroschisis spectrum is a condition called ‘closed gastroschisis’ [37] with significant closure of the abdominal wall defect around the prolapsed midgut. There are a number of possible sequelae resulting from this abdominal ring closure. These include at the most severe end complete midgut infarction, intestinal reabsorption and a normal abdominal wall appearance, and this is described as a vanishing midgut. The next level of severity involves a small right-sided mummified midgut remnant and a complete ring closure [37]. The least severe is simple luminal occlusion without any vascular impairment. In most cases there is some remnant of the extra-abdominal bowel identified to the right of the umbilicus either as a shrunken nonviable mass or occasionally obvious gangrenous bowel of normal length. The intra-abdominal proximal bowel is dilated by the time of birth and has a variable length. It is possible that this observation of decreased external component and increasing intra-abdominal bowel dilatation could possibly be iden-

Table 2. Incidence of gastroschisis: location and time

Country	Year	Incidence/10,000 births
England	1987–1994	1–2
	1995	4.4
UK/Wales	1987	0.7
	1991	1.4
Norway	1989	1.3
	1998	3.2
Denmark	1970–1974	1.22
	1975–1979	1.67
	1980–1984	1.09
Europe (19 registries)	1985–1989	1.29
	1996–1998	1.54
Australia	1980	0.48
	1993	3.16 (NS)
		(OR 2.23, 95% CI 1.33–3.72)

NS = Nonsignificant difference.

Table 3. Postnatally assessed gastroschisis: simple (no atresia) vs. complex (atresia) [36, 37]

	Simple	Complex
Patients	245	57
Birth GA, weeks	36.8	36
BW, kg	2.7	2.3
Primary repair, %	71	72
Silo, %	29	28
First feed, days	14.9	21.4
LOS, days	32.9	74.3
Survival	231 (94%)	44 (77%)

GA = Gestational age; BW = birth weight; LOS = length of stay in hospital.

tified prenatally by ultrasound. The key ultrasonic feature is the presence of dilated intra-abdominal bowel loops which may allow consideration for early delivery (≥ 35 weeks) of the affected fetus. Dilatation of the external bowel component, the use of umbilical artery Doppler or superior mesenteric artery Doppler has not been helpful in predicting postnatal gastrointestinal function or bowel atresia. Crawford et al. [39] reported that Doppler may assist in the prediction of perinatal asphyxia with fetal distress necessitating cesarean section.

Evaluation of the morbidity in infants with antenatally diagnosed anterior abdominal wall defects shows that

infants with gastroschisis when compared to omphalocele require longer periods of parenteral nutrition and hospital admission. In the gastroschisis group, the time to start feeding related independently to prolong hospital stay, and the presence of structural bowel abnormalities related independently to both prolonged parenteral nutrition and hospital stay with a positive predictive value of 100%. The conclusion was that infants with gastroschisis, particularly those with small bowel atresia, suffered greater morbidity than infants with omphalocele without lethal abnormalities [40]. Additional morbidity with complex gastroschisis was related to short bowel syndrome. Short bowel syndrome results in dehydration or malabsorption due to intestinal resection especially of the ileum with or without the colon [41].

Prenatal Evaluation Including Differential Diagnosis

The separation of gastroschisis into prenatal classifications of simple and complex has not been possible on a consistent basis. The differential diagnosis of prenatally diagnosed anterior abdominal wall defects should include bladder extrophy, cloacal extrophy, cystic cord lesion, urachal cysts along with gastroschisis and omphalocele. Other syndromes and sequences which have been associated with abdominal wall defects include amniotic band syndrome, limb body wall complex, and pentalogy of Cantrell [42]. Some other commonly associated pathological findings in gastroschisis, in addition to intestinal atresia, are hypoplastic gallbladder, Meckel diverticulum and hydronephrosis. Reiss et al. [43] reported that 4 of 12 fetuses with gastroschisis had developed deformations of the urinary tract. Three of the fetuses had bladder herniation through the abdominal wall defect with 2 of the 3 fetuses having upper urinary tract dilation. The 4th fetus developed bilateral hydronephrosis with a normally situated bladder.

Intrauterine growth restriction is common in the gastroschisis population. Seventy percent of infants with gastroschisis are below the 50th percentile in weight. This shift in mean birth weight is highly significant. The prevalence of intrauterine growth restriction is increased in infants with gastroschisis but is overestimated with prenatal ultrasound due to smaller abdominal circumference measurements [44, 45]. Fries et al. [44] reported no difference in the postnatal outcome for those growth-retarded infants compared to non-growth-retarded infants with gastroschisis, but the lack of a statistically significant difference is probably a reflection of the small population size with 10 growth-restricted and 11 non-growth-restricted infants.

The risk of stillbirth is higher in fetuses with gastroschisis. Broth et al. [46] reported on 78 fetuses with gastroschisis and had a stillbirth rate after 28 weeks of 85 per 1,000 births compared to control group rate of 5.4 per 1,000 births, and a neonatal death rate within 28 days of birth of 17.5 per 1,000 births compared to control group rate of 4.7 per 1,000 births. Recommendations are made for close fetal monitoring in the third trimester and possibly early intervention if abnormal surveillance results are identified. Monitoring in the form of umbilical arterial Doppler ultrasound with nonstress fetal heart rate analysis could be considered. One possible etiology for intrauterine death may be severe cord compression due to a herniated dilated bowel. Kalache et al. [47] reported an unusual umbilical flow velocity waveform (diastolic notching) which was associated with normal umbilical arterial Doppler indices, a brain sparing effect and non-reactive fetal heart rate pattern. At postnatal surgery, severe cord compression by the dilated herniated bowel was thought to be associated with the diastolic notching and non-reactive fetal heart rate tracing.

Prenatal ultrasound is not able to accurately identify fetuses with gastroschisis and bowel atresia. Bowel wall thickness and bowel dilatation has been evaluated and has not been predictive of immediate neonatal outcome. This finding was not recommended as an appropriate indication for preterm delivery in the absence of other evidence of fetal compromise [48, 49].

Pregnancy and Delivery Management

Huang et al. [50] reported that term delivery of fetuses with antenatally diagnosed gastroschisis resulted in earlier closure of the defect and shorter time to full feeds. Time periods that were evaluated were birth at <35 weeks, 35–37 weeks, and >37 weeks. The age at first and full feeding and length of hospitalization were all significantly higher with birth at 35–37 weeks than when birth was >37 weeks. The usual recommendation for timing of delivery is related to a gestational age when lungs are mature but with the understanding that prolongation of intrauterine life may increase the risk of gastrointestinal morbidity.

While controversy may still exist regarding the obstetrical management of fetuses with gastroschisis including fetal surveillance, there is no clear evidence of any advantage of elective cesarean section over vaginal delivery with a vertex presentation [51–53].

The recommendation for delivery at a tertiary referral center to better coordinate the obstetrical, neonatal, and pediatric surgery care is supported by the differences in

neonatal outcome comparing 'in-born' and 'out-born' neonates. Robilio et al. [54] found that respiratory distress syndrome, meconium aspiration and sepsis appeared as a complication more often in transported (out-born) infants and recommended delivery of fetuses with gastroschisis at a tertiary care facility. Kitchanan et al. [55] identified increased morbidity in 'out-born' neonates with gastroschisis and related this to factors such as temperature, prenatal care, hydration status, care of the defect and vascular compromise of prolapsed gut during prolonged transportation. The neonatal management is directed to limit fluid and protein loss and prevent hypothermia. A silastic bag is immediately placed over the exposed abdominal contents to minimize handling of the bowel and prevent vascular compromise. Gastrointestinal decompression, intravenous fluids, albumin/saline infusion, and broad-spectrum antibiotics are recommended. Metabolic acidosis should be corrected and the type of repair performed is related to the degree of bowel inflammation, bowel matting, size of the abdomen relative to the eviscerated bowel and surgical preference.

Surgical Repair

Primary abdominal wall closure is preferred and a silo is created only when primary closure is not possible [1, 56]. The success of primary closure is dependent on the amount of visceroperitoneal disproportion. An intra-abdominal pressure measurement of <20 mm Hg by intragastric or intravesical assessment when the external contents are returned to the abdominal cavity indicates that primary fascial closure is possible. Excessive abdominal wall tension can lead to vena cava compression, compromised respiratory function, urethral obstruction, and bowel ischemia [1]. Primary closure advantages are shorter interval to oral feeding, reduced hospital stay and decreased surgery [1].

Increased abdominal pressures require the use of delayed fascial closure techniques using temporary coverage with silastic/Dacron intra-abdominal pouch or the use of mobilized lateral skin flaps [56]. Skin flaps allow secondary closure of fascia at several months of age [56]. More recently other approaches have been considered including primary reduction in the neonatal intensive care unit with and without anesthesia [57, 58], and the nonoperative initial placement of a preformed silo followed by delayed fascial closure [59–61]. Schlatter et al. [62] reported improved outcomes for gastroschisis using a preformed silo and fascial closure within 24 h compared to a historic control group of primary closure on the 1st day of life after appropriate fluid resuscitation. The use of the preformed

silo approach was associated with improved fascial closure rates, fewer ventilator days, more rapid return of bowel function and fewer complications [62]. Infants with intrauterine bowel damage (ischemia, necrosis) require excision and primary bowel anastomosis or possibly temporary intestinal stomas [56]. Bowel atresias lead to primary or secondary bowel repair approaches, dependent on the location and amount of 'chemical' peritonitis/matting of the bowel [56]. Detailed discussion of the management of atresia with gastroschisis is beyond the scope of this review but recent articles give direction for selective approaches [35–37]. The level of atresia was most commonly jejunoileal (80%) [36, 37]. For proximal atresias, delayed primary repair is a safe satisfactory approach while distal atresias are more obvious, often complicated by perforation or infarction and may benefit from early enterostomy [35]. Delayed repair of the atresia after a period of bowel decompression and parenteral nutrition is preferred but there are situations (colonic atresia, necrotic intestine, complicated atresia) when this may not be possible [37]. Short bowel syndrome [41] occurs in this group as a result of bowel resection due to atresias, necrotizing enterocolitis and volvulus. This resection disturbs the normal absorptive processes for nutrition and fluids especially with involvement of the terminal ileum or with massive intestinal resection of infarcted bowel. There are short- and long-term problems with malabsorption, leading to disruptions in fluid balance, weight loss, anemia and vitamin deficiencies [41].

Postnatal Outcome

Durfee et al. [63] reported their experience of 26 fetuses with a prenatal diagnosis of gastroschisis at gestational ages of 16–36 weeks. In 9 of 21 fetuses, followed by serial ultrasound, bowel dilatation developed and prompted the delivery of 2 fetuses. Two of the 26 study fetuses were electively terminated. The remaining 24 fetuses were born alive and had immediate repair of gastroschisis at birth. Nineteen infants (79%) had postnatal complications including 3 neonatal deaths, 10 with gastrointestinal complications, 6 with infectious complications and 6 with anomalies involving other systems (genital, urinary, cardiac, central nervous system, and respiratory). Only 5 infants (21%) had completely uncomplicated post-surgical courses. Hospital stays for survivors ranged from 10 to 98 days with a mean of 38 days. Contemporary management of gastroschisis shows that antenatal diagnosis is made in 98% of cases. Associated intestinal atresia is present in 8–10% but the presence of atresia was not an independent risk factor for mortality. The

mortality rate from gastroschisis is less than 10% with sepsis being the most common (70%). Strategies designed to improve morbidity must focus on optimizing management of those factors associated with recovery such as intestinal atresia, prematurity and the use of a spring-loaded silo. Driver et al. [64, 65] showed no correlation between the timing of abdominal wall closure and outcome. Time should be taken to optimally resuscitate a newborn infant prior to surgical closure as this does not have an adverse influence upon the outcome. The use of a spring-loaded silo followed by elective repair permits gentle gradual reduction of the viscera and, when compared to early primary repair, the spring-loaded silo was associated with significantly lower airway pressures, early extubation, fewer complications, and decreased length of stay and hospital charges [66]. Sharp et al. [67] reported that the age at first enteral feeds was significantly related with the length of hospital stay and duration of total parenteral nutrition. The possible physiological reasons that account for the benefits of early enteral feeding include the presence of substances in the milk (glutamine, arginine, insulin-like growth factors) that are trophic to the gastrointestinal tract, development of gastrointestinal motor activity, or the release of trophic enteric hormones. This study showed that the method of delivery of the infant (vaginal 68%; non-elective cesarean section 28.5%; elective cesarean section 3.5%), age at repair, length of anesthetic time, duration of postoperative paralysis, and gestational age was not associated with the length of stay or duration of total parenteral nutrition. This study had an 89.7% survival of live births with gastroschisis. All of the infants in this study were out-born.

The long-term outcomes [63–67] are generally related to the degree of gastrointestinal compromise and the presence of gastrointestinal atresia. Approximately 10% of patients with gastroschisis will have hypoperistalsis syndrome. These infants remain dependent on parenteral nutrition for an indefinite period, some times permanently. Hospitalization for infants with gastroschisis requiring staged closure is much longer, related to the need for gradual reduction, greater visceral peritoneal disproportion and a second procedure to achieve fascial closure. Inguinal hernias will develop in most infants with gastroschisis because of increased intra-abdominal pressure. Occasionally incisional hernias may develop. There have been no long-term sequelae from gastroschisis reported if there is no associated hypoperistalsis syndrome or short bowel syndrome.

Fetal Therapy: Present Status

The 'gold standard' for gastroschisis treatment is post-natal surgical repair. In utero fetal therapy is unproven, and randomized trials will be needed both in animal models as well as human studies.

Many different animal models have been utilized to evaluate different aspects of gastroschisis pathology. These models include fertilized chick eggs, rat, rabbit, and ewe. Thirteen-day-old fertilized chick eggs were used to assess amniotic fluid exchange for the prevention of neural tissue damage in myelomeningocele. The conclusion was that exposure of the myelomeningocele to the amniotic fluid causes structural neural tissue damage that can be prevented by amniotic fluid exchange [68]. This amniotic fluid damage could be extended to gastroschisis considerations. The chick embryo gastroschisis model was used to evaluate the effect of amnio-allantoic fluid pH on the intestinal pathology. Fourteen-day-old fertilized chick eggs were used, with appropriate control groups to compare the gastroschisis response to normal amnio-allantoic fluid pH, placebo exchange with species-specific physiological serum saline and exchange with alkalized amnio-allantoic fluid. Results showed a significant decrease in intestinal damage both macroscopically and microscopically in the group exposed to the alkalized amnio-allantoic fluid compared to the normal amnio-allantoic fluid or the placebo physiological saline fluid [18]. Another study looking at amnio-allantoic fluid exchange and its effect on bowel contractility in the chick embryo with gastroschisis used normal physiological saline as the exchange fluid. The intestines were thickened and covered by fibrosis peel in the gastroschisis with the no-exchange group only compared to the exchange and control group. There was a statistically significant decrease in bowel contractility in the gastroschisis-only group compared to controls and this decreased contractility was significantly reversed in the gastroschisis with exchange group. In addition the gastroschisis-only group had significantly fewer parasympathetic ganglia per 10 plexus than the control group or the exchange group. The conclusion was that amniotic fluid exchange prevents functional and morphological changes in gastroschisis and the expectation would be an improved clinical result with intrauterine environment pretreated by amniotic fluid exchange [69]. Intestinal damage in gastroschisis was also shown to correlate with the concentration of intra-amniotic meconium in a 5-day-old fertilized chick egg model. A threshold level of meconium concentration was identified to induce intestinal damage showing serosal thickening, inflammation, focal fibrin, and collagen deposits [19].

The evaluation of meconium and its relationship to bowel damage in gastroschisis has been evaluated in rat and rabbit models as well. Correia-Pinto et al. [70] utilized pregnant rats at 18.5 days gestational age. Four experimental groups were utilized to evaluate minimal, moderate, and elevated levels of meconium and its effect on the bowel. The group with anal ligation (minimal meconium) had neither bowel peel nor adherence while the comparison in the moderate to severe meconium group showed increasing degrees of bowel peel coverage and adherence.

In the pregnant rabbit model, at 23–25 gestational days, induction of fetal diuresis was initiated with intra-amniotic furosemide compared to a placebo injection and analysis of amniotic fluid samples 6 h later. There was no change in the amniotic fluid factors in the control group while in the furosemide group there was no change in the urea nitrogen or creatinine levels but there was a significant decrease in bilirubin, amylase and alkaline phosphates. The conclusion was that induction of fetal diuresis with intra-amniotic furosemide was effective in diluting intestinal waste products from the amniotic fluid [71].

The consideration of meconium as one of the amniotic fluid irritants in gastroschisis has only recently been identified. Traditionally, in utero meconium passage was thought to occur only during fetal distress. Ciftci et al. [72] challenge this idea showing the meconium stain amniotic fluid is not related to meconium passage after distress but reflects impaired clearance of amniotic fluid, which already has meconium, caused by in utero physiologic defecation. The presence of intestinal enzymes in the amniotic fluid of healthy fetuses and its absence in fetuses with intestinal obstruction support the idea that meconium passage during fetal life is a normal physiologic event [73–75]. Proximal intestinal dilatation in fetuses with colonic atresia or anorectal malformations favors this theory. Langer et al. [14] showed that bowel damage in gastroschisis was dependent on amniotic fluid contact and that most of the damage occurred late in gestation. In utero defecation is also gestational age-dependent and becomes more prevalent in the last few weeks of gestation [72, 74]. Human meconium has been shown to contain large concentrations of interleukin-8, which is a powerful inducer of neutrophil chemotaxis [76]. Interleukin-8 has been identified as elevated in amniotic fluid and is part of the acute inflammatory exudate along with activated neutrophils in human fetal gastroschisis [77]. This association of meconium, interleukin-8, and acute inflammatory exudate in gastroschisis may allow clinical strategies to be developed that are directed towards anti-inflammatory

effects. This leads to the consideration of amniotic fluid exchange with an artificial amniotic fluid replacement in cases of normal amniotic fluid volume or artificial amniotic fluid infusion in cases with oligohydramnios or low amniotic fluid volume [78–82].

A new fetal rat model for gastroschisis has recently been identified with the pathophysiology appearing to resemble human gastroschisis [17]. In addition, a fetal lamb model has been used to evaluate amnio-infusion in a pregnant ewe model in which gastroschisis was created in utero [80]. The non-amnio-infused fetuses showed increases in bowel muscular thickness, serous fibrosis and plasma cell infiltration.

Consideration of the human published data can be evaluated in two broad categories. One is amnio-infusion to correct the oligohydramnios associated with gastroschisis and secondly the use of amniotic fluid exchange to dilute or remove inflammatory substances from the amniotic fluid and thereby decrease the inflammatory response on the exposed bowel.

Transabdominal amnio-infusion both as a single infusion and serial infusion in the management of gastroschisis with severe oligohydramnios has been reported [79, 82]. The in utero treatment for human fetal gastroschisis is summarized in table 4 [78–80, 82] for both the amnio-infusion with oligohydramnios and the amnio-exchange populations. Luton et al. [80] reported a nonrandomized gastroschisis cohort comparing amnio-infusion treatment with no amnio-infusion, but the small numbers may have prevented significant differences from being identified as only a shorter duration of curarization after surgery was significant ($p = 0.019$) while there was a trend for shorter delay to full oral feeding (not significant) and shorter hospitalization (not significant).

Amnio-infusion in fetal gastroschisis has been reported to produce a significant improvement of diastolic flow in the extra-abdominal superior mesenteric artery. No similar change was seen in the intra-abdominal superior mesenteric or in the umbilical artery. The conclusion was that amnio-infusion induces modifications in the vascularization of exteriorized bowel in gastroschisis and this could partly explain the beneficial effect of this procedure on the fetal gut [83].

Table 4. In-utero treatment of human fetal gastroschisis**A** Amnio-infusion (AI) with associated oligohydramnios (4 patients)

Author	GA DX	AI, n	GA, AI	Vol/AI	GA birth	Mode Del	Other
Dommergues et al. [79]	19	3	30–35	350–500	36	C/S	PROM 36/52 BD 23 mm
	19	5	32–36	400–900	36.5	C/S	PROM 36.5/52 BD 27 mm
Sapin et al. [82]	12.5	5	27.5–31	total 2,250	31	C/S	BD moderate
	19	1	31	420	34	C/S	BD 25 mm

B Amnio-exchange (AE, 11 patients)

Author	GA DX	AE, n ¹	GA, AE	vol cm ³ mean	GA birth	Mode Del	Other
Aktug et al. [78]	24	4 (1)	29–34	400–600	36	C/S	Single case
Luton et al. [80]	20.3 ± 6	1 (4)	32.3 ± 3.2	500 ± 239	36.9 ± 1.3	SVD 8	10 cases
		2 (4)	(26–38)	(300–1,000)		C/S 2	Mean AE to del
		3 (2)					4.6 ± 3.6 weeks

¹ Number of amnio exchanges and number of patients having that number of AEs in parentheses.

GA = Gestational age; DX = diagnosis; vol = volume; C/S = cesarean section; PROM = premature rupture of membranes; BD = bowel dilatation.

Omphalocele

Pathology

The spectrum of severity of omphalocele abnormalities can vary from a small umbilical hernia (hernia into the cord) to a large abdominal wall defect with extrusion of all abdominal viscera (giant omphalocele). Omphalocele is a defect in the ventral abdominal wall characterized by an absence of abdominal muscles, fascia, and skin, which are covered by a membrane consisting of peritoneum and amnion [84, 85]. The umbilical cord inserts into the membrane covering the omphalocele at a location far from the abdominal wall. The omphalocele defect is reported to be caused by an abnormality that occurs during the process of body in-folding at 3–4 weeks of gestation [86]. During embryonic development, 3 areas of body in-folding occur simultaneously and each is associated with a distinct type of omphalocele. Cephalic folding defects result in a high or epigastric omphalocele as seen in the pentalogy of Cantrell (epigastric omphalocele, anterior diaphragmatic defect, sternal cleft, pericardial defect and associated intracardiac defects). Lateral folding defects result in the 'classic' omphalocele with a mid-abdominal defect. Caudal folding defects result in a low or hypogastric omphalocele as seen in bladder or cloacal extrophy.

The finding that omphalocele can be part of a large number of unique chromosomal and genetic syndromes shows that no specific etiology has been identified for omphalocele and that abdominal wall defects may be the final pathway in a number of diverse primary developmental insults [87] (table 5). A number of candidate genes using knockout mouse models and teratogens have identified that disruption of at least 2 separate systems, transcription control and cellular second messengers, can lead to abnormal development of the anterior abdominal wall [88–91].

Recurrence risk for abdominal wall defects are related to the specific etiology [87] (table 5). Recurrence risk for omphalocele, if related to chromosomal abnormality, would be dependent on maternal age at the estimated date of delivery of the fetus with the omphalocele. If maternal age was >35 years, the risk for chromosomal recurrence would be quoted as an age-related risk at the subsequent pregnancy while for women <35 years an empiric risk of 1% would be quoted for a chromosomal risk. If there is a positive family history for omphalocele, recurrence risk would be related to the proposed genetic inheritance pattern: 50% for autosomal dominant, 25% for autosomal recessive, and 50% in male fetuses for X-linked disease. Non-syndromic or isolated omphaloceles are generally considered to be sporadic with no significant increased recurrence risk.

Table 5. Omphalocele as component of multiple anomaly syndrome/sequence

Condition	Genetics	Pathologic affect
Chromosomal	trisomy 18 trisomy 13 triploidy	MCA, IUGR MCA, IUGR MCA, IUGR
Pallister-Killian (tetrasomy 12p)	denovo or familial translocation	DH, short femur polyhydramnios
Beckwith-Wiedemann Limb-body wall complex (amniotic band syndrome)	sporadic (AD, AR, MF)	gigantism
CHARGE association	sporadic	MCA
Pentalogy of Cantrell	sporadic	MCA, IUGR
Siromelia	sporadic	MCA
Shprintzen syndrome	AD	MCA
Carpenter syndrome	AR	facial/brain craniosynostosis

AD = Autosomal dominant; AR = autosomal recessive; MF = multifactorial; MCA = multiple congenital anomalies; IUGR = intrauterine growth restriction; DH = diaphragmatic hernia.

Table 6. Incidence of omphalocele

Country	Time period	Incidence
UK (England, Wales) [93]	1987–1995	1.13 decreased to 0.77/10,000 births
UK (West Midland) [94]	1995–1996	3.32/10,000 births (including TA and SB)
France [95]	1979–1998	2.18/10,000 births (including TA and SB)
Denmark [90]	1970–1989	2.07/10,000 births (LB, SB)

TA = Therapeutic abortion; SB = stillbirth; LB = live born.

Beckwith-Wiedemann syndrome (BWS) [92] patients have chromosomal abnormalities involving 11p15 in 1% or less of cases. Clinically available molecular genetic testing can identify several different types of 11p15 abnormalities in patients with BWS: in 50% of patients, loss of methylation is observed and in 10–20% of patients, paternal uni-parental disomy for chromosome 11p15 is observed. Research testing reveals mutations in the CDKN1C gene in 5–10% of sporadic cases and 40% of familial cases. Most patients with BWS have normal chromosomes with only 15% having a family history consistent with autosomal dominant transmission of BWS. Identification of an underlying genetic mechanism if present helps to determine recurrence risk for subsequent prenatal diagnosis or pregnancy.

Incidence and Epidemiology

The incidence of omphalocele is reported to be 1 in 4,000–7,000 live births (table 6) [93–96]. The incidence

of omphalocele increases to 1 in 300–4,000 births if both live birth and stillbirths are combined. The overall incidence of abdominal wall defects is 20 times greater in still-born than in live-born infants [97–100].

Omphalocele is more likely to be associated with multiple anomalies and have a chromosomal or genetic syndrome etiology [87] (table 5) when compared to other abdominal wall defects such as gastroschisis. Multiple anomalies are seen in 67–88% of fetuses with omphaloceles. Cardiac anomalies (septal defects, teratology of Falot and ectopia cordis) are present in 50% of omphalocele cases. Gastrointestinal anomalies (diaphragmatic hernia, intestinal duplications and atresia) occur in 40% of omphalocele cases. Musculoskeletal, genitourinary and central nervous system anomalies are commonly associated as well. Chromosomal anomalies are associated in 30–40% of omphaloceles and include trisomy 13, 18, and 21 as well as sex chromosome abnormalities including Turner syndrome (45,X), Klinefelter syndrome (47,XXY),

and triploidy (69,XXX). Chromosomal anomalies are more likely to be associated with omphaloceles containing bowel only and are much less likely in omphaloceles with liver herniation only. Genetic syndromes that are associated with omphalocele include BWS, pentalogy of Cantrell, and bladder cloacal extrophy.

Genetic inheritance of omphaloceles have reported pedigrees consistent with autosomal dominant, autosomal recessive and X-linked inheritance [101–105].

Other factors which have been reported to be associated with omphalocele include preconception use of multivitamins, maternal febrile illness, IVF/ICSI, and consanguinity [95]. Preconception multivitamin use identified a reduction in non-syndromic omphalocele by 60% with an odds ratio of 0.4 (95% CI 0.2–1.0) [106]. Erickson et al. [107] reported that maternal febrile illness with no vitamin supplementation had an odds ratio of 3.3 for omphalocele while febrile illness with vitamin supplementation had an odds ratio of 0.0. Assisted reproductive technology with the use of IVF or ICSI had a relative risk of 3.3 for omphalocele (95% CI 1.3–6.9) [108]. Other reports indicated that these results showed a marginal statistical significance that may be due to chance [108]. A large national registry of congenital malformations in France indicated an increase risk for abdominal wall defects with consanguinity. Parenteral consanguinity had a risk of 7.6% compared to control of 1.6% ($p < 0.01$) [95].

Prenatal Evaluation

Prenatal testing is available by ultrasound and maternal serum α -fetoprotein. The use of routine prenatal screening test such as maternal serum screening for α -fetoprotein at 15–20 weeks and routine ultrasound at 16–22 weeks will identify up to 80% of abdominal wall defects. Maternal serum α -fetoprotein screening has been reported as being positive in 42% of omphaloceles [109]. The sensitivity of ultrasound and screening is estimated at 80% [110–112]. Ultrasound images show that the liver and/or gut are present in a circumscribed mass at the abdominal cord insertion site [91]. Eighty percent of omphaloceles contain liver with varying amounts of small bowel. A ‘giant’ omphalocele is present when the majority of the liver is extra-abdominal. The stomach and bladder may occasionally be located in the omphalocele. A membrane consisting of amnion, peritoneum, and Wharton’s jelly surrounds the mass. Ascites may be present within the omphalocele or within the abdomen. Twenty percent of omphaloceles contain gut and fluid only (small omphalocele). In utero rupture of the omphalocele is a rare complication and may be distinguished from gastroschisis due

to the size of the defect and the presence of exposed liver. Polyhydramnios may be associated with omphalocele. Additional investigations should include amniocentesis [84, 85, 92, 113] (chromosomal, α -fetoprotein and molecular analysis), fetal echocardiography [84, 91] and MRI [114]. Prenatal testing is offered by chromosome analysis for families with an inherited chromosome abnormality or by molecular genetic testing for families with a defined molecular mechanism [92].

Pregnancy and Delivery Management

Pregnancy management includes counseling about fetal morbidity and mortality with isolated omphalocele, associated anomalies or genetic syndromes. For fetuses with an isolated omphalocele (small to giant), serial ultrasound evaluation every 2–4 weeks can be utilized to evaluate fetal growth, amniotic fluid volume and for fetal physiological assessment by biophysical profile and non-stress monitoring in the third trimester due to the increased risk of intrauterine death. Consultation at a tertiary level center with maternal fetal medicine, neonatology, and pediatric surgery is strongly recommended due to the multi-disciplinary care required by these newborns [84, 85]. Rates of preterm delivery range from 26 to 65% and intrauterine growth restriction from 6 to 35% with a high rate of an emergency cesarean delivery due to fetal distress with or without labor [100, 107–117].

Delivery should be at term if possible in a center with appropriate perinatal facilities for surgical management of the neonate. There appears to be no advantage for delivery by cesarean section except for those fetuses with a ‘giant’ omphalocele containing the majority of the liver as this type of defect may result in dystocia and liver damage with a vaginal birth [118, 119].

Surgical Repair

Following delivery, newborn care should be directed towards preoperative stabilization, involving airway stabilization and sterile wrapping of the abdominal defect to prevent heat and minimize insensible fluid losses [84, 85]. Major effort is made to avoid trauma and contamination of the omphalocele sac. The fetal trunk and legs can be enclosed in a sterile plastic drawstring bag. Peripheral vascular access should be established to administer intravenous fluids and antibiotics. Mechanical ventilation is frequently necessary due to secondary lung hypoplasia with large omphaloceles. Prompt decompression of the stomach is important initially followed by intermittent gastric suction.

The importance of postnatal evaluation cannot be overemphasized to rule out genetic syndromes which may not have been diagnosed in utero. Infants with an unruptured omphalocele do not require urgent surgery allowing time for patient stabilization and newborn assessment to rule out associated anomalies prior to attempting defect closure [120]. Appropriate clinical assessment and diagnostic testing should include echocardiogram (repeat) and renal evaluation [84, 85].

For the last two decades, the preferred method of omphalocele repair is primary fascial closure. The benefits are a lower incidence of sepsis and biliary obstruction/fistula as well as reduced operations and mortality [84].

Intraoperative management consists of removal of the amniotic sac, evaluation for associated intestinal malrotation with lysis of bands obstructing the duodenum, and intestinal evaluation for possible atresias [85]. Attempts at primary fascial and abdominal wall closure are guided by intra-abdominal pressure values (intra-gastric, intravesical) of <20 mm Hg after returning viscera to the abdominal cavity [85]. Increased intra-abdominal pressure requires alternate techniques using gradual reduction of the viscera over 5–7 days using a temporary silastic/Dacron extra-abdominal pouch or the omphalocele membrane with sequential ligation of the pouch or membrane sac [85]. Once the viscera are returned to the abdomen, surgical removal of the pouch and secondary abdominal wall closure can be accomplished [121]. Giant omphaloceles have associated respiratory factors (lung hypoplasia) which make primary closure more difficult. Combined techniques with silastic pouch, elastic bandage wrapping, mobilization of lateral skin flaps and stretching of the abdominal wall may be required.

For the few defects that cannot be closed safely within 7–10 days, simple skin coverage with fascial closure using the 'Gross' technique can be used [120]. Non-operative techniques recommend operation site or mercurochrome for coverage options [84, 120]. These methods all require a subsequent ventral hernia repair which may be difficult and prolong hospitalization.

Postnatal Outcome

Overall neonatal survival depends on the severity of the associated anomalies (most commonly cardiac defects) and may vary from 30 to 70% [85]. Long-term morbidity is usually related to respiratory and feeding abnormalities, with an extended stay in the neonatal nursery [121–124].

Cardiopulmonary performance in young children and adolescents born with large abdominal wall defects were

evaluated at ages 7–18 years of age. At evaluation they exhibited normal cardiorespiratory function with decreased time of exercise on a treadmill and decreased maximal oxygen consumption. These findings were felt to reflect the lack of physical activity with an overall lower degree of fitness. Conclusions were that no limitations to motor performance should exist for these patients and their well-being may be greatly improved by regular exercise [125]. Gastrointestinal reflux was evaluated in a cohort of 42 children with abdominal wall defects at a median age of 12 months. Those children with a large defect omphalocele had a high incidence of gastroesophageal reflux (43%) complicated by esophagitis during the first few years of life [126]. Garcia et al. [127] reported that the 2 main causes of postoperative morbidity in newborns with an abdominal wall defect were infection and acute renal failure.

Fetal Therapy

The literature and the contents of fetal surgery meetings were reviewed with no fetal therapy for omphalocele being identified.

Long-Term Childhood Follow-Up of Omphalocele and Gastroschisis

The long-term follow-up of children with prenatally diagnosed omphalocele reported that 4 of 7 children with omphalocele had major associated malformations (2 BWS, 1 porencephalic cyst, 1 skeletal defects) [128]. These children presented handicap issues related to the associated malformations but not to the abdominal wall defect. The other 3 children with isolated omphalocele were developing normally. Kaiser et al. [129] reported on the quality of life of a cohort of children from 1970 to 1998 diagnosed with omphalocele and gastroschisis. There were 35 children with omphalocele and 31 with gastroschisis and 40 of 43 survivors were examined in 1990. The data of 30 patients were renewed in 1999 and 12 new cases were added. Total follow-up was 1–28 years. Primary closure had been possible in 25 omphaloceles and 20 gastroschises. Eighteen children with omphalocele and 8 with gastroschisis had additional anomalies which were treated simultaneously with the abdominal wall defect. Twenty percent of babies with omphalocele died due to additional severe congenital anomalies and 12.9% of gastroschisis because of infectious complications. No deaths occurred in the last decade studied. Long-term follow-up revealed normal growth and development of the children

without additional severe congenital anomalies. Most children with isolated omphalocele and gastroschisis are participating without problems in normal activities and education without reduction in their quality of life.

Adequate long-term follow-up studies are limited and while there are a small number of retrospective cohort studies available, more long-term data are needed for adequate counseling and parental choice prenatally.

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