



# TEXAS

Department of State Health Services  
Birth Defects Epidemiology and Surveillance

## BIRTH DEFECT RISK FACTOR SERIES: ATRESIA/STENOSIS OF THE SMALL INTESTINE

### DESCRIPTION

Defects of the small intestine include both atresia and stenosis. Atresia involves closure or disconnection of a portion or multiple portions of the small intestine while stenosis is a narrowing, webbing, or incomplete closure of a portion of the small intestine (Garza 2005). Small intestinal atresia/stenosis most frequently affects the duodenum (~50%), followed by the jejunum (~35%); the ileum (~15%) is least likely to be affected (Forrester 2004, Cragan 1993). This defect is usually diagnosed prenatally via ultrasound or shortly after delivery, as the intestinal blockage will cause abdominal distention, difficulty in feeding, and the bowel movements (Garza 2005).

Most cases of small intestinal atresia/stenosis do not occur with other birth defects; the exception to this is duodenal atresia/stenosis (Forrester 2004, Garne 2002, Haeusler 2002, Harris 1995, Cragan 1993, Camilla 1990). Approximately 50% of infants with duodenal atresia/stenosis have another anomaly, including cardiac, genitourinary, or anorectal defects, and annular pancreas (Garza 2005, Bianchi 2000). Duodenal atresia is also associated closely with trisomy 21; however, chromosomal abnormalities are not associated with the jejunum or ileum atresia/stenosis (Haeusler 2002, Torfs 1998, Kallen 1996, Harris 1995, Cragan 1993). A severe form of duodenal atresia/stenosis is described as "apple-peel" deformity. This name is derived from the appearance of the intestine as it spirals around the blood supply and resembles an apple peel (Yamanaka 2000).

### EMBRYOLOGY

At approximately week 3 of gestation, the hepatobiliary system and pancreas are developing (Garza 2005). As these organs are forming, the duodenum is a solid structure. Between the 8<sup>th</sup> to 10<sup>th</sup> weeks of gestation, a vacuolation process occurs whereby the duodenum becomes a hollow structure. Failure of the vacuolation process may result in duodenal atresia and stenosis (Sencan 2002). It has also been suggested that small intestinal atresia/stenosis may be due to vascular disruption during development (Werler 2003).

### GENETIC FACTORS

Small intestinal atresia/stenosis has been reported to run in families (Gahukamble 2003, Gahukamble 2002). This defect has also been connected with deletions of chromosome 22q11 (most often associated with DiGeorge syndrome) and chromosome 12q24.3 (Doray 2002, Yamanaka 2000). Both of these chromosomes have been tentatively linked to digestive system development. Additionally, an as-yet unidentified portion of chromosome 2p23-p24 has also been suggested as a causal factor for this defect when it is associated with Feingold syndrome (van Bokhoven 2005). Further examination of the chromosome indicated that a microdeletion of the gene MYCN might also contribute

to developmental disruption of the digestive system. MYCN is activated by Sonic Hedgehog (Shh) signaling; if a portion of the gene is missing, then Shh signaling is disrupted. This disruption has been shown to cause a variety of defects, including tracheo-esophageal fistula and esophageal atresia (van Bokhoven 2005).

Other studies indicate that fibroblastic growth factors (fgf) (signaling molecules that are involved in organogenesis) may contribute to small intestinal atresia/stenosis when they malfunction (Fairbanks 2004, Fairbanks 2003). An absence of specific fibroblastic growth factors or their receptors disrupts the signaling pathways; this disruption may cause several different defects. The authors suggest an autosomal recessive inheritance of this defect (Fairbanks 2004, Fairbanks 2003).

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## OUTCOME

Small intestinal atresia/stenosis has a variable outcome depending on the location and severity of the defect; the presence of additional defects and/or chromosomal abnormalities also contributes to the probability of survival (Garza 2005). Minor defects can be repaired surgically, and generally the prognosis is good (Garza 2005). However, repair of major defects including multiple intestinal atresias have not been as successful (Bilodeau 2004).

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## DEMOGRAPHIC AND REPRODUCTIVE FACTORS

With respect to race/ethnicity, several studies have reported small intestinal atresia/stenosis to be more common in African-Americans than in whites (Harris 1995, Cragan 1993). One investigation observed no significant difference in risk of small intestinal atresia/stenosis in infants born to Vietnamese women compared to infants born to non-Hispanic white women in California (Shaw 2002). Another study found that rates for small intestinal atresia/stenosis were higher for Far East Asians than for Caucasians (Forrester 2004). Higher occurrence rates for this defect are not associated with mixed-race ancestry (Yang 2004).

One study failed to identify any secular trends in small intestinal atresia/stenosis over time (Forrester 2004, Cragan 1993). Another found no seasonal variation in intestinal atresia rates (Bound 1989).

Review of the literature failed to identify any studies that examined the relationship between small intestinal atresia/stenosis and geographic location. One investigation failed to identify any association between duodenal atresia or jejunoileal atresia and altitude (Castilla 1999).

The influence of maternal age on small intestinal atresia/stenosis risk has been variously reported to be U-shaped (Forrester 2004, Harris 1995) or higher for women who are less than 20 years of age (Francannet 1996), although one study failed to identify any association between maternal age and these defects (Cragan 1993).

No statistically significant relationship between these conditions and infant sex has been reported (Forrester 2004, Rittler 2004, Haeusler 2002, Harris 1995, Cragan 1993).

Risk for small intestinal atresia/stenosis increases with lower birth weight and lower gestational age (Rasmussen 2001, Martinez-Frias 2000, Cragan 1993, Mili 1991); however there does not appear to be an increased risk for this defect with large for gestational age infants (Lapunzina 2002). Small intestinal atresia has been associated with intrauter-

ine growth retardation (Khoury 1988). One investigation reported no effect of parity on risk for these defects (Harris 1995). Small intestinal atresia/stenosis is more common among multiple gestation pregnancies (Martinez-Frias 2000, Mastroiacovo 1999, Francannet 1996, Harris 1995, Cragan 1994, Cragan 1993, Ramos-Arroyo 1991), although one study reported no association between plurality and small gut atresia (Kallen 1986).

One study identified higher risk of duodenal atresia with consanguinity (Martinez-Frias 2000), while another found no association between parental consanguinity and intestinal atresia (Rittler 2001). However, two more recent studies have indicated that inherited factors contribute to the etiology of this defect (Gahukamble 2003, Gahukamble 2002). Higher rates of small intestinal atresia/stenosis have been reported in a consanguineous Arab population even in the absence of teratogenic or environmental factors (Gahukamble 2002).

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## FACTORS IN LIFESTYLE OR ENVIRONMENT

**Maternal education** does not appear to affect risk for small intestinal atresia/stenosis (Martinez-Frias 2000). One investigation reported no association between **parental farming** occupation and **pesticide** exposure and risk of intestinal atresia (Kristensen 1997). Another investigation failed to identify any significant association between either duodenal atresia or jejunoileal atresia and proximity to various types of **industry** (Castilla 2000). An article that reviewed recent studies of **paternal occupation** and birth defects reported increased risk of small intestinal atresia and paternal occupation of motor vehicle operator (Chia 2002).

**Maternal diabetes, hyperthyroidism, hypothyroidism, and other acute and chronic maternal diseases** have not been associated with small intestinal atresia or duodenal atresia, although one study noted increased rates of esophageal/intestinal atresia with preexisting diabetes and gestational diabetes (Aberg 2001). **Maternal infectious diseases** have been suggested to increase risk for ileal atresia (Martinez-Frias 2000, Francannet 1996, Becerra 1990, Khoury 1989). One investigation reported no association between maternal **fever, upper respiratory infection, or allergy** and small intestinal atresia/stenosis (Werler 2002).

Prenatal use of vasoconstrictive drugs, including **cocaine, amphetamines, decongestants, and nicotine** has been associated with intestinal atresia (Werler 2003, Hoyme 1990), although other studies have reported no association between fetal cocaine exposure and birth defects (Behnke 2001). One investigation found elevated rates of small intestinal atresia/stenosis/web with maternal use of **pseudoephedrine** and pseudoephedrine in combination with **acetaminophen** (Werler 2002). **Thalidomide** and **hydantoin** have been linked to increased risk of duodenal atresia (Jones 1988). One study reported a potential association between **methylene blue** used during amniocentesis and jejunal atresia (van der Pol 1992). Aspirin, phenylpropanolamine, ibuprofen, antihistamines, guaifenesin, dextromethorphan, vitamins, iron, other minerals, **and** ovulation induction have not been reported to increase risk of small intestinal atresia/stenosis (Werler 2002, Martinez-Frias 2000, Francannet 1996). Studies have reported no association between cephalosporin antibiotics, ampicillin, or the benzodiazepines nitrazepam, medazepam, tofisopam, alprazolam, and clonazepam and intestinal atresia/stenosis (Eros 2002, Czeizel 2001a, Czeizel 2001b, Holmes 2001). Exposure to calcium channel blockers (Sorenson 2001), corticosteroids (Park-Wyllie 2000), marijuana

(Fried 2000), chemotherapy (Cardonic 2004), and fluoxetine (Prozac™) (Chambers 1996) have not been found to be risk factors for small intestinal atresia/stenosis.

No association between maternal **folic acid** or **multivitamin** use and intestinal atresia has been reported (Botto 2004, Czeizel 1996). Furthermore, a study that examined **co-trimoxazole**, a combination of trimethoprim and sulfamethoxazole that is a folic acid antagonist, failed to find any association between the medication and atresia/stenosis of the small intestine (Czeizel 1990).

Living in proximity to a landfill sites and solid waste incinerators has not been found to be a risk factor for small intestinal atresia/stenosis (Cordier 2004, Harrison 2003).

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## PREVALENCE

The reported prevalence for small intestinal atresia/stenosis has shown variation between studies, ranging between 0.6 and 3.1 per 10,000 births for duodenal atresia/stenosis and 0.4 and 1.4 for other small intestinal atresia/stenosis (Table 1). Differences in prevalence may be due to differences in case inclusion criteria.

<b>Reference</b>	<b>Location</b>	<b>Time period</b>	<b>Rate per 10,000 live births</b>	<b>Other*</b>	<b>Total rate</b>
Texas DSHS 2005	Texas	1999-2002			3.1
Haeusler 2002	Europe	1996-1998	1.0	1.0	
Martinez-Frias 2000	Spain	1976-1998	0.6	0.4	1.2
Martinez-Frias 2000	Latin America	1967-1996	0.6	0.5	1.2
Torfs 1998	California, USA	1983-1993	2.3		3.9
Stoll 1996	France	1979-1987			3.0
Harris 1995	France	1976-1990	0.7	0.8	
Harris 1995	Sweden	1973-1990	1.1	0.5	
Harris 1995	California, USA	1983-1990	1.0	0.9	
Papp 1995	Hungary	1988-1990	2.0		
Cragan 1993	Georgia, USA	1968-1989	1.4	1.4	2.8
Castilla 1990	Central and South America	1982-1986	0.7	0.6	

\*Other small intestinal atresia/stenosis

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***Please Note:*** *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information. This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.*