Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 7s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Biochemical Pathways in Neonatal Intestinal Atresia: Vascular and Genetic Perspectives

Ian Pranandi[*1]

[*1]Department of Biochemistry, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta 14440, Indonesia

[*]**Corresponding Author:**
Email ID: ian.pranandi@atmajaya.ac.id

Cite this paper as: Ian Pranandi, (2025) Biochemical Pathways in Neonatal Intestinal Atresia: Vascular and Genetic Perspectives. *Journal of Neonatal Surgery*, 14 (7s), 713-719.

ABSTRACT

Neonatal intestinal atresia (NIA) is a congenital condition characterized by the obstruction or absence of a segment of the intestine, leading to life-threatening complications in neonates. The etiology of NIA is multifactorial, involving both vascular and genetic factors. Vascular disruptions during fetal development may lead to ischemic necrosis and resorption of intestinal segments, while genetic mutations affecting developmental pathways contribute to structural anomalies. The involvement of key signaling pathways, including Notch, Wnt, and Hedgehog, suggests that molecular disruptions play a crucial role in intestinal morphogenesis. Additionally, epigenetic modifications and extracellular matrix defects have been implicated in the pathophysiology of NIA, further highlighting the complexity of its developmental origins.

Despite advances in prenatal imaging and neonatal surgery, NIA remains a significant cause of morbidity, often requiring extensive surgical intervention and long-term nutritional support. Early genetic screening and fetal Doppler studies may provide better risk stratification and earlier diagnosis, improving perinatal outcomes. Furthermore, emerging research on targeted molecular therapies and gene-editing technologies, such as CRISPR-Cas9, offers promising avenues for future intervention. Current studies suggest that gene-environment interactions, particularly maternal health factors and in utero exposures, may influence the severity and manifestation of NIA.

Given the multifaceted nature of this disorder, a comprehensive understanding of its biochemical pathways is crucial for developing effective treatment strategies. This literature review explores the vascular and genetic mechanisms implicated in NIA, with an emphasis on their molecular underpinnings and clinical implications. Advances in stem cell research and tissue engineering may provide alternative therapeutic options in the future, potentially reducing dependence on surgical interventions. By elucidating the intricate interactions between genetic and environmental factors, novel approaches in diagnosis, prevention, and treatment can be developed to improve patient outcomes and quality of life.

Keywords: *Neonatal intestinal atresia, vascular disruption, genetic mutations, Notch signaling, Wnt pathway, Hedgehog signaling, epigenetics, extracellular matrix, molecular therapies, CRISPR, tissue engineering*

1. INTRODUCTION

Neonatal intestinal atresia (NIA) is a congenital condition that presents as complete obstruction of the intestinal lumen due to the absence or discontinuity of the bowel.[1] The incidence of NIA varies, with duodenal atresia being more common than jejunoileal or colonic atresia.[2,3] Two major etiological perspectives—vascular and genetic—have been proposed to explain the pathogenesis of this disorder. The vascular disruption theory suggests that intrauterine ischemic events result in necrosis and resorption of the affected bowel segment, while the genetic hypothesis implicates mutations in key developmental signaling pathways.[4,5] This review examines these perspectives by analyzing the associated biochemical pathways and their implications for understanding NIA.

NIA is a significant cause of neonatal morbidity and mortality, requiring prompt surgical intervention to restore intestinal continuity and function. The clinical presentation of NIA depends on the location and severity of the atretic segment.[1,6] Proximal atresia, such as duodenal atresia, often presents with polyhydramnios, bilious vomiting, and failure to pass meconium, whereas distal atresia, such as jejunoileal or colonic atresia, may manifest with abdominal distension and delayed passage of stool. The standard approach to diagnosis includes prenatal ultrasound, which may detect polyhydramnios and a dilated proximal bowel, as well as postnatal imaging studies such as abdominal radiographs and contrast studies.[2,7] Despite advances in neonatal surgery and postoperative care, affected neonates remain at risk for complications such as short bowel syndrome, intestinal dysmotility, and nutritional deficiencies.[6,8]

Understanding the pathogenesis of NIA is essential for developing targeted interventions that may prevent or mitigate its occurrence. Research has increasingly focused on the interplay between genetic susceptibility and environmental insults that lead to intestinal malformations.[4,9] While vascular disruption is often cited as the primary mechanism for jejunoileal atresia, genetic factors have been strongly associated with duodenal atresia and syndromic conditions, such as trisomy 21. Additionally, epigenetic modifications and maternal factors, including smoking, infections, and medication use, have been implicated in the etiology of NIA.[6,10] This review aims to provide a comprehensive analysis of the biochemical pathways involved in the vascular and genetic origins of NIA, highlighting their implications for early diagnosis, prevention, and treatment strategies.

In addition to vascular and genetic factors, there is increasing evidence that inflammation and immune-mediated mechanisms may contribute to the development of NIA. Studies have suggested that intrauterine exposure to pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), may play a role in disrupting normal intestinal development.[8,11] These cytokines can induce apoptosis and impair angiogenesis, leading to intestinal malformations.[11,12] Furthermore, maternal infections during pregnancy, such as cytomegalovirus (CMV) and toxoplasmosis, have been associated with an increased risk of congenital intestinal defects.[13,14] This highlights the potential role of immune-mediated pathways in the pathogenesis of NIA and suggests that maternal health and inflammatory status may be critical factors influencing fetal gut development.

2. VASCULAR PERSPECTIVE: ISCHEMIC DISRUPTIONS IN FETAL DEVELOPMENT

The vascular disruption hypothesis posits that intestinal atresia arises from an intrauterine vascular insult, leading to segmental necrosis and resorption of affected bowel regions. Various ischemic events, including thromboembolism, volvulus, and vascular malformations, have been suggested as underlying causes.[4,8] One of the key biochemical regulators of the cellular response to hypoxia is Hypoxia-Inducible Factor-1 Alpha (HIF-1α), which is upregulated during oxygen deprivation. HIF-1α plays a pivotal role in activating vascular endothelial growth factor (VEGF), a critical mediator of angiogenesis. When VEGF signaling is compromised due to prolonged hypoxia, mesenteric vascularization becomes insufficient, leading to localized ischemic necrosis and subsequent resorption of the intestinal tissue.[15,16]

Additionally, coagulation abnormalities have been implicated in the pathogenesis of NIA. Conditions such as protein C deficiency, Factor V Leiden mutations, and prothrombin gene mutations are known to increase the risk of thromboembolic events, which may contribute to intestinal ischemia in utero.[17] In these scenarios, excessive thrombin production leads to clot formation, reducing mesenteric blood flow and causing infarction of the affected segment. Studies have demonstrated an association between thrombophilic disorders and congenital intestinal atresia, suggesting that hypercoagulability in the fetal circulation may be a contributing factor.[18]

Another important factor influencing fetal mesenteric perfusion is congenital heart disease (CHD). Fetuses with CHD often exhibit reduced systemic and mesenteric blood flow, increasing the likelihood of ischemic events. Umbilical cord anomalies, such as true knots or velamentous cord insertion, may also predispose the developing intestine to vascular insufficiency. The degree of vascular compromise determines the extent of atresia, ranging from partial stenosis to complete luminal obliteration.[19]

Several experimental models have been developed to investigate the role of vascular compromise in the development of intestinal atresia. Animal studies have demonstrated that surgically induced mesenteric ischemia in fetal models leads to bowel atresia, supporting the hypothesis that disruption in blood supply plays a critical role in disease pathogenesis.[20] Furthermore, histological analysis of resected atretic bowel specimens has revealed evidence of prior ischemic injury, including fibrosis and inflammatory infiltration, reinforcing the concept that vascular disruptions during fetal development contribute to NIA.[21]

In addition to hypoxia and thrombosis, inflammation may also play a role in vascular-mediated intestinal atresia. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) have been implicated in vascular injury and endothelial dysfunction. These cytokines can exacerbate ischemic damage by promoting apoptosis and inhibiting angiogenesis, thereby reducing the ability of the developing intestine to recover from transient vascular insults. This suggests that both primary ischemic events and secondary inflammatory responses may contribute to the pathophysiology of NIA.[8,11]

Furthermore, advances in fetal imaging and Doppler ultrasonography have provided insights into the hemodynamic changes associated with intestinal atresia.[2] Studies have demonstrated abnormal mesenteric arterial flow patterns in fetuses diagnosed with NIA, suggesting that compromised perfusion precedes the development of structural defects. These findings highlight the potential for prenatal diagnostic tools to identify at-risk fetuses and enable early intervention strategies aimed at preserving intestinal integrity.[2,7]

Another potential contributor to the vascular disruption hypothesis is oxidative stress, which plays a crucial role in endothelial dysfunction and tissue injury. Increased reactive oxygen species (ROS) production in hypoxic conditions can damage endothelial cells, disrupt vascular integrity, and impair angiogenic responses. Oxidative stress-induced apoptosis in

endothelial and intestinal epithelial cells may further compromise gut development, leading to atresia.[22] Studies suggest that antioxidants such as superoxide dismutase (SOD) and glutathione peroxidase play protective roles in counteracting oxidative stress, and their deficiency may exacerbate the impact of ischemic insults.[23] Future research into oxidative stress modulation may provide novel therapeutic approaches for preventing NIA.

Additionally, the role of maternal factors in vascular disruption should not be overlooked. Maternal conditions such as preeclampsia, diabetes, and hypertension have been associated with impaired placental perfusion, which can negatively affect fetal mesenteric blood flow.[24] Placental insufficiency may contribute to a chronic hypoxic environment in utero, predisposing the developing intestine to ischemic injury.[25] Epidemiological studies suggest that neonates born to mothers with hypertensive disorders of pregnancy have a higher incidence of gastrointestinal anomalies, further supporting the link between maternal health and fetal vascular integrity.[24,26] Addressing maternal risk factors and optimizing prenatal care could play a crucial role in mitigating the risk of NIA.

A deeper understanding of the molecular pathways underlying vascular dysfunction in NIA may offer potential therapeutic targets. Pharmacological agents that modulate angiogenesis, such as VEGF agonists or HIF stabilizers, have been explored in preclinical studies as potential strategies for preventing ischemic-related congenital defects. Although such interventions are still in experimental stages, they represent a promising avenue for future research aimed at mitigating the impact of vascular disruptions on fetal intestinal development.[27,28]

Table 1[22,27] summarizes key biochemical factors involved in intestinal atresia, highlighting their functions and the impact of their dysregulation on vascular integrity and intestinal development.

Table 1: Biochemical Mediators of Vascular Disruption in NIA

Biochemical Factor	Function	Effect on Intestinal Atresia
HIF-1α	Regulates oxygen homeostasis	Impaired response leads to hypoxia and atresia
VEGF	Promotes angiogenesis	Deficiency disrupts intestinal vascularization
Protein C	Anticoagulant pathway regulator	Deficiency increases risk of thrombosis
TNF-α	Promotes inflammation	Exacerbates endothelial injury and vascular compromise
IL-6	Modulates immune response	Contributes to ischemic tissue damage
ROS	Induces oxidative stress	Leads to endothelial dysfunction and apoptosis
SOD	Antioxidant enzyme	Protects against oxidative stress-induced damage

3. GENETIC PERSPECTIVE: DEVELOPMENTAL SIGNALLING PATHWAY

While vascular disruption provides a compelling explanation for NIA, genetic factors have also been implicated in its pathogenesis. The Notch, Wnt/β-catenin, and Hedgehog (Hh) signaling pathways are crucial regulators of intestinal morphogenesis, and mutations affecting these pathways may lead to atresia.[29,30,31]

The Notch signaling pathway plays a key role in cell fate determination and differentiation within the intestinal epithelium. Notch receptors interact with their ligands, such as Delta-like and Jagged proteins, to modulate the balance between absorptive enterocytes and secretory cells. Disruptions in Notch signaling, particularly mutations in NOTCH1 or JAG1 genes, have been linked to defective gut epithelial development. Experimental models with Notch inhibition exhibit abnormal crypt-villus architecture and intestinal lumen obstruction, closely resembling NIA pathology.[29,32]

The Wnt/β-catenin signaling pathway is another essential regulator of intestinal development. Wnt ligands bind to Frizzled receptors, stabilizing β-catenin and promoting cell proliferation in the intestinal stem cell niche. Dysregulation of this pathway can impair villus formation and intestinal tube elongation, contributing to atresia. Studies have identified mutations in Wnt-related genes as potential contributors to congenital gastrointestinal defects, further supporting the role of Wnt signaling in NIA.[30,33]

Additionally, the Hedgehog (Hh) signaling pathway, involving Sonic Hedgehog (SHH) and its receptor Patched (PTCH1), is critical for gut mesenchymal-epithelial interactions. Proper Hedgehog signaling ensures coordinated growth of the intestinal smooth muscle and enteric nervous system. Mutations in SHH or PTCH1 disrupt these interactions, leading to abnormal gut tube morphogenesis and intestinal atresia. Research has demonstrated that reduced Hedgehog activity results in diminished intestinal smooth muscle development, which may contribute to the luminal narrowing observed in NIA.[31,34]

Recent studies suggest that genetic variations affecting extracellular matrix (ECM) proteins may also play a role in intestinal atresia. ECM components such as collagen, laminin, and fibronectin are essential for maintaining gut structure and function.

Mutations affecting ECM-related genes may lead to defective basement membrane integrity, impairing normal intestinal morphogenesis. The interplay between ECM and signaling pathways such as Wnt and Notch further highlights the complexity of intestinal development and the potential for multiple genetic disruptions leading to atresia.[35,36]

Epigenetic modifications, including DNA methylation and histone modifications, have also been implicated in congenital gastrointestinal malformations. Studies indicate that aberrant methylation patterns in genes regulating intestinal development can alter gene expression, potentially contributing to the formation of atretic segments. Environmental factors, such as maternal diet, exposure to toxins, and gestational diabetes, have been suggested to influence epigenetic regulation of these key genes, underscoring the potential for both genetic and environmental interactions in NIA pathogenesis.[37,38]

Furthermore, syndromic forms of NIA provide additional insights into the genetic basis of the disease. Conditions such as Feingold syndrome, which is caused by MYCN gene mutations, often present with intestinal atresia along with microcephaly and digital anomalies. Similarly, Fanconi anemia, a disorder associated with mutations in DNA repair genes, has been linked to congenital gastrointestinal defects. These syndromic associations suggest that disruptions in fundamental developmental pathways can manifest as multiple congenital anomalies, including intestinal atresia.[10,39]

Genome-wide association studies (GWAS) and whole-exome sequencing have identified novel genetic variants that may contribute to NIA susceptibility. Rare de novo mutations affecting developmental regulators, including genes involved in cellular adhesion and tissue remodeling, have been observed in affected individuals. These findings suggest that a broader network of genetic interactions may underlie NIA, beyond the traditionally studied signaling pathways.[35,37]

Gene-environment interactions are an area of growing interest in understanding the etiology of NIA. While specific genetic mutations may predispose an individual to atresia, external factors such as maternal hypoxia, intrauterine infections, and nutritional deficiencies may act as triggers, exacerbating the developmental defects.[36,38] Investigating these interactions may provide valuable insights into preventive strategies and therapeutic interventions aimed at reducing the incidence of NIA.

Additionally, advances in genetic engineering techniques, such as CRISPR-Cas9, have opened new avenues for studying NIA-related gene mutations. Researchers have begun using gene-editing tools to create animal models with specific genetic disruptions, allowing for a better understanding of how these mutations influence intestinal development.[38,40] These models offer valuable opportunities for testing potential therapeutic interventions, including gene therapy and targeted molecular treatments aimed at correcting the underlying genetic defects.

Moreover, emerging research suggests that non-coding RNAs, particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), may regulate key genes involved in intestinal development. Dysregulation of these RNA molecules has been linked to congenital malformations, including gastrointestinal anomalies.[41,42] Understanding the role of non-coding RNAs in NIA pathogenesis may provide novel biomarkers for early diagnosis and potential targets for therapeutic intervention.

Recent studies have also highlighted the role of mitochondrial dysfunction in congenital gastrointestinal disorders, including NIA. Mitochondria play a critical role in cellular energy production and apoptosis regulation, both of which are essential for proper tissue development. Mutations in mitochondrial DNA or nuclear genes regulating mitochondrial function may impair intestinal epithelial cell differentiation, leading to developmental abnormalities.[43,44] Further research is needed to elucidate how mitochondrial defects contribute to the pathogenesis of NIA and whether mitochondrial-targeted therapies could provide new treatment strategies.

In addition, studies have suggested that alterations in mechanotransduction pathways, which regulate how cells sense and respond to mechanical forces, may also play a role in NIA development. The intestinal tract undergoes significant mechanical stretching and peristalsis during fetal development, and disruptions in mechanotransduction signals may affect normal morphogenesis. Key mechanosensitive proteins, such as YAP/TAZ in the Hippo signaling pathway, have been implicated in regulating intestinal epithelial growth and differentiation.[45,46] Future research exploring these mechanobiological mechanisms may provide new insights into the etiology of NIA and potential intervention strategies.

Table 2[29,31] summarizes key signaling pathways, their associated genes, and their roles in intestinal development, highlighting how disruptions in these pathways contribute to structural and functional abnormalities in the intestine.

Table 2: Developmental Signaling Pathways Implicated in NIA

Signaling Pathway	Key Genes	Function	Effect on Intestinal Development
Notch	NOTCH1, JAG1	Regulates epithelial differentiation	Disruptions lead to defective crypt-villus architecture
Wnt/β-catenin	CTNNB1, WNT3	Controls cell proliferation	Dysregulation impairs villus formation and intestinal tube elongation

Hedgehog	SHH, PTCH1	Governs mesenchymal-epithelial interactions	Mutations lead to abnormal smooth muscle and enteric nervous system development
ECM-related	COL1A1, LAMA1	Maintains gut structural integrity	Defective ECM proteins impair morphogenesis
Epigenetic Factors	DNMT3A, HDAC1	Modulates gene expression	Aberrant methylation patterns affect developmental genes

4. CONCLUSION

Neonatal intestinal atresia arises from a complex interplay of vascular and genetic factors. The vascular disruption hypothesis emphasizes the role of ischemic insults, while genetic research highlights mutations in developmental pathways. Further studies are required to delineate the precise molecular mechanisms, which may lead to targeted therapies aimed at preventing or mitigating NIA. A deeper understanding of these biochemical pathways may also facilitate earlier diagnosis and improved surgical outcomes for affected neonates.

Future research should focus on integrating genetic screening into routine prenatal care to identify fetuses at risk for developing NIA. With advancements in next-generation sequencing and genome-wide association studies, novel genetic markers associated with intestinal atresia may be discovered. Identifying these markers early in gestation may allow for potential therapeutic interventions or closer monitoring of high-risk pregnancies. Additionally, investigating gene-environment interactions may help clarify how maternal health, nutritional status, and external exposures contribute to the manifestation of NIA.

Another promising area of research is the development of targeted molecular therapies. With increasing knowledge of signaling pathways such as Notch, Wnt, and Hedgehog, therapeutic strategies aimed at modulating these pathways could provide new treatment avenues. For instance, small-molecule inhibitors or activators targeting these pathways may promote proper intestinal development and prevent malformations. Moreover, gene-editing technologies such as CRISPR-Cas9 hold the potential to correct specific genetic mutations associated with NIA, paving the way for future personalized medicine approaches.

Overall, a multidisciplinary approach involving pediatric surgeons, geneticists, neonatologists, and molecular biologists is crucial to advancing our understanding of NIA. Improved diagnostic techniques, early genetic screening, and innovative therapeutic strategies will be key to reducing the burden of this condition and improving outcomes for affected neonates.

REFERENCES

[1] Singh V, Pathak M. Congenital neonatal intestinal obstruction: retrospective analysis at tertiary care hospital. J Neonatal Surg. 2016;5(4):49. doi:10.21699/jns.v5i4.393.

[2] Chen D, Tam KH, Zhang Y, Xiao S, Yang C, Tang X. Prenatal diagnosis of midgut volvulus with jejunal atresia by ultrasonography. J Obstet Gynaecol Res. 2020;46(7):1203-1206. doi:10.1111/jog.14296.

[3] Kayima P, Ssewanyana Y, Ozgediz D, Sekabira J. Efforts to improve outcomes among neonates with complex intestinal atresia in a low-income country: a retrospective cohort study. Pediatr Surg Int. 2024;40(5):567-574. doi:10.1007/s00383-024-05639-7.

[4] Kamal A, Khan K, Inayat ur R, Khan A. Small gut atresia in neonates. J Ayub Med Coll Abbottabad. 2010;22(2):64-66.

[5] Alam MS, Elghote SE, Kamel SMM, Kumar C, Shedabale DS. Intestinal atresia leading to intussusception: an unconventional submission. Cureus. 2024;16(9):e69723. doi:10.7759/cureus.69723.

[6] Basak A, Sil A, Sarkar M. Intestinal atresia: a retrospective study of 36 neonates and risk factors to mortality in a tertiary care center, Tripura. Int J Contemp Pediatr. 2025;12(2):215-220. doi:10.18203/2349-3291.ijcp20250087.

[7] Virgone C, D'Antonio F, Khalil A, Jonh R, Manzoli L, Giuliani S. Accuracy of prenatal ultrasound in detecting jejunal and ileal atresia: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015 May;45(5):523-529. doi:10.1002/uog.14651.

[8] Saha H, Halder A, Chatterjee U, Saha K. Clinicopathological study of intestinal smooth muscles, interstitial cells of Cajal, and enteric neurons in neonatal jejuno-ileal atresia with special reference to muscle morphometry. J Pediatr Surg. 2019 Nov;54(11):2291-2299. doi: 10.1016/j.jpedsurg.2019.06.003.

[9] Exome sequencing identifies mutations in the gene TTC7A in French-Canadian cases with hereditary multiple intestinal atresia. *J Med Genet*. 2013;50(5):324-329. doi: 10.1136/jmedgenet-2012-101483.

[10] Avitzur Y, Guo C, Mastropaolo LA, Bahrami E, Chen H, Zhao Z, et al. Mutations in tetratricopeptide repeat

domain 7A result in a severe form of very early onset inflammatory bowel disease. *Gastroenterology*. 2014 Apr;146(4):1028-39. doi: 10.1053/j.gastro.2014.01.015.

[11] Nusinovich Y, Revenis M, Torres C. Long-term outcomes for infants with intestinal atresia studied at Children's National Medical Center. *J Pediatr Gastroenterol Nutr*. 2013 Sep;57(3):324-9. doi: 10.1097/MPG.0b013e318299fd9f.

[12] Wilasco MI, Uribe-Cruz C, Santetti D, et al. IL-6, TNF-α, IL-10, and nutritional status in pediatric patients with biliary atresia. J Pediatr (Rio J). 2017;93(5):517-524. doi:10.1016/j.jped.2016.11.009.

[13] Goelz R, Hamprecht K, Klingel K, Poets CF. Intestinal manifestations of postnatal and congenital cytomegalovirus infection in term and preterm infants. J Clin Virol. 2016;83:29-36. doi:10.1016/j.jcv.2016.08.289.

[14] Schleiss MR. Cytomegalovirus infection in the neonate and premature infant. Infect Disord Drug Targets. 2011;11(5):449-465. doi: 10.2174/187152611797636721.

[15] Zhou J, Zhang H, Gu P, et al. Hypoxia-inducible factor 1α regulates autophagy to affect apoptosis in trophoblast cells. J Matern Fetal Neonatal Med. 2017;30(3):362-371.

[16] Ietta F, Wu Y, Winter J, et al. Dynamic HIF1A regulation during human placental development. Biol Reprod. 2006;75(1):112-121. doi: 10.1095/biolreprod.106.051557.

[17] Tempfer CB, Brunner A, Bentz EK, Langer M, Reinthaller A, Hefler LA. Intrauterine fetal death and delivery complications associated with coagulopathy: a retrospective analysis of 104 cases. J Womens Health (Larchmt). 2009;18(4):469-74. doi:10.1089/jwh.2008.0938.

[18] Maslow AD, Breen TW, Sarna MC, Soni AK, Watkins J, Oriol NE. Prevalence of coagulation abnormalities associated with intrauterine fetal death. Can J Anaesth. 1996;43(12):1237-43. doi:10.1007/BF03013432.

[19] Bracher I, Padrutt M, Bonassin F, Santos Lopes B, Gruner C, Stampfli SF, et al. Burden and impact of congenital syndromes and comorbidities among adults with congenital heart disease. Int J Cardiol. 2017;240:159-164. doi:10.1016/j.ijcard.2017.02.118.

[20] Li Y, Liu Y, Shi Y, et al. Melatonin attenuates intestinal injury and inhibits TLR4/MyD88/NF-κB signaling pathway in a neonatal necrotizing enterocolitis rat model. Int J Clin Exp Med. 2017;10(3):5112-5120. doi:10.1155/2022/6920577.

[21] Jung E, Romero R, Yeo L, Diaz-Primera R, Marin-Concha J. The fetal inflammatory response syndrome: the origins of a concept, pathophysiology, diagnosis, and obstetrical implications. *Semin Fetal Neonatal Med*. 2020;25(4):101146. doi:10.1016/j.siny.2020.101146.

[22] Schoots MH, Gordijn SJ, Scherjon SA, van Goor H, Hillebrands JL. Oxidative stress in placental pathology. Placenta. 2018;69:153-161. doi:10.1016/j.placenta.2018.03.003.

[23] Sultana Z, Maiti K, Aitken J, Morris J, Dedman L, Smith R. Oxidative stress, placental ageing-related pathologies and adverse pregnancy outcomes. Am J Reprod Immunol. 2017;77(5):e12653. doi:10.1111/aji.12653.

[24] Nzelu D, Dumitrascu-Biris D, Nicolaides KH, Kametas NA. Chronic hypertension: first-trimester blood pressure control and likelihood of severe hypertension, preeclampsia, and small-for-gestational-age neonates. Am J Obstet Gynecol. 2018;218(3):337.e1-337.e7. doi: 10.1016/j.ajog.2017.12.235.

[25] Gaccioli F, Lager S. Placental nutrient transport and intrauterine growth restriction. Front Physiol. 2016;7:40. doi:10.3389/fphys.2016.00040.

[26] Atwani R, Aziz A, Saade G, Reddy UM, Kawakita T. Maternal implications of fetal anomalies: a population-based cross-sectional study. Am J Obstet Gynecol MFM. 2024;6(1):101440. doi:10.1016/j.ajogmf.2024.101440.

[27] Reeson P, Choi K, Brown CE. VEGF signaling regulates the fate of obstructed capillaries in mouse cortex. eLife. 2018;7:e33670. doi:10.7554/eLife.33670.

[28] Apte RS, Chen DS, Ferrara N. VEGF in signaling and disease: beyond discovery and development. *Cell*. 2019;176(6):1248-1264. doi:10.1016/j.cell.2019.01.021.

[29] Ishiguro H, Okubo T, Kuwabara Y, Kimura M, Mitsui A, Sugito N, et al. NOTCH1 activates the Wnt/β-catenin signaling pathway in colon cancer. *Oncotarget*. 2017;8(36):60378-60389. doi:10.18632/oncotarget.19534.

[30] Nusse R, Clevers H. Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. Cell. 2017;169(6):985-999. doi:10.1016/j.cell.2017.05.016.

[31] Briscoe J, Thérond PP. The mechanisms of Hedgehog signalling and its roles in development and disease. Nat

Rev Mol Cell Biol. 2013;14(7):416-429. doi:10.1038/nrm3598.

[32] Andersson ER, Sandberg R, Lendahl U. Notch signaling: simplicity in design, versatility in function. Development. 2011;138(17):3593-3612. doi:10.1242/dev.063610.

[33] Steinhart Z, Angers S. Wnt signaling in development and tissue homeostasis. Development. 2018;145(11):dev146589. doi:10.1242/dev.146589.

[34] Lu Y, Zhu Y, Deng S, Chen Y, Li W, Sun J, et al. Targeting the Sonic Hedgehog pathway to suppress the expression of the cancer stem cell (CSC)-related transcription factors and CSC-driven thyroid tumor growth. *Cancers (Basel)*. 2021;13(3):418. doi:10.3390/cancers13030418.

[35] Goulet O, Olieman J, Ksiazyk J, Spolidoro J, Tibboe D, Köhler H, et al. Neonatal short bowel syndrome as a model of intestinal failure: physiological background for enteral feeding. *Clin Nutr*. 2013;32(2):162-171. doi:10.1016/j.clnu.2012.09.007.

[36] Al-Zaiem MM, Alsamli RS, Alsulami EA, Mohammed RF, Almatrafi MI. Hereditary multiple intestinal atresia: a case report and review of the literature. *Cureus*. 2022;14(10):e30870. doi:10.7759/cureus.30870.

[37] Jardine S, Dhingani N, Muise AM. TTC7A: steward of intestinal health. Cell Mol Gastroenterol Hepatol. 2019;7(3):555-570. doi:10.1016/j.jcmgh.2018.12.001.

[38] Samuels ME, Majewski J, Alirezaie N, et al. Exome sequencing identifies mutations in the gene TTC7A in French-Canadian cases with hereditary multiple intestinal atresia. J Med Genet. 2013;50(5):324-329. doi:10.1136/jmedgenet-2012-101483.

[39] Muise AM, Walters TD, Glowacka WK, et al. Polymorphisms in E-cadherin (CDH1) result in a mis-localised cytoplasmic protein that is associated with Crohn's disease. Gut. 2009;58(8):1121-1127. doi:10.1136/gut.2008.175117.

[40] Li S, Zhu M, Pan R, Fang T, Cao Y, Chen S, et al. Functional screen of inflammatory bowel disease genes reveals key epithelial functions. Genome Med. 2021;13(1):177. doi:10.1186/s13073-021-00996-7.

[41] Tang Q, Zou Z, Zou C, Zhang Q, Huang R, Guan X, et al. MicroRNA-93 suppresses colorectal cancer development via downregulation of the Wnt/β-catenin pathway. *Tumour Biol*. 2015;36(3):1701-1710. doi:10.1007/s13277-014-2771-6.

[42] Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116(2):281-297. doi:10.1016/s0092-8674(04)00045-5.

[43] Bindi E, Alganabi M, Biouss G, Liu J, Li B, Miyake H, et al. Hepatic oxidative injury: role of mitochondrial dysfunction in necrotizing enterocolitis. Pediatr Surg Int. 2021;37(3):325-332. doi:10.1007/s00383-020-04816-8.

[44] Zhang Y, Yi S, Luan M. Advances in non-apoptotic regulated cell death: implications for malignant tumor treatment. *Front Oncol*. 2025;15:1519119. doi:10.3389/fonc.2025.1519119.

[45] Ballouhey Q, Fourcade L, Richard L, Bellet C, El Hamel C, Vallat JM, et al. Epithelial changes of congenital intestinal obstruction in a rat model. *PLoS One*. 2020;15(4):e0232023. doi:10.1371/journal.pone.0232023.

[46] Humphrey JD, Dufresne ER, Schwartz MA. Mechanotransduction and extracellular matrix homeostasis. Nat Rev Mol Cell Biol. 2014;15(12):802-812. doi:10.1038/nrm3896.