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INTRAHEPATIC CHOLESTASIS OF PREGNANCY: THE INFLUENCE OF NEONATAL OUTCOMES DESPITE THERAPEUTIC APPROACH ON MOTHERS

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Abstract. *Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-associated liver disorder characterized by maternal pruritus and elevated serum bile acids, with generally favorable maternal prognosis but significant perinatal risks. This narrative review analyzes current evidence regarding the pathophysiological mechanisms of ICP, available pharmacological treatment, and the impact of bile acid levels on neonatal outcomes. Adverse outcomes – including stillbirth, preterm birth, and respiratory distress syndrome—are strongly correlated with serum bile acid concentrations above 100 μmol/L, through mechanisms such as fetal arrhythmias, placental vasoconstriction, and impaired surfactant secretion. Management requires individualized monitoring of bile acids, administration of ursodeoxycholic acid for maternal symptom relief, close fetal surveillance, and consideration of delivery at 36–37 weeks in severe cases to reduce fetal risk.*

Keywords: *Intrahepatic cholestasis of pregnancy, bile acids, neonatal outcomes, stillbirth, preterm birth, ursodeoxycholic acid.*

Introduction. In our days intrahepatic cholestasis of pregnancy (ICP) is a unique, reversible disorder linked to gestation which is characterized by pruritus and elevated liver function tests, a great impact on neonatal outcomes associated with a high incidence of adverse results [15]. First mention of these symptoms was described seventy years ago by Svanborg and Thorling as a periodically pattern among pregnant women who presented in the third trimester intense pruritus and jaundice with spontaneous resolution after birth [2, 35]. Nowadays intrahepatic cholestasis of pregnancy (ICP) is a liver disorder without inflammation or proliferation of mesenchymal cells, characterized by pruritus of palms and soles, sometimes extended to the other parts of body which increased its intensity on night. Also called ictus gravidarum, can have a significant impact on fetal morbidity after 36 weeks of gestation and neonatal outcomes [18].

On the other hand, biochemical profile of these disease is defined by elevated liver function tests (LFTs) and/or elevated serum bile acids (BA) [10].

ICP has an estimated 0.5–1% of the global population affected, ranges from 0.6% in Oceania to rates of 3% to 5% in parts of Asia, Europe and South America with a great incidence in late autumn and winter in temperate climates [3, 13]. The relationship between the considerable prevalence of ICP in different geographical areas, seasons and ethnic groups reveals differences in genetic susceptibility and environmental factors. Knowing as a reversible condition for mothers, ICP often resolve rapidly after childbirth without long-term health risks, but the condition is associated with substantial perinatal morbidity [10].

A recent study revealed associations between maternal hypercholanemia and increased risks of spontaneous preterm birth, low weight at birth, meconium-stained amniotic fluid, high rates of ICU admission with neonatal respiratory

distress. When serum bile acid concentrations exceed 100 μmol/L intrauterine fetal demise need to be consider [34].

Literature data tend to evaluate the degree of ICP through the spectrum of biochemical analyses and the clinical symptoms of the mother without including neonatal results in the classification of the disease. This scientific essay aims to shed light on the pathophysiology of ICP and its direct influence on the intrauterine state of the fetus and the neonatal outcome. At the same time, pharmacological intervention and timing of birth were analyzed in terms of their influence on the intrauterine condition and neonatal outcomes. To highlight conclusive data we have used recent guidelines, large cohort studies, historical and newer approach of bile acid pathophysiology in pregnancy. Data have been collected through January 2026 based on a searched on the Google Scolar, PubMed and ACOG.

1. Pathophysiology. The major role in maintaining bile acid homeostasis is played by the enterohepatic circuit. Synthesis of bile acids is maintained by a negative feedback trough the farnesoid X receptor (FXR) which is activated intracellular by bile acids. FXR plays a different role: in liver down-regulates cholesterol 7 alpha-hydroxylase (CYP7A1) and limit future bile acid synthesis, meanwhile in the ileum stimulates the production of fibroblast growth factor 19 (FGF19) with a hormonal potential on suppression hepatic bile acids synthesis [8]. Through enterohepatic circuit 95% of bile acids are reabsorbed in the terminal ileum by apical sodium-dependent bile acid transporter (ASBT), returned to liver via portal vein and entered into hepatocytes through sodium taurocholate cotransporting polypeptide (NTCP) and organic anion transporting polypeptides (OATPs) [20, 30].

In our days four pathways of bile acids synthesis from cholesterol are known, two primary and two minors are described in literature:1) the neutral one is initiated by enzyme CYP7A1 mentioned above and predominates in human; 2) the acid one is conducted by mitochondrial sterol 27-hydroxylase (CYP27A1); 3) the 25-hydroxylase pathway active in the liver and peritoneal macrophages; 4) and the 24-hydroxylase pathway occurring exclusively in the brain, in neurons and astrocytes [10, 20].

The neutral pathway produces the principal bile acids like cholic and chenodeoxycholic. After production they are conjugated to glycine or taurine. Conjugation improved their solubility and with bile salt export pump (BSEP) help, bile acids are secreted into the bile ducts and stored in gallbladder. During food intake they are expressed into the duodenum, where they play a key role in the emulsification and facilitation lipids and lipophilic vitamin absorption [20].

2. Etiology. We must look on ICP like a multi-factorial disease and not just a simple dis-regulation in acids bile homeostasis. Ongoing evidence demonstrates the impact of genetic susceptibility, hormonal and microbiome imbalance, placental alteration, dysfunction of immune system, susceptibility to environmental factors and iatrogenic influence [28]. All these factors acting together pictured clinical and labs modification of ICP in predisposed pregnancies.

The geographic prevalence of ICP reveals the genetic susceptibility of some ethnic groups. Genetic susceptibility is confirmed by studies conducted on monozygotic and dizygotic twins, as well as the analysis of family history which revealed frequent involvement of pregnant women who know that their mothers or sisters have presented ICP. The support the hypothesis of genetic involvement in the mechanism of bile acid secretion and circulation as a key factor in the etiopathogenesis of ICP [13].

Mutations in 2 genes: 1) ABCB4{ATP-binding cassette, subfamily B, member 4} which encodes multidrug resistance protein 3 (MRP3), a canalicular phospholipid floppase essential for the formation of protective bile micelles, mutation of this gene was identified in up to 15–20% of women with ICP, and mutation of ABCB11 gene ,which encoding the bile salt export pump, have been found in very severe, recurrent or early-onset cases [34].

The hormonal imbalance in ICP is manifested not by the high levels of estrogen and progesterone in pregnancy, but by the accumulation of specific metabolites with cholestatic action that modify the enterohepatic circuit by influencing the receptors involved in the negative feedback of bile acids.

Thus, sulphated progesterone metabolites such as epiallopregnanolone sulphate and allopregnanolone sulphate apply inhibitory effects on the farnesoid X receptor, disrupt bile acid efflux, nurture intrahepatic retention that leading to a cholestatic phenotype in genetically susceptible women [6]. On the other hand, high levels of 17β-estradiol during late trimester interact with FXR reducing transporter expression at the hepatocyte canalicular surface and impairing compensatory bile acid efflux into the systemic circulation [7].

A healthy intestinal microbiome in pregnancy tends to possess a hydrolase activity on bile salts facilitating their deconjugation and excretion into the intestinal lumen. On the other hand, alteration of the intestinal microbiota has been observed in pregnant women with ICP with the proliferation of Bacteroides fragilis species that possess hydrophobic actions on bile salts and incresed their hepatotoxic and cholestatic action. The observations tend to position intestinal dysbiosis in ICP not as a secondary effect of the disease but as one of its etiological factors [10, 13, 34].

We tend to believe that the placenta represents the passive barrier between mother and fetus, forgetting that it is a separate organ that reacts to bilateral changes in the homeostasis of the pregnant woman and the fetus. In the case of mothers affected by ICP, the placenta is overloaded by the excretion of bile acids, in addition to undergoing structural and molecular changes that compromise its barrier function and expose the fetus to high concentrations of bile salts [21].

The first placental mechanism affected is the transport of bile acids via OATP1A2 and OATP1B3 receptors, thus the transport of fetal bile acids to the maternal system is reduced and the fetus is receiving the double load of its own and maternal bile acids [2]. The second mechanism affected is the enzymatic one such as SRD5A1 and AKR1C2 which contributes to the local synthesis of sulphated progesterone metabolites, which exert an inhibitory action on FXR and alter the circuit of steroid metabolites potentiating their cholestatic effect [14]. Last comes the placental restructuring at the histological level characterized by reduced intervillous space, an increased prevalence of syncytial

knots and enhanced capillary growth within terminal villi. This characteristic pattern for intrauterine hypoxic conditions tends to show the vasoconstrictive effect of bile acids on the intervillous circulation [20].

The immunological profile of pregnant women with ICP shifts from an anti-inflammatory Th2-profile to a Th1 pro-inflammatory one due to the synthesis of cytokines such as tumour necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin-6 (IL-6) and interleukin-12 (IL-12), alongside decreased levels of interleukin-4 (IL-4) and transforming growth factor-beta 2 (TGF-β2), affecting the maternal - fetal immune tolerance and promoting systemic inflammation [1, 20, 41].

Environmental factors such as the cold season, a diet low in selenium and zinc leading to low levels of glutathione in the maternal body, low serum levels of vitamin D during conception and pregnancy lead to increased oxidative stress in pregnant women affected by ICP [14]. Some of medications prescribed in pregnancy like antibiotics (azithromycin, amoxicillin), proton pump inhibitors (lansoprazole, omeprazole) and high doses of progestogen hormones used IVF-assisted pregnancies, have a more pronounced cholestatic and hepatotoxic action in population susceptible to ICP [22, 37, 39]

3. Clinical Presentation and Diagnosis

The onset of cholestasis gravidarum is characterized by the appearance of cutaneous pruritus localized on the palms and soles, especially at night, with a tendency to spread over the entire body without underlying skin lesion and association with systemic illness [36]. Typical these symptoms resolve in several days after birth and supports the diagnosis of ICP. Sometimes symptoms of intrahepatic cholestasis of pregnancy include jaundice of the skin, intense coloration of urine, steatorrhea, right upper quadrant discomfort and fatigue but these are rare. It remains unclear which biological changes appear first, clinical signs or bile acids elevation [12].

An analysis of the guidelines reveals different approaches regarding the level of bile acids detected in the blood and the necessity in fasting before collecting samples. The European Association for the Study of the Liver accepts a non-fasting total bile acid level of 10 μmol/L or greater in the presence of pruritus as sufficient for diagnosis while the UK, Australian and Canadian recent guidelines recommend a higher threshold of 19 μmol/L or greater for non-fasting samples because of the influence of postprandial bile acid fluctuations.

The classical approach of the diagnostic ICP remains the general acceptation on the serum level of bile acids. Thus, the pathology studied is classified by the authors according to the level of bile acids in mild 10–39 μmol/l; moderate 40–99 μmol/l and severe ≥100 μmol/l [32]. Where the risk of adverse perinatal outcomes appears to increase substantially, by levels greater than 100 μmol/L [32].

If the bile acid levels are within the reference range, but the clinical picture persists, the general recommendation is to repeat the tests in two weeks. Other changes in the biochemical analysis are the elevation of transaminases up to 10–20 times their normal value, which often occurs before the elevation of bile acids. Alkaline phosphatase which is elevated in the third trimester of pregnancy is not specific for ICP.

Because the symptoms of ICP are similar to other liver diseases, it is necessary to make a differential diagnosis with diseases such as hyperemesis gravidarum, acute viral hepatitis, autoimmune hepatitis, Wilson's disease, primary sclerosing cholangitis, primary biliary cirrhosis, symptomatic cholelithiasis, cytomegalovirus, Epstein-Barr infection, acute fatty liver of pregnancy, HELLP syndrome and drug-induced hepatitis. Each of the conditions listed above has diagnostic criteria compared to ICP [35].

Considering the toxic action of bile acids on the intrauterine state of the fetus, at the first suspicion of ICP, careful monitoring of the pregnant woman and initiation of pharmacological treatment as soon as possible are necessary. Current recommendations regarding the management of pregnant women with ICP provide the following:

- Measurement of serum bile acid levels and liver transaminases is recommended in patients with suspected ICP (Grade 1B).
- Ursodeoxycholic acid (UDCA) is recommended as the first-line therapy for the treatment of maternal symptoms of ICP (Grade 1A).
- Antenatal fetal surveillance is suggested at a gestational age when delivery would be undertaken in response to abnormal fetal testing, or at the time of diagnosis if the diagnosis is established later in pregnancy (Grade 2C).
- For patients with total bile acid levels ≥100 μmol/L, delivery is recommended at 36 0/7 weeks of gestation due to the substantially increased risk of stillbirth at this gestational age (Grade 1B).
- In patients with bile acid levels <100 μmol/L, delivery is recommended between 36 0/7 and 39 0/7 weeks of gestation (Grade 1C).
- Administration of antenatal corticosteroids for fetal lung maturation is recommended when delivery occurs before 37 0/7 weeks of gestation, if not previously administered (Grade 1A).
- Preterm delivery before 37 weeks of gestation is not recommended in patients with a clinical diagnosis of ICP without laboratory confirmation of elevated bile acid levels (Grade 1B) [24].

4. Neonatal Outcomes in ICP. Preterm birth in ICP is the most common neonatal complication in ICP. Preterm birth in ICP happened due to the exaggerated expression of oxytocin receptors potentiated by high levels of bile acids in maternal blood, as well as their vasoconstrictive action on the chorionic veins, leading to fetal distress that induces emergency termination of pregnancy. Even moderate elevations in serum bile acid concentrations (20–39 μmol/L) are associated with increased incidence of spontaneous preterm birth [8].

A sure sign of fetal distress is the presence of thick meconium. Its incidence in births of mothers affected by

ICOP is very high due to the action of bile acids on the fetal enteric nervous system. Bile acids tend to increase gut mobility and relax anal sphincter; both facilitate the passage of meconium into the amniotic liquid. These factors impose to continuous fetal monitoring and timely delivery because the risk of meconium aspiration and neonatal respiratory distress [42].

The incidence of intrauterine fetal death (stillbirth) in severe ICP is 3.4% compared with general population 0,3%. The main mechanism implicated is bile acid toxicity on the fetal myocardium leading to fetal atrial flutter and supraventricular tachycardia, PR interval prolongation and altered heart rate variability. The fetal myocardial performance index (MPI), particularly the left ventricular modified MPI (LMPI), has been studied as a marker of fetal cardiac dysfunction in intrahepatic cholestasis of pregnancy, but in the absence of standardized cut-off values limits wide use in clinical approach was denied [42].

The most common neonatal complication of children born to mothers with ICP is respiratory distress syndrome (RDS) with a prevalence of 17-29% compared to the general population. The mechanism responsible for RDS is the accumulation of maternal bile acids in the fetal circulation and the impairment of surfactant secretion by activating phospholipase A2, leading to degradation of phosphatidylcholines and impaired alveolar stability, as well as triggering inflammatory responses via macrophage activation [17].

In 2008 De Luca proposed to stratify neonatal risk prospectively and a predictive score for neonatal RDS, integrating maternal serum bile acid concentration, duration of exposure and gestational age at delivery, calculated as follows:

RDS risk score = [maternal bile acids within 24 h of delivery (μmol/L) × exposure time (number of days between ICP diagnosis and delivery)]/gestational age at delivery (days)

A score ≥ 9 identified infants at high risk of RDS, with sensitivity of 85% and specificity of 87%, supporting its clinical utility in decision-making regarding antenatal corticosteroids and mode/timing of delivery [11].

In conclusion, children born to mothers diagnosed with ICP are twice as frequently admitted to the neonatal intensive care unit (NICU) for care given to prematurity, respiratory distress, meconium aspiration, congenital pneumonia, and nervous system disorders.

A study conducted in Sweden before the introduction of ursodeoxycholic acid (UDCA) as first-line therapy elucidated a delay in neuromotor development in children born to mothers with ICP [30].

5. Therapeutical management. Pharmacological use of ursodeoxycholic acid (UDCA) which is a hydrophilic (non-toxic) bile acid that replaces hydrophobic (toxic) bile acids in human bile, thereby reducing hepatocyte damage, remains to be the first line therapeutic approach. UDCA helps to reduce maternal pruritus and normalize lab findings. Unfortunately, this pharmacological agent has no effect on the intrauterine fetal's condition [5].

In refractory cases some experimental agents like including S-adenosylmethionine (SAMe), cholestyramine, guar gum and active charcoal are used. But these agents have been studied with inconsistent results and are not routinely recommended due to limited efficacy and potential side effects [38].

Thus, in cases refractory to treatment, assessing the optimal time for delivery is essential. And when bile acids values exceed 100 μmol/L, fetal demise becomes crucial for delivery. Stronger recommendation is planned delivery between 36 and 37 weeks in pregnancies complicated by severe ICP or earlier if risk factors such as fetal distress, twin gestation or preeclampsia are present. In case of mild disease (bile acids < 40 μmol/L), expectant management until 38 weeks is preferred.

Based on the above, it is up to the clinician to quantify the risk of premature birth versus the risk of prolonged exposure of bile acids to the fetus [25].

6. Future approach. The main interest of ICP evolution is to find the point of onset of fetal distress. Several studies have analyzed the involvement of the fetal heart in ICP, thus altering CTG variability, supraventricular arrhythmias, and modified myocardial performance index (mMPI) which was assessed echocardiographically. However, the data need to be studied in larger cohorts to be included in current guidelines.

New pharmacological agents need to be studied and evaluated for their effects in pregnancy. Among those obeticholic acid and norucholic acid (norUDCA) are being investigated. They have been shown to improve bile transport mechanisms affected in ICP and have anti-inflammatory action. However, there is little data on their use in humans.

7. Conclusion. Nowadays intrahepatic cholestasis of pregnancy is a well-known condition with a major impact on the fetal condition and subsequently on the health of the newborn. The pathogenetic mechanisms of bile acids lead to premature birth with all of the neonatal complications associated with it, intrauterine growth restriction, low birth weight, heart rate disorders such as intraparum bradycardia, dense amniotic fluid, up to intrauterine fetal death when bile acids exceed 100 μmol/L.

Ursodeoxycholic acid remains the only valid preparation with a dual benefit on maternal pruritus and choleretic action. However, the reduction of the clinical picture in the mother is not conclusive with the condition of the fetus once the oxidative and proinflammatory mechanisms of ICP have been initiated. Additional therapies such as rifampin need to be evaluated for safety in pregnancy, while markers such as fetal myocardial performance index need to be approved for widespread use.

Thus, to improve perinatal outcomes, pregnant women suspected of having ICP require strict evidence, individual approach to the case, fetal monitoring through CTG and velometric indices, as well as finding the right time for delivery. Future studies are needed to evaluate the mechanisms that indicate the subtle onset of fetal distress for an active management which will reduce the toxic action of bile acids on the fetus [39].

REFERENCES

1. Abu-Hayyeh, S., Papacleovoulou, G., Lövgren-Sandblom, A., Tahir, M., Oduwole, O., Jamaludin, N.A., et al. Intrahepatic cholestasis of pregnancy levels of sulfated progesterone metabolites inhibit farnesoid X receptor resulting in a cholestatic phenotype. Hepatology. 2013;57:716-726.
2. Arthuis, C., Diguisto, C., Lorphelin, H., et al. Perinatal outcomes of intrahepatic cholestasis during pregnancy: an 8-year case-control study. PLoS One. 2020;15(2):e0228213. doi:10.1371/journal.pone.0228213.
3. Bacq, Y., Gendrot, C., Perrotin, F., Lefrou, L., Chrétien, S., Vie-Buret, V., et al. ABCB4 gene mutations and single-nucleotide polymorphisms in women with intrahepatic cholestasis of pregnancy. J Med Genet. 2009;46:711-715.
4. Bolukbas, F.F., Bolukbas, C., Balaban, H.Y., Aygun, C., Ignak, S., Ergul, E., et al. Intrahepatic cholestasis of pregnancy: spontaneous vs in vitro fertilization. Euroasian J Hepatogastroenterol. 2017;7:126-129.
5. Cemortan, M., Sagaidac, I., Cernețchi, O., Ostrofeț, C. Aspectele clinice ale sarcinii, nașterii și rezultatele perinatale la femeile cu colestază intrahepatică de sarcină. Buletin Perinatol. 2022;93(1):75-79.
6. Chemortan, M.I., Sagaidak, I.V., Cernetckii, O., Ostrofeț, C. Assessment of clinical symptoms in women with intrahepatic cholestasis of pregnancy. Arch Balk Med Union. 2022;(3):238-243.
7. Chen, S., Ahlqvist, V.H., Sjöqvist, H., Stephansson, O., Magnusson, C., Dalman, C., et al. Maternal intrahepatic cholestasis of pregnancy and neurodevelopmental conditions in offspring: a population-based cohort study of 2 million Swedish children. PLoS Med. 2024;21:e1004331.
8. De Luca, D., Alonso, A., Autilio, C. Bile acid-induced lung injury: update of reverse translational biology. Am J Physiol Lung Cell Mol Physiol. 2022;323:L93-L106.
9. Di Simone, N., Santamaria Ortiz, A., Specchia, M., Tersigni, C., Villa, P., Gasbarrini, A., et al. Recent insights on the maternal microbiota: impact on pregnancy outcomes. Front Immunol. 2020;11:528202.
10. Fan, H.M., Mitchell, A.L., Williamson, C. Endocrinology in pregnancy: metabolic impact of bile acids in gestation. Eur J Endocrinol. 2021;184:R69-R83.
11. Fuchs, C.D., Simbrunner, B., Baumgartner, M., Campbell, C., Reiberger, T., Trauner, M. Bile acid metabolism and signalling in liver disease. J Hepatol. 2025;82:134-153.
12. Girling, J., Knight, C.L., Chappell, L. Intrahepatic cholestasis of pregnancy: Green-top Guideline No. 43 June 2022. BJOG. 2022;00:1-20.
13. Han, B., Sheng, Y., Wang, L., Feng, H., Hou, X., Li, Y. Intrahepatic cholestasis of pregnancy or azithromycin-induced intrahepatic cholestasis: a case report. Medicine (Baltimore). 2017;96:e9346.
14. Huang, S., Liu, Y., Guo, N., Liu, X., Li, G., Du, Q. Serum profiles of inflammatory cytokines associated with intrahepatic cholestasis of pregnancy. J Matern Fetal Neonatal Med. 2022;35:10072-10081.
15. Jamshidi Kerachi, A., Shahlaee, M.A., Habibi, P., Dehdari Ebrahimi, N., Ala, M., Sadeghi, A. Global and regional incidence of intrahepatic cholestasis of pregnancy: a systematic review and meta-analysis. BMC Med. 2025;23:129.
16. Larson, S.P., Kovilam, O., Agrawal, D.K. Immunological basis in the pathogenesis of intrahepatic cholestasis of pregnancy. Expert Rev Clin Immunol. 2016;12:39-48.
17. Lee, R.H., Greenberg, M., Metz, T.D., Pettker, C.M. Society for Maternal-Fetal Medicine Consult Series #53: intrahepatic cholestasis of pregnancy: replaces Consult #13, April 2011. Am J Obstet Gynecol. 2021;224:B2-B9.
18. McIlvride, S., Dixon, P.H., Williamson, C. Bile acids and gestation. Mol Aspects Med. 2017;56:90.
19. Mihalcean, L., Caproș, H., Surguci, M., Cojocari, N. Perinatal outcomes of intrahepatic cholestasis of pregnancy. In: Congresul consacrat aniversării a 75-a de la fondarea Universității de Stat de Medicină și Farmacie „Nicolae Testemițanu”. Chișinău; 2020. p. 605.
20. Niemyjska-Dmoch, W., Kosiński, P., Węgrzyn, P., Luterek, K., Jezela-Stanek, A. Intrahepatic cholestasis of pregnancy and theory of inheritance of the disease: literature review. J Matern Fetal Neonatal Med. 2023;36:2279020.
21. Ontsouka, E., Epstein, A., Kallol, S., Zaugg, J., Baumann, M., Schneider, H., et al. Placental expression of bile acid transporters in intrahepatic cholestasis of pregnancy. Int J Mol Sci. 2021;22:10434.
22. Ovadia, C., Perdones-Montero, A., Spagou, K., Smith, A., Sarafian, M.H., Gomez-Romero, M., et al. Enhanced microbial bile acid deconjugation and impaired ileal uptake in pregnancy repress intestinal regulation of bile acid synthesis. Hepatology. 2019;70:276.
23. Ovadia, C., Williamson, C. Intrahepatic cholestasis of pregnancy: recent advances. Clin Dermatol. 2016;34:327-334.
24. Reyes, H., Báez, M.E., González, M.C., Hernández, I., Palma, J., Ribalta, J., et al. Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy in Chile. J Hepatol. 2000;32:542-549.
25. Sanchon-Sanchez, P., Herraez, E., Macias, R.I.R., Estiu, M.C., Fortes, P., Monte, M.J., et al. Relationship between cholestasis and altered progesterone metabolism in the placenta-maternal liver tandem. Biochim Biophys Acta Mol Basis Dis. 2024;1870:166926.
26. Sarkar, M., Brady, C.W., Fleckenstein, J., Forde, K.A., Khungar, V., Molleston, J.P., et al. Reproductive health and liver disease: practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;73:318.
27. Smith, D., Rood, K.M. Intrahepatic cholestasis of pregnancy. Clin Obstet Gynecol. 2020;63(1):134-151.
28. Society for Maternal-Fetal Medicine (SMFM). Society for Maternal-Fetal Medicine Consult Series #53: intrahepatic cholestasis of pregnancy.
29. Svanborg, A. A study of recurrent jaundice in pregnancy. Acta Obstet Gynecol Scand. 1954;33:434-444.
30. Tang, B., Tang, L., Li, S., Liu, S., He, J., Li, P., et al. Gut microbiota alters host bile acid metabolism to contribute to intrahepatic cholestasis of pregnancy. Nat Commun. 2023;14:1305.
31. Thorling, L. Jaundice in pregnancy; a clinical study. Acta Med Scand Suppl. 1955;302:1-123.
32. US Preventive Services Task Force. Screening for hypertensive disorders of pregnancy: US Preventive Services Task Force final recommendation statement. JAMA. 2023;330:1074-1082.
33. Vander Does, A., Levy, C., Yosipovitch, G. Cholestatic itch: our current understanding of pathophysiology and treatments. Am J Clin Dermatol. 2022;23:647-659.
34. Wang, H., Yan, Z., Dong, M., Zhu, X., Wang, H., Wang, Z. Alteration in placental expression of bile acids transporters OATP1A2, OATP1B1, OATP1B3 in intrahepatic cholestasis of pregnancy. Arch Gynecol Obstet. 2012;285:1535-1540.
35. Williamson, C., Geenes, V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol. 2014;124:120-133. doi:10.1097/AOG.0000000000000346.
36. Williamson, C., Nana, M., Poon, L., Kupcinskas, L., Painter, R., Taliani, G., et al. EASL clinical practice guidelines on the management of liver diseases in pregnancy. J Hepatol. 2023;79:768-828.
37. Xiao, J., Zong, Y., Sun, Y., Shi, H., Chen, D., et al. Molecular pathogenesis of intrahepatic cholestasis of pregnancy. Can J Gastroenterol Hepatol. 2021;2021:6679322.

38. Yayi, H., Danqing, W., Shuyun, L., Jicheng, L. Immunologic abnormality of intrahepatic cholestasis of pregnancy. Am J Reprod Immunol. 2010;63:267-273.

39. Zecca, E., De Luca, D., Marras, M., Caruso, A., Bernardini, T., Romagnoli, C. Intrahepatic cholestasis of pregnancy and neonatal respiratory distress syndrome. Pediatrics. 2006;117:1669-1672.

40. Zhang, Y., Shi, D., Abagyan, R., Dai, W., Dong, M. Population scale retrospective analysis reveals potential risk of cholestasis in pregnant women taking omeprazole, lansoprazole, and amoxicillin. Interdiscip Sci. 2019;11:273-281.

41. Zhou, Q., Yuan, Y., Wang, Y., He, Z., Liang, Y., Qiu, S., et al. The severity of intrahepatic cholestasis during pregnancy increases risks of adverse outcomes beyond stillbirth: evidence from 15,826 patients. BMC Pregnancy Childbirth. 2024;24:476.

42. Zu, Y., Yang, J., Zhang, C., Liu, D. The pathological mechanisms of estrogen-induced cholestasis: current perspectives. Front Pharmacol. 2021;12:761255.

REFERENCES

1. Abu-Hayyeh S., Papacleovoulou G., Lövgren-Sandblom A., Tahir M., Oduwole O., Jamaludin N.A., et al. Intrahepatic cholestasis of pregnancy levels of sulfated progesterone metabolites inhibit farnesoid X receptor resulting in a cholestatic phenotype. Hepatology. 2013;57:716-726.

2. Arthuis C., Diguisto C., Lorphelin H., et al. Perinatal outcomes of intrahepatic cholestasis during pregnancy: an 8-year case-control study. PLoS One. 2020;15(2):e0228213. doi:10.1371/journal.pone.0228213.

3. Bacq Y., Gendrot C., Perrotin F., Lefrou L., Chrétien S., Vie-Buret V., et al. ABCB4 gene mutations and single-nucleotide polymorphisms in women with intrahepatic cholestasis of pregnancy. J Med Genet. 2009;46:711-715.

4. Bolukbas F.F., Bolukbas C., Balaban H.Y., Aygun C., Ignak S., Ergul E., et al. Intrahepatic cholestasis of pregnancy: spontaneous vs in vitro fertilization. Euroasian J Hepatogastroenterol. 2017;7:126-129.

5. Cemortan M., Sagaidac I., Cernețchi O., Ostrofeț C. Aspectele clinice ale sarcinii, nașterii și rezultatele perinatale la femeile cu colestază intrahepatică de sarcină. Buletin Perinatol. 2022;93(1):75-79.

6. Chemortan M.I., Sagaidak I.V., Cernetckii O., Ostrofeț C. Assessment of clinical symptoms in women with intrahepatic cholestasis of pregnancy. Arch Balk Med Union. 2022;(3):238-243.

7. Chen S., Ahlqvist V.H., Sjöqvist H., Stephansson O., Magnusson C., Dalman C., et al. Maternal intrahepatic cholestasis of pregnancy and neurodevelopmental conditions in offspring: a population-based cohort study of 2 million Swedish children. PLoS Med. 2024;21:e1004331.

8. De Luca D., Alonso A., Autilio C. Bile acid-induced lung injury: update of reverse translational biology. Am J Physiol Lung Cell Mol Physiol. 2022;323:L93-L106.

9. Di Simone N., Santamaria Ortiz A., Specchia M., Tersigni C., Villa P., Gasbarrini A., et al. Recent insights on the maternal microbiota: impact on pregnancy outcomes. Front Immunol. 2020;11:528202.

10. Fan H.M., Mitchell A.L., Williamson C. Endocrinology in pregnancy: metabolic impact of bile acids in gestation. Eur J Endocrinol. 2021;184:R69-R83.

11. Fuchs C.D., Simbrunner B., Baumgartner M., Campbell C., Reiberger T., Trauner M. Bile acid metabolism and signalling in liver disease. J Hepatol. 2025;82:134-153.

12. Girling J., Knight C.L., Chappell L. Intrahepatic cholestasis of pregnancy: Green-top Guideline No. 43 June 2022. BJOG. 2022;00:1-20.

13. Han B., Sheng Y., Wang L., Feng H., Hou X., Li Y. Intrahepatic cholestasis of pregnancy or azithromycin-induced intrahepatic cholestasis: a case report. Medicine (Baltimore). 2017;96:e9346.

14. Huang S., Liu Y., Guo N., Liu X., Li G., Du Q. Serum profiles of inflammatory cytokines associated with intrahepatic cholestasis of pregnancy. J Matern Fetal Neonatal Med. 2022;35:10072-10081.

15. Jamshidi Kerachi A., Shahlaee M.A., Habibi P., Dehdari Ebrahimi N., Ala M., Sadeghi A. Global and regional incidence of intrahepatic cholestasis of pregnancy: a systematic review and meta-analysis. BMC Med. 2025;23:129.

16. Larson S.P., Kovilam O., Agrawal D.K. Immunological basis in the pathogenesis of intrahepatic cholestasis of pregnancy. Expert Rev Clin Immunol. 2016;12:39-48.

17. Lee R.H., Greenberg M., Metz T.D., Pettker C.M. Society for Maternal-Fetal Medicine Consult Series #53: intrahepatic cholestasis of pregnancy: replaces Consult #13, April 2011. Am J Obstet Gynecol. 2021;224:B2-B9.

18. McIlvride S., Dixon P.H., Williamson C. Bile acids and gestation. Mol Aspects Med. 2017;56:90.

19. Mihalcean L., Caproș H., Surguci M., Cojocari N. Perinatal outcomes of intrahepatic cholestasis of pregnancy. In: Congresul consacrat aniversării a 75-a de la fondarea Universității de Stat de Medicină și Farmacie „Nicolae Testemițanu". Chișinău; 2020. p. 605.

20. Niemyjska-Dmoch W., Kosiński P., Węgrzyn P., Luterek K., Jezela-Stanek A. Intrahepatic cholestasis of pregnancy and theory of inheritance of the disease: literature review. J Matern Fetal Neonatal Med. 2023;36:2279020.

21. Ontsouka E., Epstein A., Kallol S., Zaugg J., Baumann M., Schneider H., et al. Placental expression of bile acid transporters in intrahepatic cholestasis of pregnancy. Int J Mol Sci. 2021;22:10434.

22. Ovadia C., Perdones-Montero A., Spagou K., Smith A., Sarafian M.H., Gomez-Romero M., et al. Enhanced microbial bile acid deconjugation and impaired ileal uptake in pregnancy repress intestinal regulation of bile acid synthesis. Hepatology. 2019;70:276.

23. Ovadia C., Williamson C. Intrahepatic cholestasis of pregnancy: recent advances. Clin Dermatol. 2016;34:327-334.

24. Reyes H., Báez M.E., González M.C., Hernández I., Palma J., Ribalta J., et al. Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy in Chile. J Hepatol. 2000;32:542-549.

25. Sanchon-Sanchez P., Herraez E., Macias R.I.R., Estiu M.C., Fortes P., Monte M.J., et al. Relationship between cholestasis and altered progesterone metabolism in the placenta-maternal liver tandem. Biochim Biophys Acta Mol Basis Dis. 2024;1870:166926.

26. Sarkar M., Brady C.W., Fleckenstein J., Forde K.A., Khungar V., Molleston J.P., et al. Reproductive health and liver disease: practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;73:318.

27. Smith D., Rood K.M. Intrahepatic cholestasis of pregnancy. Clin Obstet Gynecol. 2020;63(1):134-151.

28. Society for Maternal-Fetal Medicine (SMFM). Society for Maternal-Fetal Medicine Consult Series #53: intrahepatic cholestasis of pregnancy.

29. Svanborg A. A study of recurrent jaundice in pregnancy. Acta Obstet Gynecol Scand. 1954;33:434-444.

30. Tang B., Tang L., Li S., Liu S., He J., Li P., et al. Gut microbiota alters host bile acid metabolism to contribute to intrahepatic cholestasis of pregnancy. Nat Commun. 2023;14:1305.

31. Thorling L. Jaundice in pregnancy; a clinical study. Acta Med Scand Suppl. 1955;302:1-123.

32. US Preventive Services Task Force. Screening for hypertensive disorders of pregnancy: US Preventive Services Task Force final recommendation statement. JAMA. 2023;330:1074-1082.

33. Vander Does A., Levy C., Yosipovitch G. Cholestatic itch: our current understanding of pathophysiology and treatments. Am J Clin Dermatol. 2022;23:647-659.
34. Wang H., Yan Z., Dong M., Zhu X., Wang H., Wang Z. Alteration in placental expression of bile acids transporters OATP1A2, OATP1B1, OATP1B3 in intrahepatic cholestasis of pregnancy. Arch Gynecol Obstet. 2012;285:1535-1540.
35. Williamson C., Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol. 2014;124:120-133. doi:10.1097/AOG.0000000000000346.
36. Williamson C., Nana M., Poon L., Kupcinskas L., Painter R., Taliani G., et al. EASL clinical practice guidelines on the management of liver diseases in pregnancy. J Hepatol. 2023;79:768-828.
37. Xiao J., Zong Y., Sun Y., Shi H., Chen D., et al. Molecular pathogenesis of intrahepatic cholestasis of pregnancy. Can J Gastroenterol Hepatol. 2021;2021:6679322.
38. Yayi H., Danqing W., Shuyun L., Jicheng L. Immunologic abnormality of intrahepatic cholestasis of pregnancy. Am J Reprod Immunol. 2010;63:267-273.
39. Zecca E., De Luca D., Marras M., Caruso A., Bernardini T., Romagnoli C. Intrahepatic cholestasis of pregnancy and neonatal respiratory distress syndrome. Pediatrics. 2006;117:1669-1672.
40. Zhang Y., Shi D., Abagyan R., Dai W., Dong M. Population scale retrospective analysis reveals potential risk of cholestasis in pregnant women taking omeprazole, lansoprazole, and amoxicillin. Interdiscip Sci. 2019;11:273-281.
41. Zhou Q., Yuan Y., Wang Y., He Z., Liang Y., Qiu S., et al. The severity of intrahepatic cholestasis during pregnancy increases risks of adverse outcomes beyond stillbirth: evidence from 15,826 patients. BMC Pregnancy Childbirth. 2024;24:476.
42. Zu Y., Yang J., Zhang C., Liu D. The pathological mechanisms of estrogen-induced cholestasis: current perspectives. Front Pharmacol. 2021;12:761255.

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ВНУТРИПЕЧЁНОЧНЫЙ ХОЛЕСТАЗ БЕРЕМЕННОСТИ: ВЛИЯНИЕ НА НЕОНАТАЛЬНЫЕ ИСХОДЫ НЕСМОТРЯ НА ПРОВОДИМУЮ ТЕРАПИЮ У МАТЕРЕЙ

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Аннотация. *Внутрипечёночный холестаз беременности (ВХБ) – это заболевание печени, ассоциированное с беременностью, характеризующееся кожным зудом у матери и повышением уровня желчных кислот в сыворотке крови, при относительно благоприятном прогнозе для матери, но значительных перинатальных рисках. В данном нарративном обзоре анализируются современные данные о патофизиологических механизмах ВХБ, существующих фармакологических методах лечения и влиянии уровня желчных кислот на неонатальные исходы. Неблагоприятные исходы, включая мертворождение, преждевременные роды и синдром дыхательных расстройств, тесно коррелируют с концентрацией желчных кислот в сыворотке крови выше 100 мкмоль/л вследствие таких механизмов, как фетальные аритмии, плацентарная вазоконстрикция и нарушение секреции сурфактанта. Тактика ведения требует индивидуализированного мониторинга уровня желчных кислот, назначения урсодезоксихолевой кислоты для облегчения симптомов у матери, тщательного наблюдения за состоянием плода и рассмотрения вопроса о родоразрешении на 36–37 неделе гестации в тяжёлых случаях с целью снижения фетального риска.*

Ключевые слова: *внутрипечёночный холестаз беременности, желчные кислоты, неонатальные исходы, мертворождение, преждевременные роды, урсодезоксихолевая кислота.*