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Gastroschisis

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Introduction

Gastroschisis is defined as an abdominal wall defect that involves herniation of the gut and occasionally other abdominal organs such as the spleen and liver. It occurs mostly to the right side of the umbilicus and is characterized by the absence of a membrane covering the prolapsed organs with bowel loops floating in the amniotic fluid.

It is now commonly diagnosed during the prenatal period by means of sonography and the overall prognosis is excellent with a 90% survival rate.[1,2] Morbidity depends on associated prematurity, intrauterine growth retardation, bowel atresia, and perivisceritis resulting from contact with the amniotic fluid. The pathogenesis of gastroschisis and secondary bowel lesions are not fully understood. The management of gastroschisis is also still debated because there is no large prospective study concerning the mode, time, and place of delivery, or the type and time of initial surgery during the neonatal period.

Recent advances in the understanding of the elements responsible for the bowel damages such as digestive compounds and associated inflammation in the amniotic fluid may induce changes in therapeutic strategy, including prenatal treatment using amnioexchange.

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Prevalence and Epidemiology

The total prevalence of gastroschisis, including live births, stillbirths, and terminations

of pregnancy, is approximately one to 4 in 10000 live births[1–6] with a sex ratio approximately 1 (Table 1). Although the total prevalence varies among geographic areas,[2,7,8,9] studies of several international registries or referral centers report a global increase of gastroschisis during recent years.[1,2,7,10] No etiology has yet been implicated in this global increase, and prospective studies are warranted to identify potential etiologies.

Several maternal risk factors have been identified in association with gastroschisis. Goldbaum et al[11] found an increased risk from maternal age less than 25 years old with the highest risk in mothers less than 20 years old (odds ratio, 4.1). Werler et al reported that relative risks in 20- to 24-year-old and less than 20-year-old mother groups were, respectively, 5, 4, and 16.[12] More recently, several studies have reported similar results, confirming that young maternal age is a major risk factor for fetal gastroschisis.[1,2,7,13] It occurs more frequently in primiparas[2,13,14] and is associated with low socioeconomic status, poor maternal education, and drug abuse (tobacco, alcohol, and cocaine).[12,15,16] Other teratogens have been implicated and are reported in Table 2. It has been suggested that these substances may have vasoreactive effects during embryonic development.

Some isolated associations have been described with aneuploidy, trisomy 13, 18, 21, and monosomy 22,[17] and some familial cases have also been reported.[18–26] The role of genetic, epigenetic, and environmental factors is not yet clearly established.[27]

TABLE 1. Increasing Incidence of Gastroschisis

	Period of Study	Incidence per 10000 Live Births
Baerg et al	1985–1990/1996–2000	1.85/4.06
Penman et al	1987/1995	1.60/4.40
Rankin et al	1986/1996	1.48/4.72
Kazaura et al	1968/1998	0.50/2.90
Hougland et al	1971/2002	0.36/3.92

TABLE 2. Potential Teratogens Implicated in Gastroschisis and Epidemiologic Associations

Potential teratogens
Tobacco
Alcohol
Cocaine
Aspirin
Ibuprofen
Pseudoephedrine
Acetaminophen
Phenylpropanolamine
Epidemiologic associations
Young maternal age and short interval between menarche and first pregnancy
Low socioeconomic status
Poor maternal education

Pathogenesis of Gastroschisis and Bowel Lesions

The pathogenesis of gastroschisis is not clearly understood; the most cited mechanism is the premature regression, by the fifth or sixth weeks of gestation, of the right omphalomesenteric artery or of the right umbilical vein.[28,29] This premature regression leads to a failure of mesodermal components of the abdominal wall; intestinal malrotation is almost constantly associated with gastroschisis. Others consider that gastroschisis may be related to an early in utero rupture of an umbilical cord hernia.[30]

Several studies in animal models yielded a better understanding of associated bowel lesions. Their cause seems to be both chemical and mechanical.[31–35] Bowel contact with the amniotic fluid is associated with a sterile inflammation of the bowel wall resulting in a fibrous coat called perivisceritis. Other bowel lesions of increasing gravity such as ischemia, perforation, stenosis, atresia, partial or complete necrosis may be present and affect morbidity, mortality, and prognosis.[36–40]

Burc et al[41] found that, in cases of gastroschisis, intraamniotic values of total protein and ferritin levels were increased and displayed a chronic inflammatory profile. In another study,[42] IL8 also displayed increased levels together with an acute inflammatory exudate composed predominantly of

neutrophil polymorphs and mononuclear cells (Table 3). Because of the occurrence of meconium stained amniotic fluid, some authors have suggested that gastrointestinal waste products might be implicated in this in utero inflammatory reaction.[41,43,44]

Most bowel histologic studies have been performed on resection samples of atretic bowel from initial or iterative surgery or performed quickly after birth on necroscopic samples; they revealed the presence of edema, fibrin deposition, fibrosis, capillary proliferation, cellular infiltration of epithelial cells, and macrophages in the bowel wall.[45,46] These results have also been described in animal models.[47–50] In a rat model, Yu et al[51] have demonstrated that late injection of dexamethasone into the amniotic fluid of fetuses with gastroschisis had beneficial effects on bowel wall thickening, normalized total DNA, induced cellular proliferation, and decreased apoptosis. In 2000, Correira-Pinto[52] demonstrated in another rat model of gastroschisis that perivisceritis was dependent on the presence of meconium. It has also been demonstrated that exchanging amnioallantoic fluid decreased bowel lesion intensity,[53] which was coincident with a decrease in gastrointestinal waste products, whereas urinary waste products did not vary.

Recently, it has been suggested that in utero defecation is a physiological event during normal fetal life and increases in the last weeks of pregnancy.[54] This has been supported by the presence of intestinal enzymes in the amniotic fluid of normal pregnancies.[55,56] Ciftci et al[54] have suggested that meconium-stained amniotic fluid is not only related to meconium passage, but perhaps to impaired clearance of amniotic fluid; digestive compounds present in the amniotic fluid could thus be responsible for the chemical mechanism leading to perivisceritis.[48,57] The exact impact of amniotic fluid on the peritoneal surface of the bowel wall is not yet completely known; however, exposure of the fetal pleural surface to amniotic fluid induces similar changes seen in the bowel wall in cases of gastroschisis.[58]

The inextensible parietal defect may induce a mechanical compression on the superior mesenteric artery or vein and be responsible for ischemic complications or venous congestion. Occlusive and subocclusive complications may also occur and be responsible for in utero vomiting, abnormal defecation,[59] and decreased clearance of amniotic fluid together with bowel hypoperistaltism.[54]

Some studies have demonstrated that bowel lesions are associated with downregulation of various genes involved in amino acid and glucose absorption[60–63] in experimental models of gastroschisis and with fetal protein loss.[64] Other studies have demonstrated that overexpression of nitrous oxide synthase[65–68] is associated with bowel hypoperastaltism.[60,69]

TABLE 3. Chronic Inflammation in Amniotic Fluid

Inflammatory exudate	+
IL6	↑
IL8	↑
IL1β	−
TNFα	−
Ferritin	↑

Prenatal Diagnosis and Sonography

Prenatal diagnosis of gastroschisis relies on sonography. Gastroschisis, in contrast to omphalocele, is not associated with an increased risk of chromosomal abnormalities or associated extragastrointestinal malformations. Some studies have produced contradictory results; although Rankin et al have reported a malformation rate of 5.3% associated with gastroschisis and Roland et al a rate of 5.5%, the EUROCAT study has reported a rate of 20.8% of associated malformations. The most common extragastrointestinal malformations associated with gastroschisis are reported in Table 4.[1,2]

Third-trimester sonography is not accurately able to identify partial necrosis and secondary atresia, but in a retrospective

TABLE 4. Malformations Associated With Gastroschisis

Hydronephrosis
Arthrogryposis
Hypoplastic gallbladder
Meckel diverticulum
Oligo-anhydramnios (intrauterine growth restriction)

study of 45 patients with a prenatal diagnosis of gastroschisis, Japaraj et al[70] found that the occurrence of polyhydramnios was significantly associated with a higher rate of severe bowel complications such as atresia, perforation, and necrotic segments in the neonatal period with a likelihood ratio at 11:7. Gestational age at first diagnosis, maximum bowel diameter, maximum bowel wall thickness, presence of other anomalies, and evidence of growth restriction have also been studied, but no significant association has been consistently found. However, bowel dilatation and bowel wall thickening are often cited in studies as prognostic factors for a worse perinatal outcome. Although data are not consistent, some authors have defined threshold values (11–18 mm) for poor prognosis and indication for preterm delivery, whereas others disagree.[37,71–83] Aina-Mumuney et al[84] found a significant correlation between gastric dilatation and length of stay in the neonatal intensive care unit (NICU) and the occurrence of a nonreactive nonstress test. The importance of bowel wall thickening is even more controversial, and no consensus emerges from the different studies.[71–82]

Recently, intraabdominal bowel dilation in the second trimester of pregnancy has been found to be highly predictive of neonatal bowel atresia in fetuses with gastroschisis. Bruner et al studied 58 fetuses with at least one prenatal ultrasound and newborn admission to their institution. Of the 58 fetuses, 48 had no intraabdominal bowel dilation and none of the newborns had bowel atresia. Ten had intraabdominal bowel dilation in the second trimester and all 10 had bowel atresia at birth ($P < 0.0001$). In 8 cases in which ultrasound was performed at <25 weeks gestation, intraabdominal bowel dilation was already present.[146]

Mesenteric vascularization has also been studied. Langer showed in a lamb model that progressive constriction of bowel induced lesions independently of contact with amniotic fluid.[31] Doppler measurements of the superior mesenteric artery may thus represent a potential tool for the evaluation of gastroschisis. Studies have contradictory results; Achiron[85] showed stability of vascular resistance from 29 weeks of gestation, and Abuhaman[82] did not find any correlation between Doppler values in the extraabdominal superior mesenteric artery and the outcome of gastroschisis. By contrast, Volumenie et al, in 2001,[86] found a significant correlation between Doppler values and length of NICU stay and between maximal bowel dilatation and length of NICU stay.

Intrauterine growth retardation (IUGR) is frequently associated with gastroschisis but may be overestimated because of the smaller abdominal circumference measurements commonly seen.[87,88]

Fetal Heart Rate Monitoring

The risk of in utero fetal death is higher in fetuses with gastroschisis.[89–92] The incidence of fetal heart rate abnormalities is approximately 10% during the third trimester of gestation and may require delivery.[64,93–100] They consist of decreased variability with or without decelerations.[101] These abnormalities may be partially the result of bowel torsion or subtorsion. They may also be related to the IUGR and oligohydramnios that often complicate gastroschisis. Adair et al[89] found a significant decrease in perinatal mortality when fetal testing was regularly performed irrespective of the occurrence of complications such as oligohydramnios and IUGR. In a study including 57 fetuses between 1982 and 1995 by Burge et al,[91] fetal distress was diagnosed in 43% of the cases, and in this group, 6 fetuses had adverse neurologic complications postnatally.

Introduction of fetal heart rate monitoring was associated, in this study, with a reduction of neurologic complications from 21% to 6%. In a recent study, Brantberg et al[102] found a high (22%) rate of fetal distress; diagnosis was made on fetal cardiotocography repeated everyday or every second day from 34 weeks of gestation. These results suggest that fetal distress is a frequent complication and that third-trimester fetal cardiotocography is a major tool for monitoring cases of gastroschisis.

Fetal Therapy

Amnioinfusion and amnioexchange have been used to reduce gestational complications and to improve neonatal outcome, but no retrospective or prospective study has yet succeeded in showing unambiguously the benefits of such techniques.[103]

Amnioinfusion consists of an injection of warmed (37°C) physiological saline. Dommergues[104] and Sapin[105] have reported the use of amnioinfusion in case of oligohydramnios associated with gastroschisis with good outcomes.

Amnioexchange consists of the replacement of the amniotic fluid volume by volume with warm (37°C) saline, and the procedure was first published in 1998 by Aktug[106] who performed 4 amnioexchanges in the same fetus with a good outcome. Amnioexchange has been proposed because of the adverse effects of amniotic fluid on bowel wall and function. In some studies using animal models of gastroschisis,[47,50] amnioexchange was responsible for an increased clearance of inflammatory compounds and gastrointestinal waste products and was associated with decreased inflammation in the bowel wall. We have shown in a comparative historic retrospective study the potential benefits of amnioexchange in humans to ameliorate the outcomes of fetuses with gastrochisis.[43] However, prospective, randomized studies in humans are needed to confirm these results and to evaluate the effects on postnatal morbidity and mortality.

Time, Mode, and Place of Delivery

The mean gestational age at spontaneous delivery in gastroschisis is approximately 36 to 37 weeks.[107] The recommended mode and timing of delivery is still debated, because labor may be deleterious to bowel loops (by compression and twisting) and ruptured membranes may contribute to neonatal infectious complications. However, most authors have found no significant benefit to cesarean section,[108–114] and it has even been associated, in one study, with worse neonatal and infant outcomes with higher mortality and morbidity rates.[115] In 2001, in a systematic review, Segel et al[116] concluded that available data do not provide evidence to support systematic cesarean section for fetuses with abdominal wall defects. More recently,[117–119] 3 other retrospective studies concluded that systematic cesarean section does not improve the outcome of infants with gastroschisis.

Because prolonged contact with amniotic fluid may be deleterious for the bowel wall and function, preterm delivery has been considered. In a recent study of 75 patients, Orkan et al[120] found no advantages in early delivery (before 36 weeks of pregnancy). In the group of patients with early delivery, the time to full feeding was delayed and total length of stay in the hospital was longer when compared with the group of patients with delivery at term. Intrauterine growth retardation is frequently associated with gastroschisis but does not constitute an indication for preterm delivery except in cases of abnormal middle cerebral artery Doppler and absent or reversed end diastolic velocities of the umbilical artery.[121]

These data suggest that cesarean section should be reserved for obstetric indications and acute fetal complications only.

The location of delivery is no longer debated, although some studies have found no advantage to neonatal outcome from prenatal transfer to a center with pediatric surgical facilities.[119,122–125] Two studies had

opposite results and concluded that inborn neonates had better outcomes than outborn ones, and more specifically, Quirk et al[115] found that inborn neonates had earlier enteral feeding and shorter hospital length of stay.

Postnatal Care

Neonatal surgical therapeutic strategy is still controversial, pitting primary fascial closure against delayed abdominal closure using temporary coverage with an intraabdominal pouch or mobilized lateral skin flaps.[126] The surgical strategy depends, most of the time, on the intraabdominal pressure during reintegration of the abdominal organs. Some studies in animal and human models[127–130] have shown that primary fascial closure is possible when intraabdominal pressure is under 20 mm Hg. In a recent study of 42 neonates, Olesevitch et al[127] demonstrated that in this situation, primary closure was associated with significantly shorter hospital stays and faster returns to full feeds when compared with delayed closure using a Silon pouch with a spring-loaded base. Most of the time, increased intraabdominal pressure necessitates assisted ventilation, vasoactive and/or myorelaxant drugs, and diuretics. Other studies have reported better outcomes for gastroschisis, particularly the length of hospital stay, when a spring-loaded silo is used for 24 hours before fascial closure.[131,132]

Delayed total enteral nutrition requires the placement of a central venous line to provide appropriate caloric and hydroelectrolytic intake but is associated with septic complications.[133,134] Parenteral nutrition is then replaced progressively by partial and complete enteral nutrition, and the total duration of bowel rest will vary, depending mostly on clinical conditions. The time of complete enteral nutrition is related to the length of hospital stay and the duration of total parenteral nutrition.[135]

Prognosis

The overall prognosis for gastroschisis is good and has improved in the past 20 years.[136,137] Survival rates greater than 90% are now common.[138,139] This result is the result of prenatal sonographic diagnosis that allows prenatal monitoring and delivery in a tertiary care center,[140,141] and improvements in parenteral nutrition, surgery, and resuscitation techniques. Short-term and long-term outcomes[135,142] are related to the quality of the exteriorized bowel loops and gastrointestinal complications. In a recent study of 181 patients, Singh et al[119] reported even lower mortality (4.4%), mainly related to short gut, and sepsis only occurred in one patient.

In the literature, most studies use the time of assisted ventilation, duration of parenteral nutrition, time to full feeds, or hospital stay length to evaluate short-term prognosis. As an example, Singh et al[119] showed that when time to full feeds was shorter than 10 days, the incidence of sepsis, the duration of total parenteral nutrition, ventilation, and hospital stay were significantly shorter. Other studies showed that the overall length of stay is approximately 80 days[143,144] and is dependent on the time of total enteral nutrition and total parenteral nutrition.[135]

Long-term general and neurologic outcome is excellent in most cases.[108,138,145]

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