A woman with an uncomplicated pregnancy presents at 33 weeks' gestation to her obstetrician with severe bloating and nausea. Fetal ultrasonography illustrates dilated loops of bowel and an enlarged fetal abdomen comparable to a fetus at 41 weeks' gestation. The infant is delivered because of fetal distress. The infant's initial radiograph is shown in the Figure. An exploratory laparotomy confirms a diagnosis of jejunal atresia.

**Figure: Initial radiograph**

Of the following, the MOST likely pathogenesis of this infant's jejunal atresia is:

1. inability to recanalize an intestinal region
2. ischemic injury
3. mechanical obstruction
4. notochord maldevelopment
5. placental vascular abnormality

You selected 2, the correct answer is 2.
Congenital intestinal atresias can reside anywhere along the gastrointestinal tract, with the majority occurring in the jejunum or ileum. The incidence of jejunoileal atresias ranges from 1 in 1,500 to 5,000 live births. Duodenal atresias occur in 1 in 20,000 to 40,000 live births, with 30% of affected children having trisomy 21. The colon is the least common site of atresias, accounting for 5% to 15% of intestinal atresias and occurring in approximately 1 in 40,000 live births.

Atresias are classified into four main types, based on their anatomic characteristics:

- **Type I**: External continuity of bowel with an intraluminal septum that completely occludes the intestinal lumen
- **Type II**: Intestinal segments proximal and distal to the atresia that have blind ends united by a fibrous band; the adjoining mesentery is usually intact
- **Type IIIA**: Intestinal regions proximal and distal to the atresia that have blind ends, which are completely separated; the adjoining mesentery has a V-shaped defect
- **Type IIIB**: Similar to type IIIA except the small bowel distal to the atresia is foreshortened and coiled similar to an apple peel; the adjoining mesentery is completely separated at the atretic region
- **Type IV**: Multiple type II or type IIIA atresias

A schematic diagram of these types is available at: [http://emedicine.medscape.com/article/939258-overview](http://emedicine.medscape.com/article/939258-overview)

Although the mechanism of colonic atresias is not completely understood, the pathogenesis of duodenal and jejunoileal atresias is well-established and known to be distinct. Initially, it was believed that all congenital intestinal atresias resulted from lack of recanalization of the intestinal tube at the end of the 8th week of fetal life. However, there were several reasons why this theory did not accurately depict the formation of jejunoileal atresias. Specifically, this embryonic malformation theory did not explain the presence of bile droplets, meconium, or lanugo hair observed distal to the jejunoileal atresia and between atretic segments. The presence of these components within the intestine occurs by the 12th week of gestation, with bile excretion beginning during the 11th week of gestation, meconium formation occurring by the 12th developmental week, and swallowed squamous epithelial cells existing in the intestine after the 12th week of gestation. Thus, the jejunoileal occlusion most likely occurs after these milestones are reached, which is well beyond the period of intestinal tube development. Indeed, the morphology of the atretic segments suggested an interruption of a previously intact bowel. Additional insight into intestinal embryology illustrated that the duodenum and possibly the ileocecal junction are the only portions of the intestine that are recanalized; this added further support that congenital intestinal atresias have distinct causes.

In 1956, Barnard demonstrated conclusively that congenital jejunoileal atresias were caused by intrauterine ischemia to a normally developed intestinal region. In these studies, pregnant dogs underwent fetal surgery to decrease the blood supply to portions of the fetal jejunum or ileum. At term delivery, the puppies had atretic jejunoileal regions. Other research provided further microscopic evidence of former injury and reparative processes in atretic jejunoileal regions.

Intrauterine ischemic injury is now believed to be the most common cause of jejunoileal atresias. These fetal accidents may be caused by volvulus, malrotation, intestinal strangulation at the umbilical ring, intestinal perforation, and/or peritonitis. Vasocostrictive drugs, such as cocaine, pseudoephedrine, and nicotine, have also been implicated as a cause of intestinal atresias. Familial cases of jejunoileal atresia are thought to most likely result from disruption of the superior mesenteric artery and/or its branches. Regardless of the inciting
factor, the intestinal segment with compromised blood supply becomes necrotic, resulting in narrowing or complete destruction of that area. Thus, the cause of the jejunal atresia in the infant in this vignette most likely results from ischemic injury.

The duodenum and possibly the ileocecal junction are the only portions of the small intestine that undergo recanalization after a solid epithelial stage. During the 5th and 6th weeks of gestation, epithelial cells of the duodenum actively proliferate, leading to temporary occlusion of the lumen of the duodenum. Vacuolization, followed by recanalization of the duodenum occurs by the end of the 8th week of gestation, re-establishing the hollow duodenum. If recanalization does not occur, duodenal stenosis or atresia develops. Thus, while jejunoileal atresia results from a secondary insult to a normally formed intestine, duodenal atresia is a primary developmental defect.

Mechanical factors are rare causes of congenital intestinal atresias. Esophageal atresia results from abnormal lateral septation of the foregut into the esophagus and trachea. While the primary mechanism for this developmental abnormality is currently unknown, some cases of esophageal atresia may result from a mechanical factor pushing the dorsal wall of the foregut anteriorly.

Further understanding of the pathogenesis of esophageal atresias stems from the use of doxorubicin in rat and mouse models. Doxorubicin administration into the peritoneum of these animals induces a prolonged and abnormal adhesion between the notochord and the endoderm. Specifically, doxorubicin exposure leads to VACTERL (vertebral, anal, cardiac, tracheoesophageal, renal, and limb) anomalies such as tracheoesophageal anomalies, intestinal malformations, and anorectal anomalies; the type of anomalies that develop correlate with the gestational timing of the animal's exposure to doxorubicin. As a result of these studies, it is proposed that failure of the foregut to detach from the notochord at the appropriate time may contribute to development of foregut duplications or esophageal atresias. Some investigators have also speculated that some cases of midgut atresias, particularly those with multiple atresias, may arise from abnormal notochord development.

Although it is possible that emboli originating in the placenta may lead to superior mesentery arterial occlusion, most infants with congenital jejunoileal atresia have normal placenta pathologies. While inherited maternal thrombophilias may increase the risk of having a newborn with jejunoileal atresia, this association is infrequent.

References:

Barnard CN, Louw JH. The genesis of intestinal atresia. Minn Med. 1956;39:745


American Board of Pediatrics Content Specification(s):

Understand the embryology of atresias, stenosis, diverticulae, duplications of the small intestine including those associated with annular pancreas

Understand the embryology and clinical manifestations of atresias, stenosis, diverticulae of the large intestine
An infant, born at 24 weeks’ gestation, is receiving small-volume feedings with his mother’s breast milk. On rounds, you discuss the development of gastrointestinal organs and the lack of pancreatic lipase produced by infants of 24 weeks’ gestation. The residents clamor for a lecture about the pancreas.

Of the following, the trophic agent that is the MOST important promoter of pancreatic growth is:

1. breast milk
2. cholecystokinin
3. gastrin
4. insulinlike growth factor
5. secretin

You selected 4, the correct answer is 2.

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Many factors influence the growth of the gut and related organs of the fetus and neonate. Examples range from transcription factors (such as math1) to enteral feeding modes (such as bolus feedings). Of the trophic agents that affect the gut that are listed, cholecystokinin is the most important in promoting pancreatic growth.

Cholecystokinin is a 33-residue peptide secreted mainly by I cells in the mucosal epithelium of the duodenum. Its secretion into the blood is stimulated by enteral amino acids and fatty acids. Cholecystokinin causes gallbladder contraction and pancreatic enzyme release, and plays a major role in the development and growth of the exocrine pancreas. Other agents important for pancreatic growth include gastrin-releasing peptide, bombesin, and pancreas transcription factor 1a.

Gastrin is a 17-residue peptide secreted from the G cells of the stomach and the duodenum. It is produced in response to the presence of peptides, individual amino acids, and fatty acids in the stomach and duodenum. Gastrin stimulates the secretion of gastric acid and the motility of the gastric antrum. It promotes growth of the intestinal mucosa, especially in the stomach, and it may have some positive effect on the growth of the pancreas.

Insulinlike growth factors I and II, also known as somatomedin C and somatomedin A, are 7- to 8-kD proteins. They are produced by many tissues throughout the body, but are made in the greatest abundance by the liver. Growth hormone increases the production of insulinlike growth hormones. They act on almost every cell in the body to promote cell multiplication and growth. They are made by epithelial cells in the intestinal mucosa and by mesenchymal cells in the lamina propria. They stimulate intestinal growth, disaccharidase activity, and glucose transport. Although insulinlike growth hormones are important to the development of the pancreatic islets, they do not have a major role in the growth of the exocrine pancreas.
Clinically, insulinlike growth factors are involved in the pathobiology of intrauterine growth restriction and Beckwith-Wiedemann syndrome.

Secretin is a 29-residue peptide secreted by the S cells of the mucosa of the small intestine. Its production is triggered by gastric acid, bile salts, and fatty acids. Secretin's actions include secretion of water and bicarbonate by the pancreas, and inhibition of gastric motility and bile flow. It does not seem to have a direct trophic effect on the pancreas, but it may cause some release of cholecystokinin by the pancreas. Exogenous secretin administration is used in the diagnosis of the Zollinger-Ellison syndrome.

Amniotic fluid swallowed by the fetus, and later enteral breast milk, contain many agents trophic to the gut, including bombesin, hepatocyte growth factor (which stimulates proliferation along the whole intestine), insulinlike growth factors, transforming growth factor alpha, and fibroblast growth factor. These peptides often survive digestion to stimulate growth, and may even be absorbed intact in the premature infant.

Enteral feedings of human milk, or formula, induce gastrin production and promote intestinal growth. Animal studies suggest that a minimum of 20% to 40% of the total nutrient intake needs to be taken enterally to maintain normal intestinal growth. Animal studies also suggest that bolus feedings result in greater gut growth than do continuous feedings.

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References:


American Board of Pediatrics Content Specification(s):

Determine dietary and hormonal agents that have trophic effects on the infant's GI tract