RMMG
Revista Médica de Minas Gerais

CASE REPORT

Intrahepatic cholestasis of pregnancy: case report

Colestase intra-hepática da gravidez: relato de caso

Rodolfo Ribeiro de Jesus[1], Marinalva Silva de Souza[2]

ABSTRACT

Objective: to report the pregnancy outcome of a patient with intrahepatic cholestasis treated at a public service in northern Brazil. **Case Report:** primiparous, 24 years old, mixed race, gestational age of 29 weeks, referred intense body pruritus, predominantly palmoplantar, anxiety and pelvic pain. She denied nausea and vomiting, vaginal discharge, other illnesses, surgeries and allergies. On clinical examination, there was no hepatomegaly or jaundice. Laboratory tests showed increased concentration of bile acid levels 43µmol/L, liver enzymes alanine transaminase 1,382U/L, aspartate aminotransferase 752U/L, lactate dehydrogenase 718U/L, gamma glutamyl transferase 43U/L and alkaline phosphatase 196U/L. She was diagnosed with intrahepatic cholestasis of pregnancy and medicated with 900 mg of ursodeoxycholic acid daily, divided into three doses; pain relievers; antihistamines; cephalexin 500mg and nitrofurantoin 100mg. At 31 weeks and three days of pregnancy, body itching, anxiety and pelvic pain were stronger and laboratory tests maintained the elevation of liver enzymes, with emphasis on alanine transaminase 1,962 U/L. It was decided to interrupt the pregnancy with an elective cesarean section, waiting for eight hours of fasting, in addition to the start of corticosteroids for fetal lung maturation. Five days after delivery, there was clinical improvement and reduction in the values of liver function tests. **Conclusion:** despite the positive outcome for the mother, premature birth resulted in the death of the newborn after a few days in the neonatal intensive care unit.

Keywords: **Intrahepatic cholestasis; Pregnancy, High-risk; Pregnancy complications; Case report.**

[1] Federal University of Amapá, Macapá, Amapá, Brazil.

[2] Department of Gynecology and Obstetrics, Faculty of Medicine, Federal University of Amapá, Macapá, Amapá, Brazil.

Responsible Editor:

Dr. Henrique Vitor Leite

Faculty of Medicine of the Federal University of Minas Gerais

Belo Horizonte, MG, Brazil.

Corresponding Author:

Rodolfo Ribeiro de Jesus

E-mail: rodolforibeirojesus@gmail.com

Supporting sources:

There were no supporting sources.

Clinical Trial Registration (If applicable):

Not applicable.

Conflict of interest:

The authors declare that they have no conflicts of interest.

Ethics Committee:

Opinion number: 5.530.704 - CAAE: 60247522.1.0000.0003

Received on: November 25, 2022

Approved on: March 18, 2023

Publication Date: August 08, 2023.

DOI: 10.5935/2238-3182.2023e33404-en

RESUMO

Objetivo: Relatar o desfecho da gravidez de uma paciente com colestase intra-hepática, atendida em um serviço público do norte do Brasil. **Relato do Caso:** Primigesta, 24 anos, cor parda, 29 semanas de gestação, referiu intenso prurido corporal, predominantemente palmoplantar, ansiedade e algia pélvica. Negou náuseas e vômitos, perdas vaginais, outras doenças, cirurgias e alergias. Ao exame clínico, sem hepatomegalia e icterícia. Os exames laboratoriais mostraram elevação da concentração dos níveis de ácidos biliares 43µmol/L, enzimas hepáticas alanina aminotransferase: 1.382U/L, aminotransferase aspartato: 752U/L, desidrogenase láctica: 718U/L, Gama Glutamil transferase: 43U/L e fosfatase alcalina: 196U/L. Com diagnóstico de colestase intra-hepática na gravidez, foi medicada com ácido ursodesoxicólico 900mg ao dia, divididos em três doses; analgésicos; anti-histamínicos; cefalexina 500mg e nitrofurantoína 100mg. Com 31 semanas e três dias de gestação, teve intensificação do prurido corporal, ansiedade, algia pélvica e os exames laboratoriais mantiveram a elevação das enzimas hepáticas com destaque para alanina aminotransferase: 1.962U/L. Optou-se pela interrupção da gestação com cesariana eletiva aguardando oito horas de jejum, iniciando corticoide para maturação pulmonar fetal. Após cinco dias do parto, houve melhora clínica e redução nos valores dos testes de função hepática. **Conclusão:** Apesar do desfecho positivo para a mãe, o parto prematuro resultou no óbito do recém-nascido após alguns dias na unidade de terapia intensiva neonatal.

Palavras-chave: Colestase intra-hepática; Gravidez de alto risco; Complicações na Gravidez; Relato de caso.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common specific liver disease of pregnancy. This liver dysfunction is rare in pregnancy but potentially serious. The main symptom is body itching without rash, combined with elevated levels of serum bile acid and/or of other liver function tests, such as alanine transaminase (ALT) and aspartate aminotransferase (AST)[1]. Overall, maternal prognosis is good. Pruritus ceases immediately after delivery, usually within a few days, and elevated liver function tests normalize within a few weeks[2]. The etiology of ICP is multifactorial and poorly understood. Genetic susceptibility, as well as hormonal and environmental factors have been proposed as possible mechanisms for the emergence of ICP[3].

Due to ethnicity, its prevalence varies greatly between geographic regions and is significantly higher in Latin American women than in Caucasian[4]. In Israel, the prevalence of ICP published in 2021 was 0.58%, which is considered higher than that reported in previous studies conducted in that country[5]. In Europe, the prevalence ranged from 0.5% to 1.5%, with the highest rate in Scandinavia. In the United States of America (USA), it ranged from 0.3% in white populations to 5.6% in populations of Latin origin[6]. Epidemiological studies indicating the prevalence of this clinical condition among pregnant women in Brazil are unknown.

ICP usually affects women aged over 35 years, with a previous history of the disease or in a first-degree relative, pre-existing liver disease, multiple gestation and seasonal variation with greater involvement in winter[7]. The pathophysiology involves reduced bile flow and consequent accumulation, leading to deposition of bile salts in the skin and placenta. The combination of hormonal, genetic and environmental factors is believed to contribute to this reduction in bile flow[6]. Molecular processes acting at the placental level have assumed importance, as well as specific histopathological changes that lead to poor fetal outcomes[8].

Unexplained pruritus with concomitant elevation of total serum bile acid level >10µmol/L and/or elevation of ALT are often used to diagnose ICP[9,10]. The disease is considered severe when bile acids are above 40µmol/L[11],

or with an ALT level greater than three times the reference value, which represents the indication for termination of pregnancy, according to the literature[4,12]. Elevated serum bile acid concentration is considered a predictor of poor perinatal outcome, including intrauterine death[4]. This clinical condition is associated with higher rates of stillbirths, premature birth and admission to the neonatal intensive care unit (neonatal ICU)[13]. There is no international consensus on diagnostic criteria to establish ICP.

The aim of therapeutic management is to reduce clinical symptoms, normalizing maternal biochemistry and preventing complications for the fetus. Pharmacological therapy is aimed at the treatment of intrahepatic cholestasis and consists of administration of ursodeoxycholic acid (UDCA) to decrease the levels of total bile acid and reduce pruritus. If treatment fails, termination of pregnancy should be considered[14]. UDCA should be used as a first-line agent for the treatment of maternal symptoms, as well as prenatal corticosteroids for fetal lung maturity[9].

Although the worldwide incidence of ICP is low, this disease characterizes a high-risk pregnancy, which motivated this study. The objective was to report the pregnancy outcome of a patient diagnosed with intrahepatic cholestasis treated at a public service in northern Brazil. The research project was approved by the Research Ethics Committee of the Federal University of Amapá on July 15, 2022 under number 5.530.704. CAAE 60247522.1.0000.0003.

Case Report

Primigravida, 24 years old, mixed race, 29 weeks pregnancy, hospitalized with intense body itching, predominantly palmoplantar, referred anxiety and pelvic pain. She denied nausea and vomiting, vaginal discharge, other illnesses, surgeries and allergies. On clinical examination, there was no hepatomegaly and jaundice. Obstetric examination did not show changes and obstetric ultrasound showed a fetus in good development and normal amniotic fluid. Laboratory tests showed high levels of bile acids 43µmol/L, liver enzymes ALT: 1,382U/L, AST: 752U/L, lactate dehydrogenase (LDH) 718U/L, gamma glutamyl transferase (GGT) 43U/L and alkaline phosphatase 196U/L. No increase in serum bilirubin levels was observed. Urinalysis showed absence of proteinuria and parameters suggestive of lower urinary tract infection. Other tests performed were within normal limits, such as blood count, electrolytes, kidney function, in addition to non-reactive rapid tests for the human immunodeficiency virus, syphilis, hepatitis B and C.

The patient remained normotensive, excluding the diagnosis of preeclampsia and HELLP syndrome (hemolysis, elevated liver enzymes and low platelets). Abdominal ultrasound showed a medium-sized liver without gallstones, non-dilated extra and intrahepatic bile ducts, and no signs of portal hypertension or other vascular abnormalities. Due to the high levels of transaminases, autoimmune liver disease was considered as a differential diagnosis. The patient was evaluated by a hepatologist who confirmed the main diagnostic - suspicion of ICP -, maintained the medication prescribed by the obstetric team, without recommending a liver biopsy; considered terminating the pregnancy and recommended postpartum patient follow-up. With the diagnosis of ICP, the patient was treated with UDCA 900mg daily, divided into three doses; antihistamines; analgesics, and cephalexin 500mg and nitrofurantoin 100mg.

At 31 weeks and three days of pregnancy, the patient had increased body itching, anxiety and pelvic pain, and laboratory tests maintained elevated liver enzyme levels ALT: 1,969U/L, AST: 718U/L, LDH: 363U/L, and GGT: 83U/L. It was decided to terminate the pregnancy with an elective cesarean section, waiting for eight hours of fasting, with the beginning of corticosteroids for fetal lung maturation. Five days after delivery, there was clinical improvement of the patient and laboratory tests showed a reduction in values of liver function tests. The patient was discharged and advised to continue follow-up with the hepatologist. The newborn was sent to the neonatal ICU and died a few days after birth.

Discussion

The main limitation of this study regards the absence of information in medical records or incomplete medical records. However, the reflection based on data obtained is relevant to improve the management of pregnant women with ICP in order to prevent the risks of maternal-fetal complications.

The management of ICP is centered on clinical and obstetric surveillance of the patient and liver function tests[15]. The clinical diagnosis of this disease is based on symptoms of body itching and supported by the presence of elevated serum levels of total bile acids[9]. Other diagnoses that may cause similar symptoms and laboratory abnormalities are excluded. Diseases that cause pruritus (gestational dermatitis and allergic reactions) and diseases that impair liver function (acute fatty liver of pregnancy, viral and autoimmune hepatitis, biliary tract obstruction, drug-induced liver damage) are cited[3].

Abdominal ultrasound is usually the first step to exclude dilated intra and extrahepatic ducts and mass lesions, as it is a very sensitive and specific test, non-invasive and relatively inexpensive[16]. Liver ultrasound helps in the differential diagnosis that should especially exclude viral and autoimmune hepatitis and rule out the possibility of obstructive cholestasis. In ICP, there are no specific findings and the bile ducts are unremarkable, that is, they are not dilated[17]. The performance of liver ultrasound should be indicated for cases with atypical symptoms, presence of comorbidities, severity of ICP and when the change in liver function is persistent[10]. The patient studied showed no alterations on the abdominal ultrasound examination, which corroborates the literature.

According to the literature, the highest incidence of ICP affects women over 35 years of age, multiparous, with history of the disease in a previous pregnancy, multiple

pregnancy, family history and preexisting liver disease[7]. These characteristics differ from our case, as the patient was young (24 years old), primiparous, with no family history of the disease or previous liver disorders. On the other hand, in a study that discussed predictors of adverse perinatal outcomes in ICP, the mean age of patients was 27.7±5.3 years (18-42 range), with 56% nulliparous and 44% multiparous. The mean pregnancy week at diagnosis was 33.1±2.8 (27-39 range)[18].

When seeking the obstetric emergency service with signs and symptoms of the disease, the patient's gestational age was 29 weeks. This corroborates the literature, which shows that ICP usually occurs at the end of the second and beginning of third trimester, when estrogen levels are at their highest in pregnancy. Elevated levels of circulating estrogen can induce cholestasis in genetically predisposed women[3].

The literature shows that generalized pruritus, predominantly affecting the palms of hands and soles of feet, worsens at night. This condition should be considered in women who develop pruritus of abrupt onset without a rash from the second half of pregnancy onwards[9]. The patient studied presented intense body itching with palmoplantar predominance, anxiety, in addition to pelvic pain, associated with high levels of bile acids, liver enzymes ALT, AST and increased LDH, GGT and alkaline phosphatase. The association of bile acid levels above 10 μmol/L and presence of pruritus are findings strongly suggestive of ICP[14,19].

Laboratory evaluation is recommended for pregnant women with pruritus with suspicion of ICP. Bile acid testing by mass spectrometry and liquid chromatography can be used to assess total (clinically most useful) and fractionated (cholic, chenodeoxycholic, and deoxycholic acid) bile acids levels. These tests are normally performed by specialized laboratories. Total bile acid levels can also be evaluated by enzyme assay[9].

The literature shows that other liver function tests, such as ALT and AST, are usually slightly elevated and do not exceed twice the upper limit of the tolerable value in pregnancy.[3] Although reference values are up to 32U/L for AST and 33U/L for ALT, our patient had AST levels of 718U/L and ALT of 1,969U/L. However, a study performed by the Society for Maternal-Fetal Medicine Consult in the USA highlighted that high levels of transaminases are not essential for the diagnosis of ICP, high levels of total serum bile acids are not sufficient to diagnose the disease, and the accuracy of the diagnosis has been questioned at an international level[9].

The patient studied did not have bilirubin alterations and, in similar cases, this is confirmed in the literature, which shows an elevation of bilirubin in about 25% of ICP cases, rarely exceeding 6mg/dL[3,9]. It was also observed that the patient had an elevation of alkaline phosphatase (196 U/L), but serum alkaline phosphatase may be physiologically elevated up to four times the reference value (35 to 104U/L), although with little significance in the diagnosis of ICP[9]. Maternal alkaline phosphatase concentration increases as it is produced by the placenta and fetal bone maturation[20].

The increase in serum GGT is less common in the ICP[21] and the levels of this substance were increased in the patient studied. Since concentrations of ALT and AST, bilirubin and GGT in pregnancy remain within pre-pregnancy reference values or are slightly decreased, any elevation in these tests requires further investigation[20]. The serum levels of transaminase and other liver enzymes of the studied patient were measured daily as values continued to be high; ALT: 1,969U/L, for example, rose by more than 50 times the reference values (33U/L). Pruritus in ICP may precede the rise in serum bile acid levels for several weeks. Therefore, if symptoms persist and there is no other explanation for the pruritus, measurement of total bile acid level and serum transaminase levels should be repeated[9].

Although investigations for pregnant women with ICP are limited, the repercussions of this condition are linked to a higher risk of preeclampsia, higher rates of cesarean section and premature delivery[22]. According to the literature, the incidence of premature births in patients with ICP ranges from 19 to 60%[23,24]. The patient studied underwent elective cesarean section and had no complications during delivery and postpartum. The premature newborn cried at birth, but after six days of hospitalization in the neonatal ICU, he died. The literature shows an increase in the incidence of prematurity and cesarean section rate, as well as in rates of hospitalization in the neonatal ICU because of ICP[13,22-24].

UDCA is the drug of choice for the treatment of ICP. Its use aims to prolong pregnancy, relieve maternal symptoms and reduce the risk of perinatal morbidity and mortality[5,13]. The mechanism of action of UDCA is unknown. Although some studies have shown a reduction in total bile acids after treatment[3,25], others have shown that its action reduced the intensity of pruritus, but did not impact the adverse effects of ICP[13,26]. Even though the initial dose is not well established, it is reasonable to start with 300 mg/day and increase to 300mg three times daily until delivery. It is safe and well tolerated by most patients, has no harmful implications for the fetus[3], and improves both bile transport and secretion, minimizing fetal exposure. Pruritus usually decreases within one to two weeks, but if it is not relieved, the dose can be adjusted to a maximum of 21mg/kg per day[9].

UDCA is recommended as a first-line therapy in national guidelines in the UK, USA, Australia and Europe[1]. Despite the generalized recommendations for the use of this drug, the evidence for its use is not robust[22]. In the United Kingdom, a survey of 527 women with ICP using UDCA found that in most of them, the mean concentrations of bile acids decreased over time, regardless of treatment. There was also a weak relationship between the concentrations of bile acids and the severity of pruritus, with no beneficial effects of the treatment on the concentration of bile acids or the pruritus index[26]. Although UDCA has not been shown to prevent the adverse outcomes of ICP, to date there is no other effective treatment for this condition[21]. The literature

is unanimous in stating that the best solution for this clinical condition is childbirth.

According to recommendation of the German Working Group on Obstetrics and Prenatal Medicine, a patient with ICP should be followed up by a hepatologist if elevated transaminase levels persist. Women should be informed about the increased risk of developing hepatobiliary sequelae[10]. The patient studied used UDCA 900mg a day, divided into three doses and remained on medication after delivery. She was instructed on the importance of continuing the use of medication and undergoing follow-up by the hepatologist.

The maternal and fetal benefits of preterm birth should be considered by the obstetrician in cases of ICP. These benefits must be clarified to the patient and the maternal risks of this disease versus preterm birth must be emphasized. Being born before 36 weeks of pregnancy implies a high potential for morbidity related to the newborn's prematurity. The American College of Obstetricians and Gynecologists supported the active management of labor induction protocols in cases of ICP. It recommended delivery starting at 36 weeks of pregnancy and the administration of antenatal corticosteroids for fetal lung maturity in patients who had delivered before 37 weeks[9].

The Royal College of Obstetrics and Gynecology, in the USA, has not endorsed routine premature delivery in pregnancies with ICP and has not defined an ideal time for these deliveries[27]. The possibility of ending pregnancy before 36 weeks was highlighted in specific situations, such as: intense itching without improvement, despite the use of UDCA; worsening of liver function (increased transaminases); or in patients with UDCA with a history of fetal complications in a previous pregnancy because of ICP[12,28]. The patient studied, with 31 weeks and three days of gestation, had the pregnancy interrupted with elective cesarean section due to exacerbation of pruritus, elevation of bile acids with values >40µmol/L and elevation of transaminases, mainly ALT: 1,969U/L.

The recurrence rate of ICP in subsequent pregnancies is high, being around 45% to 70%[10]. The patient studied was primiparous, young, and warned by obstetricians and hepatologists about the possible recurrence of intrahepatic cholestasis in the next pregnancy, with a view to monitoring and early detection of elevated liver enzyme levels, in addition to the presence of characteristic symptoms of this condition.

Conclusion

Intrahepatic cholestasis of pregnancy caused maternal morbidity related to intense body pruritus predominantly palmoplantar, anxiety and pelvic pain associated with severe elevation of bile acids and liver enzymes, especially ALT. Despite the positive outcome for the mother, premature birth resulted in the death of the newborn after a few days in the neonatal ICU.

Authors' Contribution

Conceptualization, Research, Methodology, Visualization & Writing – analysis and editing: Rodolfo Ribeiro de Jesus; Marinalva Silva de Souza.

Copyright

Copyright© 2023 Ribeiro de Jesus et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original article is properly cited.

References

1. Bicocca MJ, Sperling JD, Chauhan SP. Intrahepatic cholestasis of pregnancy: review of six national and regional guidelines. Eur J Obstet Gynecol Reprod Biol. 2018;231:180-7.
2. Jurk SM, Kremer AE, Schleussner E. Intrahepatic cholestasis of pregnancy. Geburtshilfe Frauenheilkd. 2021;81:940-7.
3. Pillarisetty LS, Sharma A. Pregnancy intrahepatic cholestasis. Treasure Island (FL): StatPearls Publishing; 2022.
4. Lee RH, Goodwin T, Greenspoon J, Incerpi M. The prevalence of intrahepatic cholestasis of pregnancy in a primarily latina Los Angeles population. J Perinatol. 2006;26(9):527-32.
5. Wolf MF, Sgayer I, Yaron L, Shnaider O, Odeh M, Bornstein J, et al. Intrahepatic cholestasis of pregnancy: prevalência e distribuição étnica no norte de Israel. Ginekol Pol. 2022;93(7):578-84.
6. Smith DD, Rood KM. Intrahepatic cholestasis of pregnancy. Clin Obstet Gynecol. 2020;63:134-51.
7. Blumenfeld J, Koo K. Navigating uncertainty: a case study of intrahepatic cholestasis of pregnancy. J Midwifery Womens Health. 2022;67(3):398-402.
8. Devalla A, Srivastava K. Unfolding newer concepts in placental pathology of obstetric cholestasis-a cause for prematurity. Int J Physiol Pathophysiol Pharmacol. 2022;14(1):16-23.
9. Lee RH, Greenberg M, Metz TD, Pettker CM. Society for Maternal-Fetal Medicine Consult Series #53: intrahepatic cholestasis of pregnancy. J Obstet Gynecol. 2021;224(2):B2-B9.
10. Hagenbeck C, Hamza A, Kehl S, Maul H, Lammert F, Keitel V, et al. Management of intrahepatic cholestasis of pregnancy: recommendations of the working group on obstetrics and prenatal medicine. Section on Maternal Disorders. Geburtshilfe Frauenheilkd. 2021;81(8):922-39.
11. Ovadia C, Seed PT, Sklavounos A, Geenes V, Di Ilio C, Chambers J, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. Lancet. 2019;393(10174):899-909.
12. Piechota J, Jelski W, Orywal K, Mroczko B. The comparison of total bile acid concentration and alcohol dehydrogenase activity as markers of intrahepatic cholestasis of pregnancy. Acta Biochim Pol. 2021 Nov;69(1):173-6.

13. Chappell LC, Bell JL, Smith A, Linsell L, Juszczak E, Dixon PH, et al. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. Lancet. 2019;394(10201):849-60.

14. Piechota J, Jelski W. Intrahepatic. Cholestasis in pregnancy: review of the literature. J Clin Med. 2020;(9):1361.

15. Wongjarupong N, Bharmal S, Lim N. Never too soon: an unusual case of intrahepatic cholestasis of pregnancy at five weeks gestation. Cureus. 2020;12(9):e10540.

16. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol. 2009;51(2):237-67.

17. Conti-Ramsden F, McEwan M, Hill R, Wade J, Abraham G, Buckeldee O, et al. Detection of additional abnormalities or co-morbidities in women with suspected intrahepatic cholestasis of pregnancy. Obstet Med. 2020;13(4):185-91.

18. Çelik S, Çalışkan CS, Çelik H, Güçlü M, Başbuğ A. Predictors of adverse perinatal outcomes in intrahepatic cholestasis of pregnancy. Ginekol Pol. 2019;90(4):217-22.

19. Varlas VN, Bohîltea R, Gheorghe G, Bostan G, Angelescu GA, Penes ON, et al. State of the art in hepatic dysfunction in pregnancy. Healthcare (Basel). 2021 Oct;9(11):1481.

20. Morrison MA, Chung Y, Heneghan MA. Managing hepatic complications of pregnancy: practical strategies for clinicians. BMJ Open Gastro. 2022;9:e000624.

21. Walker KF, Chappell LC, Haia WM, Middleton P, Thornton JG. Pharmacological interventions for treating intrahepatic cholestasis of pregnancy. Cochrane Database Syst Rev. 2020;7(7):CD000493.

22. Luo M, Tang M, Jiang F, Jia Y, Chin RKH, Liang W, et al. Intrahepatic cholestasis of pregnancy and associated adverse maternal and fetal outcomes: a retrospective case-control study. Gastroenterol Res Pract. 2021;2021:6641023.

23. Herrera CA, Manuck TA, Stoddard GJ, Varner MW, Esplin S, Clark EAS, et al. Perinatal outcomes associated with intrahepatic cholestasis of pregnancy. J Matern Fetal Neonatal Med. 2018;31(14):1913-20.

24. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol. 2009;15(17):2049.

25. Kong X, Kong Y, Zhang F, Wang T, Yan J. Evaluating the effectiveness and safety of ursodeoxycholic acid in treatment of intrahepatic cholestasis of pregnancy: a meta-analysis (a prisma-compliant study). Medicine (Baltimore). 2016 Oct;95(40):e4949.

26. Fleminger J, Seed PT, Smith A, Juszczak E, Dixon PH, Chambers J, et al. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a secondary analysis of the PITCHES trial. BJOG. 2021;128(6):1066-75.

27. Arthuis C, Diguisto C, Lorphelin H, Dochez V, Simon E, Perrotin F, et al. Perinatal outcomes of intrahepatic cholestasis during pregnancy: an 8-year case-control study. PLoS One. 2020;15(2):e0228213.

28. Saad AF, Pacheco LD, Chappell L, Saade GR. Intrahepatic cholestasis of pregnancy: toward improving perinatal outcome. Reprod Sci. 2022 Nov;29(11):3100-5.

This is an open access article distributed under the terms of the Creative Commons Attribution License.