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# Environmental Risk Factors Associated with Anorectal Malformations

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***Abstract:*** *Anorectal malformations (ARMs) are the most common congenital structural abnormalities of the digestive tract, with an incidence ranging from 1 in 5,000 to 1 in 1,000 live births. These defects are characterized by abnormal development of the rectum, anus, and surrounding structures. Although surgical procedures can reconstruct anatomical structures and the mortality rate is relatively low, postoperative care imposes significant economic and psychological burdens on affected families. These challenges can negatively impact the child's mental health and quality of life, resulting in long-term adverse outcomes. The etiology and pathogenesis of ARMs are still not fully understood. This paper provides a comprehensive review of risk factors associated with ARM, focusing on maternal and genetic susceptibility. Empirical studies indicate that environmental conditions and maternal health during pregnancy may correlate with ARM incidence. Moreover, maternal lifestyle choices—such as smoking, alcohol consumption, and vitamin intake—are considered factors that influence susceptibility in offspring. Genetic studies have revealed associations between ARM susceptibility and several genes, including CDX2, Wnt, MNX1, GLI2, and Hedgehog. Future research should further explore the complex interactions between environmental and genetic factors, offering new avenues for early diagnosis, prevention, and treatment. Such research will deepen the understanding of ARM pathogenesis and provide an important basis for formulating targeted and effective prevention and control strategies, ultimately helping reduce incidence and improve patient outcomes.*

***Keywords:*** *Anorectal Malformations, Genetic Factors, Environmental Factors, Pregnancy*

## 1. Introduction

Congenital gastrointestinal malformations encompass developmental abnormalities from the esophagus to the anus, accounting for approximately 15% of all neonatal congenital defects [1][2]. The gastrointestinal tract is composed of a series of organs that must coordinate spatially and temporally to digest food and extract essential nutrients[3]. Malformations in these organs can result in serious congenital conditions such as anorectal malformations, congenital megacolon, hypertrophic pyloric stenosis, intestinal atresia, and malrotation[4][5]. These disorders severely impair nutrient and energy absorption and are among the leading causes of neonatal mortality. In fact, congenital gastrointestinal structural abnormalities rank as the third most common cause of death among all congenital birth defects[6]. Among these, ARM has the highest incidence, estimated at 3.32 per 10,000 live births[7]. ARMs encompass a range of abnormalities affecting the rectum, anus, and surrounding structures—from minor displacement of the anal canal to complex fusions involving the rectum, vagina, urethra, and underdeveloped sphincter and pelvic floor muscles[8]. According to the Krickenbeck classification, ARM can present with or without anal openings and with or without fistulas. These include conditions such as anal atresia, rectoperineal fistula, rectourethral fistula, rectovesical fistula, rectovaginal fistula, and rectovestibular fistula[9]. Although surgical anoplasty can reconstruct anatomical features and reduce mortality[10], long-term follow-up reveals a range of complications including fecal incontinence, urinary incontinence, neurogenic bladder, and sexual dysfunction. The ongoing postoperative management places considerable financial and emotional strain on families and has serious implications for children's mental health and quality of life[11][12]. As living environments have evolved with social and economic development, modern medical research has increasingly identified both genetic and environmental factors as contributors to ARM. Environmental pollution and changing lifestyles are thought to play significant roles in ARM pathogenesis.

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## 2. Genetic Factors

ARMs are the most common congenital gastrointestinal malformations in children. Despite extensive research, the precise causes and mechanisms remain unclear. ARM development is a complex process involving multiple genes and environmental triggers. Its inheritance pattern and penetrance are still not well defined. Embryologically, it is hypothesized that ARMs arise from a developmental arrest of the urorectal septum between weeks 4 and 8 of gestation[13]. Teerlink's study identified a significant familial history among ARM patients ($p < 0.001$), providing strong evidence for a hereditary component[14]. In 2022, Stevens confirmed the crucial role of the CDX2 gene in caudal morphogenesis and cloacal derivatives in humans[15]. A 2017 case-control study by van de Putte and colleagues found that individuals with the GG genotype at rs3738880 in the GLI2 gene had an increased risk of ARM (OR = 1.61), with even higher odds among those with multiple congenital anomalies (OR = 2.09)[16]. In 2014, RC-LNg's research demonstrated that precise regulation of endodermal Shh-Wif1-Wnt-β-catenin signaling is essential; dysregulation and overexpression of Wnt inhibitors such as DKK4 can ultimately lead to ARM. In 2020, the MNX1 gene was confirmed as a pathogenic gene for Currarino syndrome, a congenital caudal anomaly complex characterized by ARM, presacral mass, and sacral anomalies[17]. In 2016, Chinese scholar Gao Hong found that absence of specific SNPs in the Hedgehog gene (rs61730970, rs200798148, and rs146535482) was associated with a significantly higher risk of ARM (OR = 1.528; OR = 1.800; OR = 1.743)[18]. These gene mutations are associated with ARM development, but in many cases, the etiology remains multifactorial and largely unknown. A growing body of research suggests that environmental factors play a critical role in both the onset and progression of ARM.

## 3. Environmental Factors

### *3.1 Maternal Health Status*

A woman's pre-pregnancy body weight is considered a significant risk factor for fetal congenital defects. Numerous studies have shown a correlation between maternal body mass index (BMI) and anorectal malformations (ARM). When maternal BMI ≥ 28.0 kg/m², the risk of ARM increases significantly (OR = 1.42)[19-21]. A 2017 case-control study by van de Putte, Romy and colleagues identified previous miscarriage as a newly observed risk factor for ARM, especially among children with multiple congenital anomalies or in pregnancies following multiple gestations (OR = 2.1)[16]. In 2022, Kathryn Ford's five-year cohort study linked ARM risk to maternal age, revealing that mothers aged ≥ 35 had a 31% higher risk of bearing children with complex ARMs. This finding was supported by a 2024 study by Samrawit Solomon, which also associated advanced maternal age with increased ARM risk (OR = 4.22)[21-22]. Both advanced maternal age and history of miscarriage significantly elevate ARM susceptibility[23][24].

In addition, studies have identified maternal smoking and alcohol consumption as risk factors. A 2016 study by Zwink and Vermes confirmed that smoking and alcohol during or prior to pregnancy can cause irreversible embryonic damage, increasing ARM risk in offspring. Anna Svenningsson (2018) confirmed that mothers smoking ≥10 cigarettes daily had a significantly higher risk of ARM in their children (OR = 1.67). Literature reviewed by Zwink and Nadine also suggested that paternal smoking and drinking during the six months preceding conception might be a potential risk factor[24][26]. However, a 2020 cohort study by Mohammed A. Almatrafi found no such association between paternal smoking and ARM risk[25], indicating the need for further research to confirm these findings. Overall, maternal obesity, advanced age, smoking, and alcohol consumption before and during pregnancy are all risk factors for ARM, warranting further exploration.

### *3.2 Pre-Pregnancy/Pregnancy-Related Illnesses*

In 2007, Jaime L. Frías and colleagues used data from Spain's Collaborative Study of Congenital Malformations to show that women diagnosed with diabetes before pregnancy had a higher risk of giving birth to infants with congenital anomalies. In 2011, Nadine Zwink's literature review confirmed that both pre-pregnancy diabetes and gestational diabetes increased the risk of ARM in offspring[27]. While the National Birth Defects Prevention Study (NBDPS) associated pre-pregnancy diabetes with most congenital anomalies, the link between gestational diabetes and ARM remained weak and inconclusive[28]. In 2018, Howley found that maternal urogenital infections were associated with defects like cleft lip, cleft palate, and gastrointestinal malformations[29]. A 2021 study by German

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scholar Melanie Kapapa revealed that early pregnancy urogenital infections significantly elevated ARM risk in offspring[23][30][31].

Additionally, a 2016 study by Nadine Zwink identified chronic respiratory diseases in mothers as significantly increasing ARM risk[24]. In 2019, Romy van de Putte used data from the Netherlands' AGORA database to demonstrate that mothers with chronic respiratory conditions using medications had a higher likelihood of giving birth to children with ARM (OR = 1.6)[32]. Similarly, a 2022 study by Wu Fang identified upper respiratory tract infections in early pregnancy as a potential risk factor for ARM, noting that most mothers did not exhibit fever but rather symptoms such as coughing, nasal congestion, and runny nose[33]. Mohammed A. Almatrafi proposed that fever during pregnancy could be a potential risk factor[25], although other researchers have not supported this claim, and further studies are needed to clarify its validity. Overall, the mechanisms by which maternal infections cause birth defects remain poorly understood and require further investigation, particularly regarding their relationship with ARM development.

### *3.3 Medication Use Before/During Pregnancy*

Emerging evidence indicates that medication use before and during pregnancy may increase the risk of ARM. A 2012 study by Shao Lin et al. found that maternal use of asthma medication during pregnancy significantly increased the risk of anorectal atresia (OR = 2.12)[34]. In 2018, Nadine Zwink's systematic review and meta-analysis concluded that preconception and gestational use of anti-asthma drugs, sleeping pills, and benzodiazepines were all associated with increased ARM risk—findings consistent across multiple studies[35].

In 2020, Kayla N. Anderson analyzed NBDPS data and found a significant correlation between atypical antipsychotic use during early pregnancy (one month before to three months after conception) and anorectal atresia/stenosis (OR = 2.8)[36]. However, in 2023, Krista F. Huybrechts conducted a multinational cohort study using registry data from five Nordic countries and the U.S. and found no such correlation[37]. These conflicting findings suggest that the relationship between atypical antipsychotic use and ARM risk requires further validation.

Elizabeth C. Ailes (2016), through NBDPS data, observed that the use of cephalosporins for urinary tract infections was associated with an elevated risk of ARM (OR = 5.01)[30]. Similarly, a 2023 study by Sarah C. Fisher—drawing from U.S. NBDPS and BD-STEPS data—found that periconceptional use of cyclobenzaprine significantly increased ARM risk (OR = 6.91)[38].

In contrast, a 2020 animal study by Wu Fang revealed that folic acid supplementation reduced the incidence of ARM and promoted fetal development[39]. Melanie Kapapa also confirmed the protective effects of folic acid[31]. However, cohort studies by Charlotte H. W. Wijers and Takehiro Michikawa did not find a consistent association between folic acid use and ARM incidence[40][41]. Additional studies suggest that deficiencies in vitamins A, B, and E during pregnancy may contribute to ARM development[41][42][43]. Overall, the mechanisms of these medications are complex. On one hand, they may influence fetal development indirectly by altering maternal endocrine or metabolic function. On the other, they may cross the placental barrier and directly affect the fetus. Therefore, medication selection during pregnancy must be approached with caution, prioritizing treatments that are both effective for the mother and safe for the developing fetus.

### *3.4 Living Environment*

Studies suggest that greater exposure to green spaces during the perinatal period may help reduce the risk of certain birth defects. Conversely, environmental exposures such as residential proximity to landfills, hazardous waste sites, chemical manufacturing plants, gas stations, or intensive agricultural areas may pose risks to fetal development[31]. Research by Zwink and colleagues has indicated that occupational exposures in both mothers and fathers could be potential contributors to ARM[27]. Professions such as cleaners, chemical scientists, hairdressers, and automobile manufacturers may expose parents to industrial chemicals and solvents. For mothers, exposure to industrial cleaning agents and solvents during pregnancy, or exposure to industrial exhaust, heavy metals, and pesticides within six months prior to conception, may lead to the accumulation of harmful substances in the body. This accumulation could compromise placental barrier function, increase placental permeability, and render embryos more sensitive to toxins. In such cases, even doses that are harmless to the mother may adversely affect fetal development[44-45].

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Some studies suggest that toxic substances may interfere with embryogenesis by binding to target molecules, disrupting hormone synthesis, or causing oxidative damage to DNA, ultimately resulting in congenital malformations[46]. Moreover, fathers are more likely than mothers to experience occupational exposure to toxic substances, especially in industrial and manufacturing settings. Hence, further research is needed to explore paternal preconception exposure to hazardous substances and its role in ARM development.

### *3.5 Assisted Reproductive Technologies and Pregnancy Planning*

With the advancement of medical technologies, the global application of assisted reproductive technologies (ART) in treating infertility has grown rapidly[47-48]. While ART has enabled many couples to conceive, increasing attention has been directed toward the health outcomes of children born through these procedures. Some studies have reported an elevated relative risk of ARM in children conceived via ART[49][50]. In 2024, Samrawit Solomon and colleagues reported that unintended pregnancies were more likely to result in children with ARM, particularly when couples did not participate jointly in pregnancy planning[22]. Unintended pregnancies may impose substantial health, social, and economic burdens on families, and elevated maternal psychological stress has been linked to an increased risk of various congenital anomalies[51].

However, current evidence is still limited, and larger studies are needed to confirm these associations. Therefore, the relationship between ART, pregnancy planning, and ARM remains a complex and evolving area of investigation. The above sections have outlined various environmental risk factors potentially associated with ARM. Nonetheless, the identification of causal relationships requires further support from large-scale epidemiological research.

## 4. Conclusion

Research both in China and abroad emphasizes the significant role of environmental factors in the development of anorectal malformations, particularly in relation to parental health status and lifestyle before pregnancy, as well as maternal exposure to harmful environmental elements during gestation. Although various environmental risk factors have been identified, the specific mechanisms remain unclear. Further investigation is essential to fully understand the environmental contributors to ARM, providing a scientific foundation for effective prevention and control strategies.

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