Gastroschisis: Embryology, Pathogenesis, Epidemiology

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Author Disclosure
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Objectives After completing this article, readers should be able to:

1. Describe normal embryology and various theories contributing to derangements in development leading to gastroschisis.
2. Delineate several theories regarding the pathogenesis of gastroschisis.
3. Explain the environmental and other risk factors linked to gastroschisis.
4. Describe the prevalence of gastroschisis in developed countries and various theories explaining it.

Introduction

Gastroschisis is a congenital anterior abdominal wall defect, adjacent and usually to the right of the umbilical cord insertion. It occurs as a small, full-thickness periumbilical cleft either immediately adjacent to the umbilicus or separated from it by a strip of skin. This results in herniation of the abdominal contents into the amniotic sac, usually just the small intestine, but sometimes also the stomach, colon, and ovaries (Figure). The abdominal wall defect is relatively small compared with the size of the eviscerated bowel, which often develops walls that are matted and thickened with a fibrous peel. Gastroschisis has no covering sac and no associated syndromes. This differentiates it from an omphalocele, which usually is covered by a membranous sac and more frequently is associated with other structural and chromosomal anomalies (Table 1). In addition, although gastroschisis may be associated with gastrointestinal anomalies such as intestinal atresia, stenosis, and malrotation, it has a much better prognosis than omphalocele.

Historical Perspective

The term gastroschisis is derived from the Greek word *laproschisis,* meaning "bellycleft." It was used in the 19th and early 20th centuries by teratologists to designate all abdominal wall defects. No clear distinctions were made between abdominal wall defects until 1953, when Moore and Stokes classified them based on their appearance at birth. They suggested that the term gastroschisis be reserved for those cases in which the defect is adjacent to the normally inserted umbilical cord and there is no evidence of a sac covering the extruded viscera. Although the first report of a case of gastroschisis was in 1733, the first report of successful closure of a small abdominal wall defect was not until 1943 by Watkins, a surgeon from Virginia.

Abbreviations

ICBDMS:	International Clearinghouse of Birth Defects Monitoring Systems
ICD-9:	International Classification of Diseases, 9th Revision
ICD-9-CM:	International Classification of Diseases, 9th Revision, Clinical Modification

Embryology

The pathogenesis of gastroschisis remains controversial. To understand various theories regarding this defect, it is essential to discuss normal development.

The gastrointestinal tract develops from the primitive digestive tube derived from the yolk sac. Early in gestation, a portion of the gut opens ventrally into the yolk sac—the midgut. At 3½ weeks' gestation, the gut becomes distinct from the yolk sac. The embryonic disk is folded into cephalic, caudal, and lateral folds, each of which converges at the umbilicus to obliterate the coelom, which forms the future

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Figure. Gastroschisis, resulting in herniation of the abdominal contents into the amniotic sac.

peritoneal cavity. At the beginning of the 6th week, the midgut elongates at a rate faster than that of the elongation of the embryonic body. This results in physiologic development of an umbilical hernia. At 10 weeks, the midgut returns rapidly to the embryonic abdominal cavity, and the layers of the cephalic, caudal, and lateral folds join to close the defect in the abdominal wall. This normal reduction of the physiologic midgut herniation followed by abdominal wall closure is key to normal development. Various theories have been developed to explain how or why this does not happen.

The vascular disruption theory is held most commonly. The embryo begins with two umbilical veins and two omphalomesenteric arteries. Between 28 and 32 days after conception, the right umbilical vein involutes. One gastroschisis theory is that premature involution can lead to ischemia, which results in a weak spot that subsequently ruptures, resulting in visceral herniation. The left omphalomesenteric artery also involutes, and the right one develops into the superior mesenteric artery. Similarly, disruption of this process may cause ischemia and the development of gastroschisis. Other theories speculating on the embryologic origins of gastroschisis are summarized in Table 2. These include rupture of an omphalocele and various intrauterine insults. Infarction due to a vascular insult and strangulation of the eviscerated bowel by the contracting umbilical ring or midgut volvulus are proposed in the pathogenesis of intestinal atresia and other gastroschisis variants, which are summarized in Table 3. However, the vascular theory is supported by the association of gastroschisis with maternal smoking and other anomalies also known to have a vascular pathogenesis.

Animal models have been developed in chicks, rabbits, lambs, and mice and may hold the key to the origin of gastroschisis. Most of these models have used teratogens that affect fetal vasculature (Table 4).

Pathogenesis

Gastroschisis is an isolated structural anomaly, and no single definitive genetic or environmental cause has been identified. However, numerous theories have been proposed.

Genetic

Gastroschisis is primarily an isolated defect occurring sporadically and having a multifactorial etiology. However, familial clusters and occurrence in twins suggest a role of heredity and an autosomal inheritance pattern with variable expression. Sibling recurrence rates range from 3% to 5%, which emphasizes the need for appropri-

Table 1. Differences Between Gastroschisis and Omphalocele

	Gastroschisis	Omphalocele
Incidence	1 in 10,000 (now increasing)	1 in 5,000
Defect Location	Right paraumbilical	Central
Covering Sac	Absent	Present (unless sac ruptured)
Description	Free intestinal loops	Firm mass including bowel, liver, etc
Associated With Prematurity	50% to 60%	10% to 20%
Necrotizing Enterocolitis	Common (18%)	Uncommon
Common Associated Anomalies	Gastrointestinal (10% to 25%) • Intestinal atresia • Malrotation Cryptorchidism (31%)	Trisomy syndromes (30%) Cardiac defects (20%) Beckwith-Weidemann syndrome Bladder extrophy
Prognosis	Excellent for small defect	Varies with associated anomalies
Mortality	5% to 10%	Varies with associated anomalies (80% with cardiac defect)

Table 2. Theories Regarding Embryogenesis of Gastroschisis

Author	Theory
Duhamel (1963)	Teratogenic insult resulting in defective differentiation of the somatopleural mesenchyme
Shaw (1975)	Rupture of a hernia of the umbilical cord at the site of involution of the right umbilical vein
DeVries (1980)	Abnormal right umbilical vein atrophy resulting in weakness and defect of abdominal wall, with failure of epidermal differentiation
Van Allen (1981, 1987)	Vascular disruption theory
Hoyme (1981, 1983)	Omphalomesenteric artery insult with disruption of umbilical ring

ate counseling for recurrence in a family that has a history of gastroschisis. Experimental studies have attempted to identify a gene responsible for gastroschisis. In 1998, a study in mice implicated the region of mouse chromosome 7 in the pathogenesis of radiation-induced gastroschisis. In another study, induction of mutation in the bone morphogenic protein-1 gene in mice resulted in a condition similar to gastroschisis; unfortunately, no mutation of this gene has been found in affected human infants. This lack of evidence for genetic predisposition further emphasizes the need to identify possible environmental factors.

Environmental

The trend of increasing birth prevalence of gastroschisis in different populations at different time periods over a wide geographic distribution suggests possible exposure to environmental teratogens (Table 5). Current research has focused on vasoactive drugs. Epidemiologic studies have shown an increased risk of gastroschisis in mothers who have reported taking vasoactive over-the-counter medications, including pseudoephedrine, phenylpropanolamine, aspirin, ibuprofen, and acetaminophen. Aspirin has been shown to increase the risk for gastroschisis in both animal and human studies. In one mouse study, gastroschisis developed after aspirin administration on day 9 of gestation (corresponds to the 4th week of human gestation), but not when aspirin was administered on days 10 and 12, implicating a window of developmental vulnerability. Use of these types of medications during upper respiratory tract infections suggests the possibility of an underlying infectious agent as another potential etiologic factor. Various risk factors associated with gastroschisis are summarized in Table 6. These factors cover a wide spectrum, including parental occupation and living near landfills, again suggesting that the pathogenesis is multifactorial.

Maternal smoking has been implicated as a risk factor for gastroschisis in various studies, several of which demonstrated a twofold increase in risk. The increased risk of fetal gastroschisis and small intestinal atresia among smokers supports a vascular pathogenesis. In addition, maternal vasoconstrictive drug use among smokers of 20 or more cigarettes per day increased the risk of fetal gastroschisis 3.6-fold and the risk of small intestinal atresia 4.2-fold.

Young maternal age and primigravida status have been associated with increasing prevalence of gastroschisis. However, young paternal age has not been identified as a significant risk factor. The association of gastroschisis with younger women who could have increased use of illicit drugs, alcohol, and smoking may point to a potential factor associated with their lifestyle. Other factors associated with increased risk are low pregnancy body mass index and maternal diet. The teenage diet may have low levels of alpha-carotene and total glutathione and high levels of nitrosamines, which may suggest a pathogenetic role for a nutrient deficiency.

Epidemiology

The prevalence of gastroschisis has increased internationally (Table 7). This increased prevalence of gastroschisis (but not of omphalocele) was first observed in Finland in the 1970s. In the 1980s, increases were observed in Strasbourg, Paris, Israel, and Atlanta, as reported by the International Clearinghouse of Birth Defects Monitoring Systems (ICBDMS). Reports of increased prevalence

Table 3. Gastroschisis Variants

Variant	Proposed Pathogenesis
Left-sided Gastroschisis	Regression of left umbilical vein
Vanishing Gut	Midgut volvulus and bowel infarction
Closed Gastroschisis	Tightening of abdominal fascial defect around the bowel, causing ischemia, resorption, and spontaneous closure

Table 4. **Animal Models of Gastroschisis**

Investigator (Year)	Species	Insult
Kimmel (1971)	Mice	Salicylates
Nielsen (1986)	Rats	Hyperthermia
Randell (1994)	Mice	Ethanol
Hillebrandt (1998)	Mice	Irradiation during preimplantation
Singh (2003)	Mice	Protein and zinc deficiency with carbon monoxide exposure

of gastroschisis continued into the 1990s, along with geographic variations attributed to maternal age. Around the same time period, reports of an increased prevalence of gastroschisis in England showed geographic variation within the country. Several of these epidemiologic studies have demonstrated an increased prevalence of gastroschisis in younger mothers.

In the United States, a similarly increased prevalence of gastroschisis has been reported in several states, which varies widely geographically (Table 8). In the past, the ratio of the number of cases of omphalocele to gastroschisis has been reported to be 3:2. However, some have suggested that the prevalence of gastroschisis has been increasing in contrast to a stable or decreasing prevalence of omphalocele, thus altering the ratio. In Florida, for example, a study analyzing cases of abdominal wall defects between 1982 and 1999 reported the ratio of number of cases of omphalocele to gastroschisis to be 1:1.

This increased prevalence occurs in phases over different time periods. For example, a study in Denmark that evaluated abdominal wall defects data from 20 birth cohorts in three nationwide registries showed an initial phase of increase in gastroschisis until 1976, followed by a decrease to the initial 1970s value in 1983, and a subsequent new increase. The average point prevalence at births of gastroschisis varied from 0.66 to 2.17 (average, 1.33) per 10,000 total births, and there was no significant overall linear trend for the entire period. An Atlanta, Georgia, study analyzing rates of gastroschisis from 1968 through 2000 also showed two distinct time periods, with a low, stable rate of gastroschisis from 1968 through 1975 (0.8 per 10,000 births) and a higher, stable rate from 1976 through 2000 (2.3 per 10,000 births), and no temporal trend observed since then.

Maternal Age

Maternal age of less than 20 years has been identified as a significant risk factor for gastroschisis, especially in developed countries. The reasons for this association remain unclear, although speculations of an unidentified teratogen related to modern lifestyle factors, including hobbies, occupation, and diet, have been made. An association with nulliparity and the use of oral contraceptives during conception could point toward teratogenic effects.

Maternal Race

Gastroschisis has been reported with increased frequency in Hispanics. In a study from Utah, 23% of the gastroschisis cohort was Hispanic. A retrospective study from Mexico reported one of the highest prevalence rates of gastroschisis of 4.93 per 10,000 in 1998 among persons

Table 5. **Potential Teratogens Associated with Gastroschisis**

- Organic chemicals/solvents
- Cyclooxygenase inhibitors (aspirin, ibuprofen)
- Decongestants
- Acetaminophen
- Oral contraceptives
- Maternal smoking
- Alcohol
- Illicit drugs (eg, cocaine, amphetamine)
- X-ray irradiation in early pregnancy

Table 6. **Risk Factors Associated With Gastroschisis**

- Parental occupation (eg, printer/computer manufacturing factories)
- Young maternal age
- Hispanic race
- Poor maternal education
- Low socioeconomic status
- Lack of prenatal care
- Nulliparity
- More than one elective abortion
- Short interval between menarche and first pregnancy
- Chorionic villus sampling
- Residence surrounding landfill sites
- Maternal diet (low alpha-carotene, low total glutathione, high nitrosamines)
- Low pregnancy body mass index

Table 7. Increased Prevalence of Gastroschisis in Developed Countries

Country	Incidence per 10,000 Births	Year
Finland	0.77	1970 to 1974
	1.4	1975 to 1979
England and Wales	0.65	1987
	1.35	1991
Southwestern England	1.6	1987
	4.4	1995
Northern England	1.48	1986
	4.72	1996
Japan	0.13	1975
	0.47	1996 to 1997
Western Australia	1	1980 to 1990
	2.4	2001
Canada	1.85	1985 to 1990
	4.06	1996 to 2000
Ireland	1.0	1991
	4.9	2000
Norway	0.5	1967 to 1974
	2.9	1995 to 1998
ICBDMS*	0.29	1974
	1.66	1998

*International Clearinghouse for Birth Defects Monitoring Systems

of Mexican origin. A study from Hawaii found a decreased prevalence in Far East Asians. In New York, there was a higher mortality rate for black infants who had gastroschisis compared with whites, and a recent study in Atlanta found that the infants who had gastroschisis born to teenage mothers and mothers 20 to 24 years of age were less likely to be born to black mothers than to white mothers.

Table 8. Increased Prevalence of Gastroschisis in the United States

State	Incidence per 10,000 Births	Year
Hawaii	2.52	1986
	3.85	1997
New York	1.32	1992
	1.65	1999
North Carolina	1.96	1997
	4.49	2000
Atlanta, Georgia	0.8	1968 to 1975
	2.3	1976 to 2000

Geographic Distribution

An association of gastroschisis with a behavioral or environmental exposure has been postulated due to its association with geographic variations in different parts of the world. The prevalence of gastroschisis may vary between rural and urban regions, although information in the literature is insufficient. In a Finnish study, an apparent increase in prevalence of gastroschisis was noted in northern Finland only, and urban residence was a correlate of the increased gastroschisis risk. In the United States, there have been reports of disparity in distribution of gastroschisis, such as preponderance in the rural part of New York. A retrospective study of a cluster of gastroschisis from Kentucky found no evidence of temporal or spatial clustering in the cases, and there was no association with county of maternal residence. Anomalies of the central nervous system, orofacial clefts, and limb reduction defects have been associated with parental exposure to pesticides. The risk of gastroschisis in rural areas, especially with farming communities, could be increased due to use of pesticides or fertilizers, but no definitive studies have confirmed this hypothesis.

Seasonal Association

Conflicting reports have suggested an association of gastroschisis with month of birth, raising the question of an infectious cause. One such study reported that 37% of gastroschisis conceptions occurred during the first quarter of the year. In another study, infants born during January, February, or March were at greater risk. However, yet another study found that month of birth was not associated with gastroschisis. Due to the seasonal variations reported and association with medications used for respiratory illnesses, a viral cause is still speculated.

Other Factors

Although the recent rapid increases in the rate of gastroschisis have been linked primarily to environmental factors, several other theories have been offered. For example, lack of differentiation between the clinical forms of abdominal wall defects either due to selection bias, previous underreporting of the defect, or misclassification of gastroschisis as omphalocele could be a factor. In a Swedish study, 8% of cases of abdominal wall defects were "unclassifiable," and in a Danish study, 20% of cases of gastroschisis were misclassified. In British Columbia, there were no reports of gastroschisis before 1969 because the condition was unknown, and previous cases were diagnosed as omphalocele. Another theory regarding the increased prevalence of gastroschisis suggests that shifts in maternal age distribution and selected termination in fetuses have occurred due to improvements in prenatal diagnosis. A study from the ICBDMS postulated underreporting of cases in countries such as France and Netherlands, where there is a high proportion of selective terminations. This also was suggested in a Danish study after induced abortions were legalized in Denmark in 1973. One study reported the incidence of abdominal wall defects in stillborn infants to be 20 times higher than in live born children.

One of the disadvantages of the epidemiologic studies evaluating changes in prevalence is the reliance on variable reporting of data to birth defects surveillance programs. For example, some studies include elective terminations in their calculations, thereby increasing their reported occurrence. Several retrospective studies use ICD-9 codes to identify patients. However, it is important to clarify that the code for gastroschisis is the same as for omphalocele. In fact, the ICD-9 code includes *all* congenital anomalies of the abdominal wall (756.79 Anomalies of the abdominal wall, other congenital anomalies of abdominal wall). Currently, individual defects cannot be separately identified based on ICD-9 codes, and chart review and medical record data are needed to separate abdominal wall defects accurately. Perhaps, the time is right to petition for a new ICD-9 code or make clinical modifications to it, identified as ICD-9-CM, in an attempt to separate these vastly different anomalies and improve data collection for future studies.

Summary

Epidemiologic studies from the United States and other developed countries around the globe have reported an increased prevalence of gastroschisis over a wide geographic distribution. Although environmental and maternal factors have been suspected, the cause of gastroschisis remains unclear, and no single cause has yet been implicated. Universally, there is a significant association of gastroschisis with young maternal age along with smoking, leading to speculations of a teratogen related to modern lifestyle that remains to be identified. Also, it is possible that gastroschisis may be related to a combination of factors working synergistically, rather than an isolated single event or exposure. This rising prevalence of gastroschisis has been described as an epidemic, emphasizing the importance of continued monitoring and evaluation of pathogenetic factors. The potential association of gastroschisis with medications, diet, and other maternal factors could have implications for pregnancy planning similar to neural tube defects. Thus, it is an important public health issue, highlighting the need for a more complete multicenter epidemiologic study.

Suggested Reading

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NeoReviews Quiz

1. Gastroschisis is a congenital anterior abdominal wall defect, adjacent and usually to the right of the umbilical cord insertion. Of the following, the *most* common anomaly associated with gastroschisis is:

   A. Beckwith-Wiedemann syndrome.
   B. Congenital heart defect.
   C. Cryptorchidism.
   D. Trisomy 21.
   E. Urinary bladder exstrophy.

2. The pathogenesis of gastroschisis remains controversial, although several theories have been proposed to explain its development. Of the following, the *most* commonly held theory of the pathogenesis of gastroschisis is:

   A. Ethanol exposure during early embryogenesis.
   B. Irradiation during preimplantation.
   C. Protein and zinc deficiency with carbon monoxide exposure.
   D. Teratogenic effect on differentiation of somatopleural mesenchyme.
   E. Vascular disruption involving omphalomesenteric blood vessels.

3. Gastroschisis is primarily an isolated defect that occurs sporadically. No specific genetic mutations or environmental factors have been identified as its cause. However, epidemiologic studies have identified a number of maternal risk factors associated with the development of gastroschisis in the fetus. Of the following, the *most* common maternal risk factor associated with fetal gastroschisis is:

   A. Advanced age.
   B. Hispanic race.
   C. Multiparity.
   D. Obesity.
   E. Urban residence.