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The Relationship Between Maternal and Fetal Factors with Anorectal Malformations

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Abstract

Children with Anorectal Malformations (ARM) may experience lifelong physical impairment if not treated properly, and may adversely affect the personal and economic existence of affected individuals, as well as families and communities. The purpose of this study was to determine the factors of the incidence of anorectal malformations in neonates from maternal aspects and fetal aspects. By using research methods in the form of literature studies from the search results of 62 findings and 38 literature based on Electronic Based. The results of the discussion state that maternal risk factors that contribute to the incidence of ARM include exposure to teratogens such as cigarettes, alcohol, pesticides, drugs, and radiation during pregnancy. And fetal risk factors that contribute to the incidence of ARM include genetic and chromosomal factors, including related syndromes such as Down syndrome and VACTERL, which are the main causes of ARM.

Introduction

Congenital abnormalities are abnormalities that have existed since birth which can be caused by genetic or non-genetic factors. Sometimes a congenital abnormality has not been found or has not been seen at the time of birth, but only discovered after the baby is born. Congenital abnormalities that still often occur in Indonesia are hirschsprung disease and anorectal malformations (Lio et al., 2022; Qinayah et al., 2024; Poerwosusanta et al., 2024; Yonas et al., 2024).

Anorectal malformation (ARM) and atresia ani are congenital abnormalities that encompass the distal anus, rectum and urogenital tract (Crétolle, 2023; Pakarinen, 2022). These congenital anomalies are frequently encountered in pediatric surgical cases. These conditions range in severity from imperforate anal membrane to complete caudal regression (Hapsari et al., 2022; Thapa & Basnet, 2020)

ARM can be classified into three types based on the location of the rectal pouch, including low, intermediate and high. The most common type of ARM in males and females is the intermediate type, namely rectourethral fistula in males and rectovestibular fistula in females (Lu et al., 2024; Wong et al., 2025). The diagnosis of ARM can be made by taking a history and physical examination. ARM infants will show abdominal distension, no anus and fistula may be found. In general, the management of ARM can be done through 3 types of surgery, including perineal surgery, posterior sagittal anorectoplasty (PSARP) and laparoscopic assisted anorectoplasty (LAARP) (Dewi, 2022; Pitaka et al., 2022).

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The incidence of ARM is 1 in 2500-5000 births; however it may be more common in some developing countries. Traditionally in ARM, neonatal diversion colostomy followed by PSARP and subsequent colostomy closure is performed, however, primary surgery without the use of colostomy is an emerging trend as colostomy is often associated with morbidity and mortality, and is generally disliked by parents in modern society aesthetically (Kumar et al., 2020).

It is estimated that around 7.9 million (6%) newborns worldwide have congenital malformations. The figure may in fact be higher due to difficulties in identifying cases in stillbirths or in interrupted pregnancies. The Ministry of Health of the Republic of Indonesia reported its surveillance results in 28 hospitals from 18 provinces from September 2014 to march 2018. A total of 1,085 babies with congenital abnormalities were reported. The results of the 2017 IDHS survey stated that of the total infant deaths of 72,000, as many as 14.8% were caused by congenital abnormalities (Ervina et al., 2023).

Sardjito Hospital data shows from the total number of births 9736 in 2013-2019 there were 363 newborns with gastrointestinal abnormalities, 188 neonates were found to have ARM. According to the Global Report on Birth Defects data varies in the data of the Ministry of Health of the Republic of Indonesia in the Southeast Asia region, Indonesia out of 1000 births there are 59.3% of babies with congenital abnormalities (Hapsari et al., 2022). Then, based on data from Bhayangkara Hospital and RSIA. Sitti Khadijah 1 Makassar obtained 13 children with ARM cases from 2017-2022 which showed that the majority of ARM patients were male (69.2%) (Islamiati et al., 2022).

ARM in neonates can be caused by various factors, including genetic factors, exposure to teratogenic substances, diseases suffered by the mother (Alexander et al., 2016; Verma, 2021). Exposure to teratogenic substances such as drugs, cigarettes, radiation, and other chemicals such as pesticides can cause changes at the cellular to molecular level. Diseases such as toxoplasmosis, CMV, syphilis, and diabetes mellitus can cause obstacles to fetal development resulting in incomplete organ formation (Ervina et al., 2023; Dhanya et al., 2024; Bittencourt & Garcia, 2002; Anderson & Gonik, 2010).

Detection of factors that contribute to the incidence of ARM is one way to minimize the incidence of ARM and improve the recovery process of children born with the condition (Bhargava et al., 2021). By detecting contributing factors, preparations can also be made for delivery in pediatric surgical facilities, perinatology, and health services that have adequate support. Children with ARM can experience lifelong physical impairment if not treated properly, and can adversely affect the personal and economic well-being of affected individuals, as well as families and communities (Ervina et al., 2023; Friedline et al., 2021; Adger et al., 2022).

The description above encourages researchers to find out more about the risk factors for the incidence of ARM in neonates through a review study with a literature review approach.

Methods

This study uses a literature study research method using literature criteria containing at least 20 references in the form of internationally accredited scientific journals (20), nationally accredited scientific journals (9), citation of lecturer writing in the form of research (1), literature reviews, case reports (6), Clinical Key References (2), and Text books, published from 2018 to 2025 to support research data on the relationship of maternal and fetal factors to ARM. In the journal search with the help of the internet with the keywords risk factors for anorectal malformation, anorectal malformation in neonates, genetic in anorectal malformation neonates, environment in anorectal malformation neonates, prenatal in anorectal malformation neonates, prematurity in anorectal malformation neonates and congenital abnormalities in

anorectal malformation neonates. With the search results of 62 findings and 38 literature based on Electronic Based.

Result and Discussion

Based on the author's search results, there are 22 journals stating that genetic anomalies, the presence of other malformations, and related syndromes (Down syndrome, VACTERL, currarino, etc.) are often associated with the incidence of ARM. Genetic mutations and chromosomal abnormalities can interfere with the embryogenesis process, especially in the development of the urorectal septum which plays a role in the separation of the gastrointestinal tract and urogenital tract. Down syndrome, caused by trisomy 21, is often associated with various congenital malformations, including impaired intestinal and rectal development. VACTERL association is a collection of anomalies including vertebral malformations, anal atresia, cardiac abnormalities, tracheoesophageal fistula, renal abnormalities, and limb abnormalities, indicating systemic embryonic developmental disorders. Meanwhile, Currarino syndrome, which is caused by mutations of the HLXB9 gene, can result in a combination of ARM with spinal malformations and presacral tumors. These factors suggest that genetic abnormalities may interfere with molecular signals important in rectal and anal development, thereby increasing the risk of ARM (Almatrafi et al., 2020; Hageman et al., 2024; Kancherla et al., 2023; Smith & Jeffrey, 2022).

There are 22 journals that link exposure to teratogens (cigarettes, alcohol, pesticides, drugs, radiation) with an increased risk of ARM. Smoking can cause fetal hypoxia as carbon monoxide and nicotine inhibit oxygen supply to fetal tissues. This may interfere with the development of the digestive and anorectal systems. Alcohol, especially if consumed in the first trimester, may trigger excessive cell apoptosis, which inhibits differentiation and migration of cells important in the formation of the urorectal septum. Pesticide exposure during pregnancy is associated with disruption of molecular pathways, such as Sonic Hedgehog (SHH) and Bone Morphogenetic Protein 4 (BMP4), which play a role in cloacal development. In addition, the use of teratogenic drugs, such as retinoids and thalidomide, can inhibit cell proliferation during embryogenesis and cause abnormalities in anorectal development (Almatrafi et al., 2020; Ervina et al., 2023; Hageman et al., 2024; Kancherla et al., 2023).

There are 18 journals stating that maternal health conditions especially diabetes, hypertension and anemia contribute to the incidence of ARM. Diabetes in pregnant women can cause maternal hyperglycemia, impaired cloacal differentiation, oxidative stress and placental dysfunction. Maternal hyperglycemia can disrupt the expression of Sonic Hedgehog (SHH) and Bone Morphogenetic Protein 4 (BMP4), leading to cloacal separation into digestive and urogenital tracts. Diabetes also increases oxidative stress, which can damage developing cells in embryogenesis. Maternal hyperglycemia also causes placental dysfunction, resulting in compromised oxygen and nutrient supply to the fetus, which may contribute to ARM (Almatrafi et al., 2020; Kancherla et al., 2023).

Hypertension in pregnant women can cause impaired placental blood flow, fetal hypoxia, and disruption of cryogenesis. Hypertension causes placental vascular dysfunction that reduces blood supply to the fetus and causes intrauterine hypoxia, which can inhibit mesodermal tissue important in the formation of the fetal digestive system. Hypertension in the first trimester can cause disturbances in angiogenesis affecting cell differentiation in the fetal gastrointestinal system. This will result in atresia or hypoplasia of the rectum and anus (Hageman et al., 2024; Kancherla et al., 2023).

Anemia in pregnant women can decrease hemoglobin levels which reduces oxygen supply to the fetus. Oxygen deficiency during embryogenesis can lead to impaired formation of the fetal digestive system. Anemic mothers also often have iron and folic acid deficiencies which are essential in the differentiation of neural crest cells that form the digestive system. These

nutrient deficiencies cause abnormalities in cloaca formation and contribute to ARM (Almatrafi et al., 2020; Kancherla et al., 2023).

There are 17 journals that mention that extreme maternal age (<20 years or >35 years) increases the risk of ARM. This is because in mothers who are too young, there is a hormonal imbalance and immaturity of the reproductive system. Adolescents have an unstable hormone system, which can affect placental development and nutrient supply to the fetus. Endometrial immaturity in young mothers can inhibit optimal fetal implantation and increase the risk of organogenesis disorders (Ervina et al., 2023; Kancherla et al., 2023; Solomon et al., 2024).

In older mothers, there is a decrease in egg quality and risk of genetic abnormalities. The older the mother, the higher the risk of aneuploidy, which can lead to chromosomal abnormalities such as trisomy 21 (down syndrome), often associated with ARM. Also, spontaneous mutations in the Sonic Hedgehog (SHH) and Bone Morphogenetic Protein 4 (BMP4) pathways are more common in older mothers, which play a role in impaired cloacal differentiation (Ali et al., 2020; Almatrafi et al., 2020; Kancherla et al., 2023).

There are 15 journals that highlight the importance of preventing nutritional deficiencies (folic acid and other micronutrients) in preventing ARM. Folic acid plays an important role in the development of the fetal nervous system, including in the embryogenesis process that occurs in the first trimester of pregnancy. Folic acid deficiency can lead to impaired neural tube formation and differentiation of cells that play a role in the formation of the gastrointestinal tract, including the rectum and anus. Deficiencies in other micronutrients such as iron, zinc and vitamin A can also affect fetal development. Zinc, for example, plays a role in the process of cell proliferation and differentiation during embryogenesis, while vitamin A has a role in organ morphogenesis (Insanilahia, 2022; Islamiati et al., 2022; Pitaka et al., 2022).

There are 14 journals on maternal factors that discuss that family history of ARM, namely genetic factors, plays a role in the incidence of ARM. Certain genetic mutations or chromosomal abnormalities inherited from parents can cause disturbances in the process of embryogenesis, particularly in the formation of the urorectal septum which plays a role in the separation of the urinary and gastrointestinal tracts during fetal development. In addition, some genetic syndromes such as VACTERL association or trisomy 21 are often associated with ARM, suggesting the involvement of hereditary factors in its pathogenesis. Studies have also shown that individuals with a family history of ARM have a higher tendency to develop similar conditions, although the clinical expression may vary (Almatrafi et al., 2020; Hageman et al., 2024; Kancherla et al., 2023; Smith & Jeffrey, 2022).

There are 10 journals that mention that intrauterine infections (TORCH, rubella, CMV, etc) can increase the risk of ARM because they disrupt embryonic development in the first trimester which is a critical period in the formation of the anorectal system. These pathogens can cause inflammation, hypoxia, and disruption in the process of cell differentiation and migration during embryogenesis. For example, CMV and rubella infections can trigger impaired vascularization that plays a role in the development of the cloaca and urorectal septum, which if disrupted can lead to ARM. Several studies have shown that infants with TORCH infections have a higher risk of multiple congenital abnormalities, including ARM, due to the teratogenic effects of viruses on organogenesis (Almatrafi et al., 2020; Ervina et al., 2023; Kancherla et al., 2023).

There are 10 journals that mention that Intrauterine Growth Restriction (IUGR) can be one of the risk factors of ARM. Fetal growth restriction occurs due to disruption of the supply of nutrients and oxygen to the fetus, which can be caused by maternal factors such as hypertension, chronic diseases, or placental insufficiency. This disruption leads to suboptimal development of the digestive system, including disruption of the embryogenesis process that plays a role in the formation of the rectum and anus. In addition, fetuses with IUGR often

experience oxidative stress and intrauterine inflammation, which can impair cell differentiation and migration during organ development. This condition is also associated with an increased risk of other congenital anomalies, such as cardiac and genitourinary abnormalities, which are often found along with ARM. Thus, suboptimal fetal growth during pregnancy may be a significant predisposing factor to the occurrence of ARM (Kancherla et al., 2023; Masitha et al., 2024; Pandey, 2021; Stenström et al., 2024; Umar Nisar et al., 2021).

There are seven journals showing that ARM is more common in male infants. Embryologically, the development of the anorectal system in male fetuses is more complex than in females. In males, separation of the cloaca into the urogenital and anorectal tracts occurs with involvement of the urorectal septum which is more prone to disruption during embryonic development. Failure in this process can lead to abnormalities such as atresia ani or rectourethral fistula, which are more common in male infants. Hormonal factors are also thought to play a role, where differences in sex hormone expression during embryogenesis can affect the development of the gastrointestinal and urogenital systems, increasing the risk of ARM in males (Ervina et al., 2023; Islamiati et al., 2022; Kancherla et al., 2023).

There are six journals that mention that babies with prematurity have a higher risk of ARM. Babies born prematurely have a shorter organ development time, so organs including the digestive system and anus may not be optimally developed. Factors such as fetal hypoxia due to lung immaturity or impaired circulation may also affect anorectal development. Prematurity can also cause placental dysfunction resulting in impaired supply of nutrients and oxygen to the fetus, which plays a role in the formation of a normal gastrointestinal system. Therefore, preterm infants have a higher risk of congenital malformations, including ARM, than term infants (Kumar et al., 2020; Pitaka et al., 2022).

There are six journals that link low birth weight to ARM risk factors. Low Birth Weight (LBW) often reflects intrauterine growth disorders that can affect organ development, including the digestive and anorectal systems. LBW may result from placental insufficiency, maternal nutritional deficiencies or other pregnancy complications, which may interfere with normal fetal development and increase the likelihood of structural malformations. The combination of LBW and prematurity can lead to impaired oxygen and nutrient supply which further impairs the development of vital organs (Kancherla et al., 2023; Pitaka et al., 2022; Sinha et al., 2024).

There are five journals that mention that multiple pregnancies can increase the risk of ARM. There is competition for resources between fetuses, including nutrients and blood supply from the placenta. This can lead to impaired embryonic development, including the formation of the digestive and anorectal systems. In addition, higher intrauterine pressure due to limited uterine space may affect the normal development of fetal organs. Multiple pregnancies also have a higher risk of preterm labor, which is associated with an increased incidence of ARM because organs are not fully developed at birth (Almatrafi et al., 2020; Kancherla et al., 2023; Solomon et al., 2024).

There are five journals that mention that fetal position in the womb (fetal malposition) can affect the development of the digestive system. During the first trimester of pregnancy, the development of the digestive system and rectum is highly dependent on the position of the fetus and the distribution of pressure within the uterus. If the fetus is in an abnormal position, such as breech or transverse, the unbalanced intrauterine pressure may inhibit the migration and differentiation of cloacal structures, which play a role in the formation of the anus and rectum. Fetal malposition leads to impaired vascularization of the perineum and pelvic region, which inhibits blood supply to developing tissues, including anorectal structures. Hypoxia or ischemia due to this vascular disruption may impair apoptosis and proliferation of cells that are important in the separation of the cloaca into genitourinary and gastrointestinal tracts. Increased mechanical stress due to abnormal fetal positioning, which may cause physical deformation of

the developing tissues, including the rectum and anus. This may inhibit the complete formation of the anal canal and lead to anorectal atresia or stenosis (Almatrafi et al., 2020; Pitaka et al., 2022; Solomon et al., 2024).

Four journals have suggested that maternal obesity increases the risk of ARM due to metabolic disturbances that occur as a result of insulin resistance and chronic inflammation that often accompanies obesity. These conditions can disrupt embryogenesis, which is a critical period in the formation of the digestive and anorectal systems. Maternal obesity is associated with an increased risk of gestational diabetes, which can lead to impaired nutrient supply and oxygenation to the fetus. Hormonal imbalances such as, high leptin levels may affect the process of cell differentiation during fetal development, contributing to structural abnormalities such as ARM. Studies have also shown that obese mothers tend to have higher systemic inflammation, which may interfere with the molecular signaling required for normal development of the gastrointestinal tract (Hapsari et al., 2022; Pitaka et al., 2022).

Four journals suggest that low levels of maternal education and awareness and unplanned pregnancies may contribute to ARM risk factors. Lack of knowledge about maternal health can lead to a lack of understanding of the importance of optimal prenatal care, including adequate nutrition and avoidance of exposure to teratogens that can impair fetal development. Mothers with low education levels tend to have limited access to quality health services, and therefore do not receive adequate prenatal screening to detect and prevent risk factors that may contribute to ARM (Almatrafi et al., 2020; Ervina et al., 2023).

Lack of awareness regarding the importance of folic acid consumption before and during pregnancy may also contribute to the increased risk of ARM, given that folic acid plays a role in the development of the fetal nervous and digestive systems. Therefore, efforts to improve maternal health education are needed to reduce the incidence of ARM and improve the well-being of mothers and babies (Kancherla et al., 2023; Smith & Jeffrey, 2022).

There are three journals that mention that antenatal history is not significant, even if the baby is born with ARM. "Insignificant antenatal history" means that no obvious prenatal risk factors were identified during pregnancy, but could still contribute to the incidence of ARM. The mechanism can be explained through several possibilities. First, genetic factors or de novo mutations undetected during pregnancy may play a role in the development of ARM, especially if there is no clear family history. Second, unrecorded or difficult-to-identify environmental exposures, such as micronutrient deficiencies, exposure to low levels of toxic substances, or subclinical infections, may interfere with the embryogenesis of the anorectal system. In addition, intrinsic fetal factors such as impaired vascularization or undetected intrauterine growth deficiency can also cause these congenital malformations. Thus, even if the antenatal history appears insignificant, hidden factors may still contribute to the risk of ARM (Almatrafi et al., 2020; Pitaka et al., 2022; Smith & Jeffrey, 2022).

There are three journals stating that oligohydramnios and polyhydramnios may contribute to ARM. Oligohydramnios, characterized by low amniotic fluid volume, may cause mechanical compression of the fetus, hindering the normal development of the digestive and anorectal systems. In addition, oligohydramnios is often associated with impaired placental vascularization, which may impair blood supply to the anorectal region and cause malformations. Meanwhile, polyhydramnios, which occurs due to fetal swallowing disorders or gastrointestinal obstruction, may be an indicator of congenital abnormalities such as esophageal atresia or intestinal obstruction, which are often associated with ARM. This disturbance in amniotic fluid balance suggests a developmental dysfunction of the gastrointestinal system, which may ultimately contribute to the occurrence of ARM (Almatrafi et al., 2020; Pitaka et al., 2022; Smith & Jeffrey, 2022).

There is one journal that links fetal hypoxia with impaired fetal organ development. Impaired vascular development and tissue differentiation during embryogenesis. Chronic hypoxia resulting from placental insufficiency or impaired oxygen exchange can cause dysregulation of molecular pathways that control the development of the digestive and anorectal systems. Lack of oxygen can inhibit cell proliferation as well as migration of neural crest cells that play a role in the formation of the enteric system, which contributes to the occurrence of congenital abnormalities such as ARM. In addition, hypoxia can also trigger oxidative stress that results in cellular apoptosis in areas crucial for anorectal development, causing structural defects. Impaired blood perfusion due to hypoxia may also result in localized vascular insufficiency in the anorectal region, further increasing the likelihood of malformations (Almatrafi et al., 2020; Pitaka et al., 2022; Smith & Jeffrey, 2022).

There is one journal that discusses Tethered Cord Syndrome (TCS) which is also a risk factor for ARM. TCS is a pathological condition in which the spinal cord undergoes abnormal retraction due to the attachment of tissue around the spinal cord. It is often associated with ARM due to impaired development of the central nervous system and autonomic nerves that control bowel and rectal function. TCS can cause impaired innervation of the anorectal region, which contributes to the development of ARM by the mechanism of disrupted nerve cell migration during embryogenesis (Smith & Jeffrey, 2022; Zhang et al., 2024).

In addition, the pressure generated by spinal cord retraction may inhibit vascularization and differentiation of tissues around the rectum and anus, ultimately increasing the risk of ARM. The association between TCS and ARM is also supported by studies showing that patients with ARM often have other neurological abnormalities, including impaired sphincter control and other congenital defects of the urogenital system. Therefore, early detection of TCS in neonates with ARM is crucial to prevent long-term complications related to bowel dysfunction and fecal incontinence (Pitaka et al., 2022; Zhang et al., 2024).

One journal mentioned that Copy Number Variants (CNVs) are also one of the risk factors for ARM. CNVs are copy number changes of DNA segments in the genome that can contribute to developmental disorders, including ARM. CNVs can cause genetic disruptions that affect important embryological pathways in rectum and anus formation, such as the Wnt pathway, Hedgehog, and transcription factors involved in mesodermal and endodermal development.

Copy number alterations of genes within specific chromosomal regions, such as duplications or deletions at 1q21.1, have been associated with congenital abnormalities, including ARM. This mechanism works by disrupting the expression of genes that regulate cell differentiation and migration during embryogenesis, resulting in impaired formation of anorectal structures. Therefore, analysis of CNVs can be an important tool in understanding the pathogenesis of ARM as well as in the early detection and management of infants at high risk for this disorder.

There is one journal that mentions that the use of assisted reproductive techniques, such as in vitro fertilization (IVF), has been associated with an increased risk of ARM. One of the main factors is the manipulation of embryos during the IVF process, which can cause stress on early fetal development, disrupting the expression of genes important in embryogenesis, including genes involved in the formation of the anorectal system. In addition, babies conceived through IVF have a higher risk of developing chromosomal abnormalities or genetic syndromes associated with ARM, such as VACTERL syndrome. Embryo hypoxia due to in vitro culture, use of cryopreservation, and epigenetic changes may also affect cell differentiation and migration necessary for normal development of the rectum and anus. In addition, IVF pregnancies are more often associated with pregnancy complications, such as prematurity and intrauterine growth disorders, which may exacerbate the risk of ARM.

Conclusion

Maternal risk factors that contribute to the incidence of ARM include exposure to teratogens such as cigarettes, alcohol, pesticides, drugs and radiation during pregnancy. Maternal health conditions, including diabetes, hypertension, anemia, and nutritional deficiencies (especially folic acid and other micronutrients), also play an important role in fetal development and may increase the risk of ARM. In addition, too young or too old maternal age, family history of ARM, intrauterine infections (TORCH, rubella, CMV), maternal obesity, and multiple pregnancies are also factors to consider.

Fetal risk factors that contribute to the incidence of ARM include genetic and chromosomal factors, including related syndromes such as Down syndrome and VACTERL, are the main causes of ARM. In addition, IUGR, prematurity, and LBW increase the likelihood of ARM. Some studies have also shown that ARM is more common in male infants and is associated with fetal malposition during pregnancy.

Based on the results of the discussion and conclusions, the authors suggest the need for further studies to explore genetic and molecular factors in ARM and how the interaction of environmental factors such as teratogenic substances and nutritional deficiencies affect the risk of ARM. And it is expected that the Health Office will develop guidelines for early detection based on prenatal screening and maternal risk factors, and improve the recording of ARM cases to improve the evaluation of incidence patterns and the effectiveness of interventions.

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