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REVIEW PAPER

Gastroschisis: embriology, pathogenesis, risk factors, prognosis, and ultrasonographic markers for adverse neonatal outcomes

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Abstract

Gastroschisis is the most common congenital defect of the abdominal wall, typically located to the right of the umbilical cord, through which the intestinal loops and viscera exit without being covered by the amniotic membrane. Despite the known risk factors for gastroschisis, there is no consensus on the cause of this malformation. Prenatal ultrasound is useful for diagnosis, prognostic prediction (ultrasonographic markers) and appropriate monitoring of fetal vitality. Survival rate of children with gastroschisis is more than 95% in developed countries; however, complex gastroschisis requires multiple neonatal interventions and is associated with adverse perinatal outcomes. In this article, we conducted a narrative review including embryology, pathogenesis, risk factors, and ultrasonographic markers for adverse neonatal outcomes in fetuses with gastroschisis. Prenatal risk stratification of gastroschisis helps to better counsel parents, predict complications, and prepare the multidisciplinary team to intervene appropriately and improve postnatal outcomes.

Keywords Gastroschisis · Embryology · Pathogenesis · Risk factors · Ultrasonographic markers

Introduction

Gastroschisis is the most common congenital defect of the abdominal wall. This defect is typically small and is located in 95% of cases to the right of the umbilical cord, through which the intestinal loops and viscera exit. Unlike omphalocele, the exposed loops are not protected from the amniotic fluid by the peritoneal membrane, so blood flow to the intestinal loops is more likely to be interrupted [1] (Fig. 1). According to data from the US Centers for Disease Control and Prevention (CDC), the prevalence of gastroschisis has increased by about 30% in the prevalence of gastroschisis from 3.6 per 10,000 births (between 1995 and 2005) to 4.9 per 10,000 births (between 2006 and 2012), but the reason for this trend is unclear [2, 3].

Classically, early maternal age (< 20 years), maternal infections (sexually transmitted diseases and urinary tract infections) and smoking are well documented risk factors for gastroschisis [4, 5]. Early diagnosis of gastroschisis during prenatal care can be made by ultrasound as early as the 12th week of pregnancy, when there is complete closure of the physiologic herniation of the intestine. However, in most cases this malformation is not diagnosed until the second trimester of pregnancy [6].

Fetal growth restriction is quite common in fetuses with gastroschisis (24–67% of cases). It is believed that this is due to the loss of substances through the externalized loops, mainly proteins, leading to nutritional depletion of the fetus. This is supported by the finding of high concentrations of proteins in the amniotic fluid of fetuses with gastroschisis. Placental insufficiency does not appear to be the cause of this growth restriction [7].

Fetal death is more common in fetuses with gastroschisis (4.5%) compared to normal pregnancies (0.6%) [8], with a progressive increase in risk in cases where expectant management was chosen beyond 37 weeks of gestation [9]. A recent meta-analysis showed that 38 weeks is the optimal timing for delivery of fetuses with gastroschisis, fetal growth restriction, and normal umbilical artery Doppler for minimizing overall perinatal mortality and resulting in the highest total quality-adjusted life-years [10]. In the past, it was believed that cesarean section was the best delivery option for fetuses with gastroschisis because it reduced the risk of

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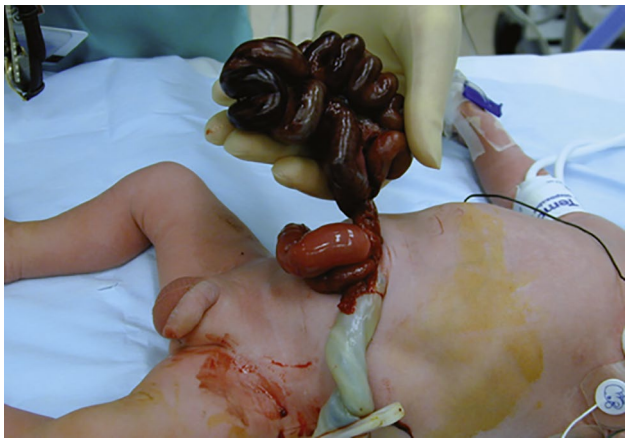

Fig. 1 Postnatal image of newborn with gastroschisis showing the abdominal wall defect right to umbilical cord insertion with exteriorization of intestinal loops without membrane coverage

trauma to the intestinal loops and avoided contact with the vaginal flora. However, several studies have shown that there is no benefit in neonatal outcomes of elective cesarean section compared to vaginal delivery [6, 11].

Neonates with gastroschisis are associated with several complications such as sepsis, necrotizing enterocolitis, short bowel syndrome, bowel obstruction, and volvulus [12]. Complex gastroschisis requires multiple neonatal surgeries and is associated with higher rates of adverse perinatal outcomes than simple gastroschisis [13].

The purpose of this article is to review the embryology, pathogenesis, risk factors, prognosis, and ultrasonographic markers for adverse neonatal outcomes in fetuses with gastroschisis.

Embriology

During the third week of embryonic development, the gastrulation process takes place, in which the bilaminar embryonic disc is converted into a trilaminar disc with the three germ layers (ectoderm, mesoderm and endoderm). This disc lies between two cavities, the amniotic cavity located dorsally, and the umbilical vesicle located ventrally [14, 15].

At the beginning of the fourth week, the trilaminar embryonic disc grows and folds around its ventral part. Cranial, caudal, and lateral folds occur simultaneously. This results in a relative constriction of the embryo in the umbilical vesicle, causing the cephalic and caudal folds to appear in the embryo. In this way, the dorsal part of the umbilical vesicle is incorporated into the embryo as the anterior (cranial) intestine and the posterior (caudal) intestine. This process is also responsible for the cranial displacement of the caudal connecting trunk, bringing it closer to the ventral surface of the embryo [14].

During lateral folding, the primordium of the abdominal wall bends relative to the median plane, incorporating a portion of the endodermal layer as the midgut. This leads to a narrowing of the communication between the midgut and the umbilical vesicle, forming the omphaloenteric duct. At this point, the umbilical cord is observed, formed by the allantois, the connecting pedicle and the omphaloenteric duct, and lined by the amnion [14].

Around the sixth week, the rapid growth of the intestine and other organs, especially the liver, forces the intestine to migrate out of the abdominal cavity, through the umbilical ring, and into the umbilical cord. The intestine rotates 90º counterclockwise around the superior mesenteric artery. This process is the physiologic herniation of the fetus, which is completed by the 11th week with the retraction of the midgut and its return to the abdominal cavity [16].

Pathogenesis

Despite the known risk factors for gastroschisis, there is no consensus on the cause of this malformation. Several theories have been proposed to explain the development of this pathology:

(1) Embryologic failure in mesenchymal differentiation after teratogenic exposure around the fourth week of embryonic development, which would impair abdominal growth, resulting in an opening through which herniation would occur. The possible teratogenic agent was not explained [17]. Feldkamp et al. [18] suggested that gastroschisis is the result of a failure in the fusion of the lateral folds, leading to an abnormal closure of the thoracic and abdominal cavities.
(2) An amniotic rupture at the base of the umbilical cord would weaken the abdominal wall, allowing the loops to herniate [19]. Although this theory did not explain the cause of such a rupture, it was taken up in 1996 by Kluth and Lambrecht [20] who argued that gastroschisis could be the result of the rupture of a small omphalocele. In 2014, Bargy and Beaudoin [21] proposed that the origin of this malformation was due to the rupture of the amnion surrounding the eviscerated loops during physiological herniation. This theory was justified by the observation of vacuolar changes in the cells of the embryos studied, caused by exposure to teratogenic agents.
(3) Possible vascular alterations such as abnormal involution of the right umbilical artery and interruption of the left omphalomesenteric artery could lead to abdominal wall weakness and infarction with necrosis of the

umbilical cord base, resulting in intestinal herniation [22, 23]. Both hypotheses were ruled out because they were not compatible with the real embryonic vascular anatomy. However, Lubinsky [24] proposed a vascular/thrombotic theory, postulating that normal involution of the right umbilical vein leaves a space in the umbilical ring that would be susceptible to thrombotic events when estrogen levels are high. This thrombosis would impair cell growth and allow abdominal organs to herniate.

Epidemiology and risk factors

Gastroschisis is a defect of the anterior abdominal wall with herniation of abdominal organs, mainly intestinal loops, without their being covered by the amniotic membrane. There is a worldwide trend of increasing incidence. In the United States, it is estimated to occur in 4–5 children per 10,000 births [25]. In Brazil, a recent study reported an incidence of 2.47 cases per 10,000 births between 2007 and 2020, an increase of 23% in the last two years compared to the first [26].

It is now believed that gastroschisis is the result of an interaction between molecular mechanisms and genetic predisposition during the first 10 weeks of embryonic development. Low maternal age seems to be the main risk factor. An American study estimated that between 2005 and 2013, 74% of gastroschisis cases were diagnosed in women under 25 years of age [27, 28]. However, high BMI seems to be a protective factor [29].

Skarsgard et al. [30] analyzed Canadian databases from 2006–2012 to establish a profile of risk factors for the occurrence of gastroschisis. The authors compared 692 pregnancies with gastroschisis with 4708 normal pregnancies (control group). It was observed that young mothers, smoking, history of pregestational/gestational diabetes and use of antidepressants had a significant association with gastroschisis. Liu et al. [31] evaluated the epidemiologic characteristics of gastroschisis in the Canadian population between 2006 and 2017 by analyzing the Canadian Health Information Institute database. The authors concluded that patients with depressive disorders and the use of cigarettes, alcohol, cocaine, cannabinoids, and opiates were associated with an increased risk of gastroschisis.

To support their hypothesis that gastroschisis is caused by accumulated exposure to potential stressors that induce an oxidative/inflammatory response, Werler et al. [32] performed a case–control study using database analysis. Exposure to 16 agents was assessed: maternal health problems, fever, intensive care unit, bronchodilators, cigarettes, alcohol, illicit drug use, opioids, anti-herpetic medications, oral contraceptives, aspirin, venlafaxine, paroxetine, ibuprofen, parity less than 12 months, and moving. It has been observed that the more stressors a woman is exposed to, the greater her risk of gastroschisis, indicating a dose–response effect. In a recent systematic review, Baldacci et al. [33] conducted a survey of epidemiologic studies published between 1990 and 2018, analyzing risk estimates between lifestyle and sociodemographic factors and gastroschisis. The authors found that smoking, illicit drug use, and alcohol consumption during pregnancy were associated with an increased risk of gastroschisis.

To assess possible risk factors, Weber et al. [34] conducted a retrospective case–control study in the state of California, United States, comparing 286 cases of gastroschisis with 1263 normal pregnancies. The cases analyzed were divided into two groups according to maternal age at delivery: <20 and ≥ 20 years. In the <20 years group, the highest odds of having a child with gastroschisis were observed in cases with frequent consumption of chocolate and moderate consumption of sweets, low iron intake, use of paracetamol in the first two months of pregnancy, and a history of urinary tract infection in the first month of pregnancy. In the ≥ 20 years group, Hispanic origin and illicit substance abuse one month before pregnancy were considered important variables.

Diagnosis

The diagnosis of gastroschisis is usually made during the second trimester of pregnancy using ultrasound. The ultrasound examination of the abdominal wall consists of an axial view of the fetal abdomen at the level of the umbilical cord insertion, which may be supplemented by a sagittal view. The color Doppler study helps to demonstrate the normal insertion of the umbilical cord with a right-sided inguinal hernia. The ultrasound findings of gastroschisis are: a reduced fetal abdomen, an anterior abdominal closure defect to the right of the umbilical cord insertion, and varying degrees of exteriorization of the abdominal contents (intestines, stomach, liver, and bladder), which are in contact with the amniotic fluid because they are not covered by the amniotic membrane [35] (Fig. 2).

Prenatal diagnosis of gastroschisis is fundamental because it allows us to advise the parents, to predict the prognosis and to adequately control the fetal vitality, as well as to plan the delivery in a tertiary hospital with a specialized team and postnatal surgical correction.

Prognosis

Complicated pregnancies with gastroschisis are associated with unfavorable outcomes, including fetal growth restriction, amniotic fluid volume alterations, fetal death, prematurity, and low birth weight, as well as the need for prolonged postpartum hospitalization [36].

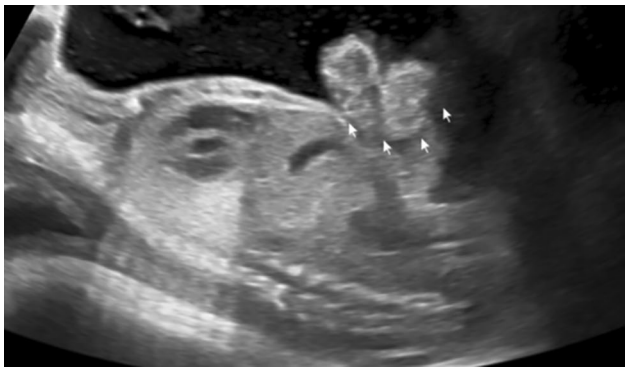

Fig. 2 Two-dimensional ultrasonography in sagittal view of a fetus with gastroschisis at 22 week's gestation, showing the appearance of the exteriorized intestinal loops in direct contact with the amniotic fluid (arrows)

Fetuses with gastroschisis often have growth restriction in 24–67% of cases [37, 38] and low birth weight in approximately 60% [39]. The mechanism responsible for these conditions is controversial, but is thought to be due to loss of protein by exudation through the walls of the herniated intestinal loops in contact with the amniotic fluid, leading to fetal nutritional depletion and subsequent growth impairment [37, 40]. Dixon et al. [41] concluded that intestinal atresia appears to protect against growth restriction. The healthy intestine, with its intact vascular supply and large surface area, would show greater protein loss than atresic loops.

Horton et al. [7] studied the parameters for calculating weight using the Hadlock formula (biparietal diameter—BPD, head circumference—HC, abdominal circumference—AC and femur length—FL) and showed that fetuses with gastroschisis had impaired intrauterine growth, mainly due to the small AC measurement. This pattern was observed in the middle of the second trimester and did not progress throughout the pregnancy. Thus, placental insufficiency does not seem to be the cause, since there is no worsening of fetal growth. On the other hand, it is believed that the fetal growth restriction index may be overestimated because most formulas for calculating fetal weight use the AC measurement, which is reduced in fetuses with gastroschisis due to herniation of abdominal contents.

Fetal death is common in pregnancies with gastroschisis, with a prevalence of 4.5 deaths per 100 pregnancies, with most cases occurring in the third trimester [8]. The cause is still under debate, but it appears to be related to compression of the umbilical cord by the herniated abdominal contents [42]. The risk begins to increase at around 35 weeks, particularly from 37 weeks, and peaks at 39 weeks. Therefore, the risk of mortality can be minimized by delivering around 37 weeks [9]. Gastroschisis also has a higher neonatal mortality rate (1.75%) compared to normal pregnancies (0.47%) [43].

The survival rate of children with gastroschisis is good, reaching over 95% in developed countries [44]. This is thought to be due to a number of factors, including prenatal diagnosis, delivery in a tertiary hospital with a pediatric surgical service, advances in neonatal intensive care, and continuous improvement in surgical techniques [45]. However, neonates may face several postnatal complications, such as prolonged hospital stay and parenteral nutrition, sepsis, necrotizing enterocolitis, short bowel syndrome, and prolonged mechanical ventilation [46].

After birth, initial management of gastroschisis includes intravenous fluids, respiratory support, and bowel protection. Surgical correction on the first day of life is one of the main goals of treatment, with reduction of herniated contents and abdominal closure to avoid abdominal compartment syndrome [47]. This technique protects the bowel loops from mechanical trauma and eliminates the risk of additional injury, possibly caused by compression of the mesenteric artery [48] (Fig. 3).

If primary closure is not possible, other techniques can be used, such as silo placement with gradual closure of the abdominal wall and closure without suture. In this type of closure, the umbilical cord is placed over the defect after the viscera have been reduced and there is circumferential contraction of the fascia and formation of granulation tissue with subsequent local epithelialization [49] (Fig. 4). An American study compared the results of surgical techniques

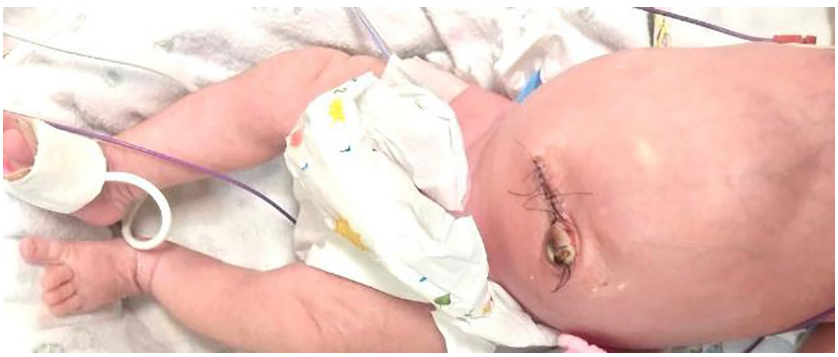

Fig. 3 Newborn after primary closure surgery for gastroschisis

and concluded that children who underwent primary closure had a shorter hospital stay and a lower risk of surgical site infection. However, they required more days of mechanical ventilation and were more likely to require nutritional support after hospital discharge [50].

In 2001, to categorize the risk of gastroschisis patients and predict adverse outcomes, Molik et al. [51] created two categories based on the presence or absence of intestinal loop anomalies at birth: simple and complex. After analyzing 103 newborns with gastroschisis, they observed that children who had intestinal atresia, volvulus, perforation, or necrosis at birth (complex cases) had higher morbidity and mortality compared to simple cases who did not have such intestinal complications. The complex cases required longer periods of mechanical ventilation, had longer paralytic ileus, and took longer to tolerate total enteral nutrition (Fig. 5).

A Canadian cohort correlated postnatal outcomes with the macroscopic appearance of the intestinal loops at birth using a lesion score (GPS—gastroschisis prognostic score) that included the following variables: matting, necrosis, atresia, and perforation. The presence of each variable was assigned a score ranging from 0 to 4. Patients with a GPS greater ≥ 4 had a mortality rate of 16% [52]. Complex gastroschisis occurs in about 17% of cases and is associated with a higher risk of complications compared to simple gastroschisis. In addition to those mentioned above, we can include short intestine syndrome, sepsis, and necrotizing enterocolitis [53]. Risk stratification helps to better counsel parents, predict complications, and prepare the medical/multidisciplinary team to intervene appropriately.

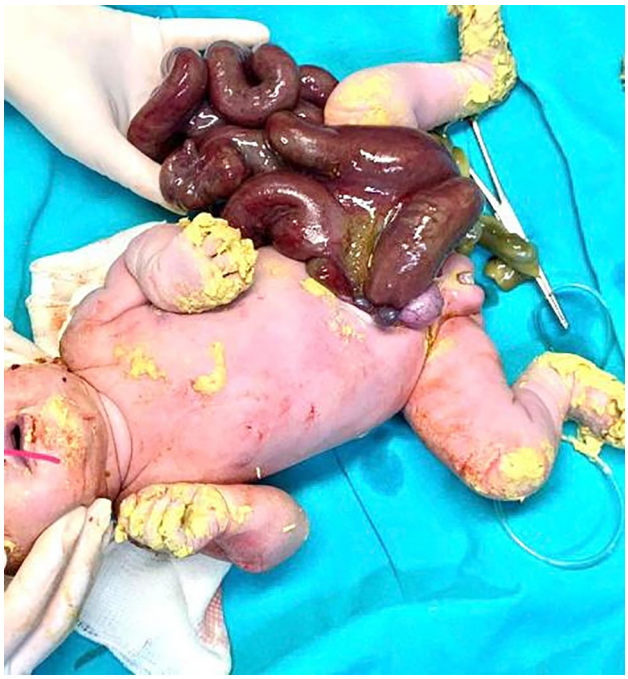

Fig. 5 Postnatal image of newborn with complex gastroschisis. Note the accentuated dilatation of intestinal loops

Prognostic ultrasonographic markers

The rate of prenatal diagnosis of gastroschisis is about 90% in the second trimester of pregnancy in developed countries [54, 55]. Although early diagnosis in the first trimester is possible, it should be remembered that during fetal embryological development, physiological herniation of the small intestine occurs, which ends around 10–12 weeks with the return of the loops to the abdominal cavity [1]. Early detection does not alter management during prenatal care or improve neonatal outcomes, but it does favor early counseling of parents [56].

Gastroschisis postnatal outcomes are known to be influenced by the presence or absence of intestinal complications. With this in mind, some studies have been conducted in recent years to identify prenatal factors that may be predictive of adverse neonatal outcomes in order to promote better prenatal counseling and planning for delivery and postnatal care. A meta-analysis by D'Antonio et al. [57] analyzed 26 studies that included 2,023 fetuses with prenatal diagnosis of gastroschisis and compared the ultrasonographic parameters (intra-abdominal intestinal dilatation—IID, extra-abdominal intestinal dilatation—EID, gastric dilatation, intestinal wall

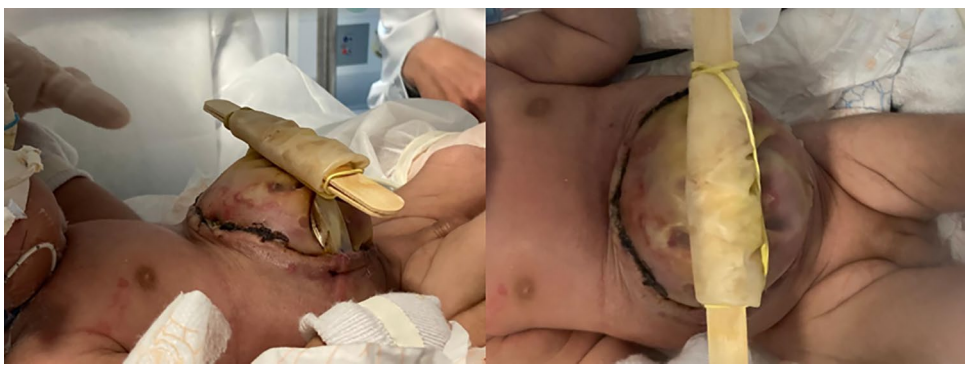

Fig. 4 Newborn image in sagittal and coronal views using silo treatment for abdominal wall closure in a case of gastroschisis

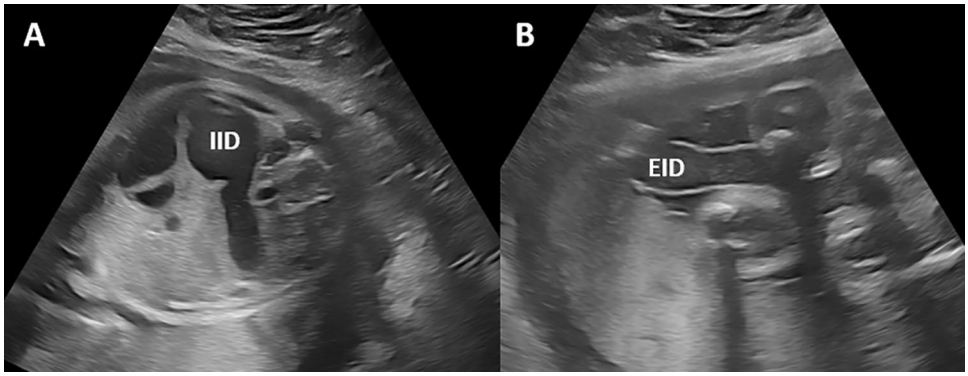

Fig. 6 Two-dimensional ultrasonography in axial view of a fetus at 29 week's gestation showing the intra-abdominal intestinal dilatation (IID) and extra-abdominal intestinal dilatation (EID)

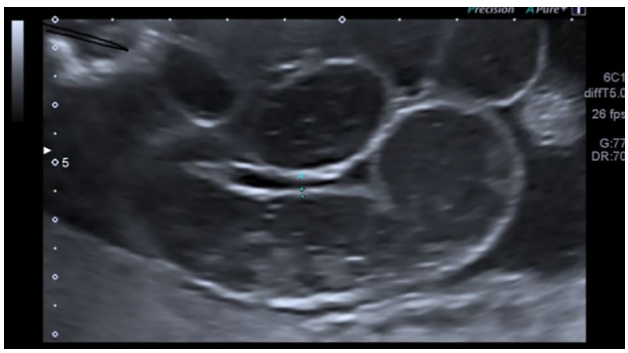

Fig. 7 Two-dimensional ultrasonography in sagittal view showing the measurement of intestine wall thickening in extra-abdominal intestine loops > 3 mm

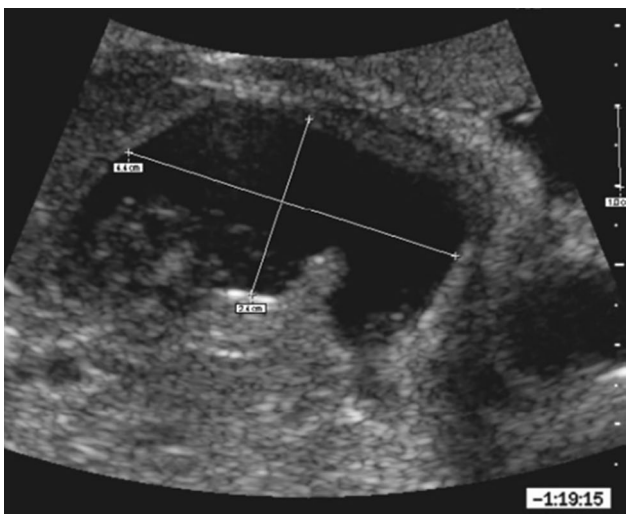

Fig. 8 Two-dimensional ultrasonography in axial view showing the stomach of a fetus with gastric dilatation at 35 weeks of gestation showing off-line measurement of its size

thickness, polyhydramnios, and small-for-gestational-age fetus) (Fig. 6) and adverse neonatal outcomes (intestinal atresia, intrauterine death, neonatal death, prolonged hospital stay, duration of parenteral nutrition, and time of total enteral nutrition). Among the variables analyzed, an association was found between increased IID and polyhydramnios and intestinal atresia.

In a retrospective study by Frybova et al. [58], ultrasound data at 30 weeks of 64 fetuses diagnosed with gastroschisis were analyzed and compared with postnatal outcomes. It was observed that fetuses with increased IID (> 10 mm) and wall thickening of the extra-abdominal intestinal loop (≥ 3 mm) (Fig. 7) had longer periods of parenteral nutrition and hospitalization. Intestinal dilatation was also found in 83% of neonates with intestinal atresia. The presence of oligohydramnios (amniotic fluid index—AFI < 8 cm) was associated with increased duration of enteral nutrition. Martillotti et al. [59] showed that increased IID is a strong predictive ultrasound marker of complex gastroschisis with high accuracy when corrected for gestational age. They established IID thresholds for the following gestational age ranges 12 mm (25–30 weeks), 19 mm (30–35 weeks), and 24 mm (35–40 weeks).

Regarding EID, Robertson et al. [60] showed that this parameter was the only one that was statistically significant as a marker for complex gastroschisis. A value greater than 10 mm was used to diagnose EID, which was present in 79% of complex gastroschisis cases ($p = 0.037$). In a retrospective cohort, Andrade et al. [61] evaluated different ultrasound parameters and their correlation with complex gastroschisis. They found that increased EID (≥ 8, ≥ 9, ≥ 10, and ≥ 11 mm at 25, 26, 27, and 28 weeks, respectively) was a good predictor of complex gastroschisis and was associated with higher mortality and longer hospital stay. To obtain at these results, we used the ratio of observed EID/expected EID for each gestational age. An association was also found between gestational age and IID and polyhydramnios (AFI > 24 cm).

The study by Mazzoni et al. [62], despite its small casuistry (21 cases), found statistical significance between IID ≥ 10 mm occurring before 30 weeks with the need for intestinal resection, increased time on total parenteral nutrition and prolonged hospitalization stay. All cases

Table 1 Prenatal ultrasonographic markers to predict adverse neonatal outcomes in fetuses with gastroschisis

Article	Type of study	Sample size	Prenatal ultrasonographic markers	Adverse neonatal outcomes	Ultrasonographic markers related to neonatal outcomes	Observation
D'Antonio et al. [57]	Meta-analysis	$N=2492$	IID, EID, wall thickness, polyhydramnios, small for gestational age	Intestinal atresia Fetal and neonatal death, length of hospital stay, time until total enteral nutrition and duration of total enteral nutrition	IID, polyhydramnios	–
Martillotti et al. [59]	Retrospective cohort	$N=117$	Fetal growth restriction, EID, IID, absence of external intestinal lumen, GD, GH, EDIL[a] and impaired mesenteric circulation	Complex gastroschisis, neonatal death	IID, EID, absence of lumen, EDIL and impaired mesenteric circulation	Values of IID: 12 mm (25–30 weeks); 19 mm (30–35 weeks); 24 mm (35–40 weeks)
Frybova et al. [58]	Retrospective cohort	$N=64$	IID, AFI, defect size, wall thickness and GH	Type of closure, need for extra surgery, length of hospital stay, duration of TPN, atresia and neonatal death	IID, wall thickness, olygohydramnios	IID < 10 mm, wall thickness < 3 mm
Robertson et al. [60]	Retrospective cohort	$N=100$	IID, EID, AFI, GH, GD, fetal growth restriction	Fetal death, neonatal death, complex gastroschisis	EID	EID > 10 mm
Andrade et al. [61]	Retrospective cohort	$N=186$	IID, EID, AFI, wall thickness, defect size, GD, GH	Complex gastroschisis, fetal death, neonatal death, time to total enteral nutrition time on mechanical ventilation, length of hospital stay, short bowel syndrome	EID, IID, polyhydramnios, GH	EID (mm): ≥ 8, ≥ 9, ≥ 10 and ≥ 11 (25, 26, 27 and 28 weeks, respectively) Values of IID according to Martillotti et al. [58]
Mazzoni et al. [62]	Retrospective cohort	$N=21$	IID, EID, EDIL, defect size, GD, AFI, wall thickness, fetal growth restriction	Type of closure (primary or not), intestinal resection, time until total enteral nutrition, duration of TPN	Fetal growth restriction, intestinal loop dilatation, thickness of EID	EID and IID > 10 mm

GD gastric dilatation; *GH* gastric herniation; *TPN* total parenteral nutrition; *AFI* amniotic fluid index; *IID* intra-abdominal intestinal dilatation; *EID* extra-abdominal intestinal dilatation

[a]EDIL (echogenic dilated intestinal loop): defined as a visible intestinal lumen measuring > 2 mm in diameter with an echogenic wall

of intestinal resection occurred in complex gastroschisis cases because the intestinal loops were atresic, volvulus or necrotic. The gestational diagnosis of growth restriction proved to be a risk factor for surgery to correct the abdominal defect at different stages. Some other ultrasound findings have been studied [gastric dilatation (Fig. 8), gastric herniation and size of the abdominal wall defect], but there is disagreement in the literature as to their significance in relation to complex gastroschisis or neonatal morbidity and mortality. Table 1 summarizes the manly studies in the literature that have evaluated prognostic ultrasonographic markers in fetuses with gastroschisis.

A recent study by Simon et al. [63] reviewed ultrasounds documenting fetal intestinal measurements in 116 pregnancies complicated by gastroschisis. They found statistical significance between utero intestinal characteristics and 11 outcomes, but with minimal meaningful clinical differences in outcomes. The IID was associated with a decrease in gestational age at delivery of 0.5 weeks and an increase in birth weight of 6.93 g.

Conclusion

Gastroschisis is the most common congenital defect of the abdominal wall and its prevalence is increasing due to the influence of numerous risk factors. Prenatal diagnosis can be made by ultrasonography, which is also the method used to monitor fetal vitality and help guide the prognosis and postnatal management. Fetal death can occur in gastroschisis, especially at the end of the third trimester. Complex gastroschisis or gastroschisis associated with fetal growth restriction, changes in amniotic fluid volume, prematurity, and low birth weight often result in unfavorable postnatal outcomes. In summary, the best postnatal outcomes for gastroschisis can be achieved with appropriate planning and follow-up by a multidisciplinary team.

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Declarations

Conflict of interest The authors declare no conflict of interests.

Ethical approval No necessary.

Consent to participate No necessary.

Consent to publish Patients gave their consent to publish the images.

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