IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

AN IN-DEPTH REVIEW OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY: PATHOPHYSIOLOGY, DIAGNOSIS, AND MANAGEMENT

B JAYAKRISHNAN[1] | PRATHIKSHA S NAIR[1] | RESHMA BABU[2]| SHAIJU S DHARAN[3]

Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Science, Marayamuttom, Thiruvananthapuram

First Author: Students[1]
Ezhuthachan College of Pharmaceutical Sciences

Corresponding Author: Assistant Professor[2], Department of Pharmacy Practice
Ezhuthachan College of Pharmaceutical Sciences

Co-Authors: Principal/HOD[3], Department of Pharmacy Practice
Ezhuthachan College of Pharmaceutical Sciences

Abstract

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder that can occur during pregnancy, typically in the third trimester. It disrupts the normal flow of bile from the liver, causing bile acids to build up in the bloodstream. This condition can lead to symptoms like intense itching (especially on the palms of the hands and soles of the feet), dark urine, light- colored stools, and jaundice (yellowing of the skin or eyes), although jaundice doesn't always occur.

The exact cause of ICP isn't completely understood, but it is believed to be linked to hormonal changes in pregnancy that affect liver function. Women who are pregnant with multiples or who have a family history of the condition may be at a higher risk. Other risk factors include being of certain ethnic backgrounds (such as South Asian or Scandinavian descent) and having a previous history of ICP.

The global prevalence of intrahepatic cholestasis of pregnancy (ICP) is estimated to be around 0.3% to 1% of all pregnancies. However, this rate can vary significantly by region, ethnic background, and local healthcare practices. In India, the prevalence of intrahepatic cholestasis of pregnancy (ICP) is estimated to be around 1-3% of pregnancies. However, this can vary depending on the region and specific population groups. Certain studies have shown that the incidence can be higher in areas where there is a greater prevalence of risk factors such as a family history of liver diseases, previous cases of ICP, or ethnic backgrounds with higher susceptibility.

ICP is more frequently diagnosed in the third trimester, so it's important for pregnant women to be aware of symptoms like intense itching, especially on the hands and feet, and seek medical advice if they experience them. ICP can be dangerous because it increases the risk of preterm birth, fetal distress, and stillbirth. So, it's important for anyone experiencing symptoms to contact their healthcare provider. Management typically involves medications to help control bile acid levels (like Ursodeoxycholic acid) and close monitoring of both the mother and baby. In some cases, early delivery may be considered to reduce risks to the baby.

KEYWORDS

UDCA: Ursodeoxycholic acid, ICP: Intrahepatic cholestasis of pregnancy

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder that occurs during pregnancy, mainly in the third trimester, and is normally characterized by impaired bile flow. This leads to the accumulation of bile acids in the bloodstream, which can result in symptoms such as intense itching (especially on the palms and soles), dark urine, light-colored stools and in some cases, jaundice (yellowing of the skin

or eyes). The condition is believed to be caused by a combination of genetic, hormonal, and environmental factors that affect the liver's ability to excrete bile properly during pregnancy. [1] While the exact cause is not fully understood, it is thought that pregnancy hormones (particularly estrogen and progesterone) may play a role in disrupting normal bile acid processing in the liver. ICP is considered a serious condition because it can increase the risk of preterm birth, fetal distress, and stillbirth. Therefore, it requires careful monitoring and management throughout the pregnancy to reduce risks to both the mother and baby.

The World Health Organization (WHO) does not provide a specific global prevalence rate for intrahepatic cholestasis of pregnancy (ICP) in its general reports. However, various studies and sources suggest that the global prevalence of ICP is estimated to be around 0.3% to 1% of pregnancies. [2,3] The rate can be higher in certain populations, with higher prevalence observed in regions like Scandinavia, South Asia, and South America, where it can range from 1% to 3% depending on the population .

Intrahepatic cholestasis of pregnancy (ICP) is influenced by several risk factors. Women with a family history of ICP or who have experienced it in a previous pregnancy are at higher risk. Ethnicity plays a role, with higher prevalence in women of South Asian, Latino, Scandinavian, and Indigenous South American descent. Other factors include carrying multiple pregnancies, being over 35 years old, and having a male fetus. Hormonal changes during pregnancy, particularly increased levels of estrogen and progesterone, may contribute to the development of ICP.[4] Women with chronic liver diseases, obesity, or underlying health conditions like diabetes are also at increased risk. These factors combine to affect the liver's ability to process bile, leading to the condition. [5]

Intrahepatic cholestasis of pregnancy (ICP) is diagnosed based on symptoms like intense itching, particularly on the palms and soles, and confirmed with blood tests showing elevated bile acids and liver enzymes. Ultrasound suggested in some cases to rule out other causes. Treatment includes ursodeoxycholic acid (UDCA) to lower bile acids and relieve itching, along with antihistamines and topical treatments for symptom relief. [6,7] Frequent fetal monitoring and liver function tests are important. If necessary, early delivery around 37 weeks may be considered to reduce risks such as preterm birth or stillbirth. Vitamin K supplementation may also be given to ensure proper clotting. The prophylatic symptoms and minimize risks to both mother and baby

PREVALENCE OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY

The World Health Organization (WHO) does not provide a specific global prevalence rate for intrahepatic cholestasis of pregnancy (ICP) in its general reports. However, various studies and sources suggest that the global prevalence of ICP is estimated to be around 0.3% to 1% of pregnancies.[8] The rate can be higher in certain populations, with higher prevalence observed in regions like Scandinavia, South Asia, and South America, where it can range from 1% to 3% depending on the population and specific risk factors.[9]
In India, the prevalence of intrahepatic cholestasis of pregnancy (ICP) is estimated to be around 1-3% of pregnancies. This rate can vary depending on regional factors and the specific population studied. Women of South Asian descent, including those in India, are considered to be at higher risk for developing ICP compared to other ethnic groups. The prevalence may also be influenced by factors like family history, previous ICP, and underlying health conditions. [10]
The prevalence of intrahepatic cholestasis of pregnancy (ICP) varies globally, with estimates ranging from 0.3% to 1% of pregnancies. However, certain risk factors can increase this rate, particularly in regions like South Asia, South America, and Scandinavia, where prevalence may rise to 2-3%. Women with a family history of ICP, previous ICP in a prior pregnancy, multiple pregnancies, or those carrying a male fetus are at higher risk. Additionally, women of South Asian and Latino descent, as well as those with underlying liver diseases, obesity, or diabetes, may be more likely to develop ICP. [12]

PATHOGENESIS OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY

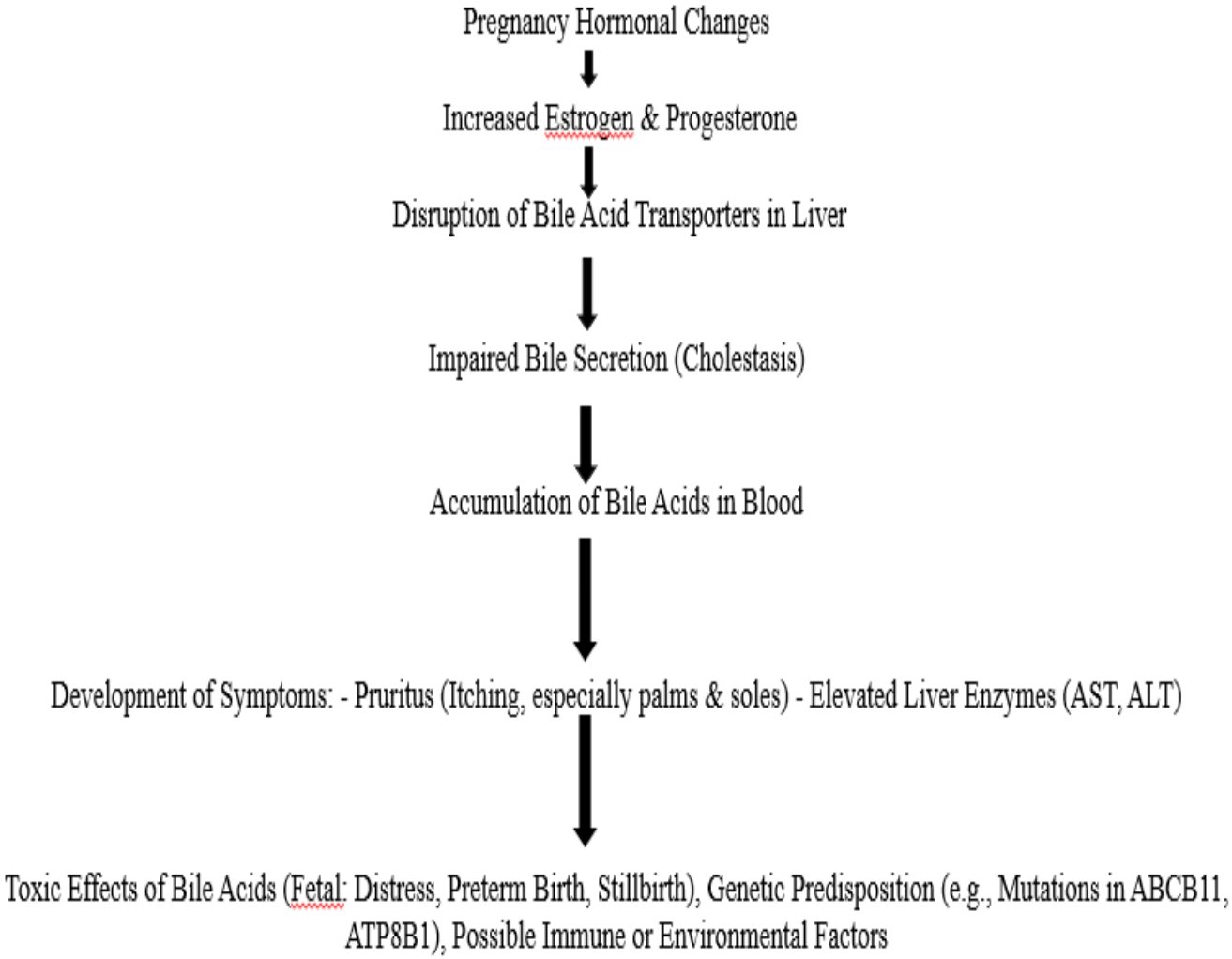
1. Hormonal Influence: Pregnancy-related hormones, particularly estrogen and progesterone, play a central role in the development of ICP. These hormones may interfere with normal bile acid transport in the liver. Increased estrogen levels may disrupt the normal function of bile acid transporters in the liver cells, leading to impaired bile secretion and bile acid accumulation in the liver and bloodstream. [13]

2. Genetic Factors: There is a genetic predisposition to ICP, with mutations in genes encoding bile acid transporters, such as ABCB11 and ATP8B1, being linked to the condition. These genetic variations can affect the liver's ability to excrete bile, leading to cholestasis. [14]

3. Impaired Bile Flow: In ICP, the normal flow of bile is obstructed at the level of the liver, causing bile acids to accumulate in the bloodstream. This buildup of bile acids leads to the pruritus (itching) characteristic of ICP, as bile acids are believed to irritate the skin and sensory nerves.

4. Bile Acid Toxicity: Elevated levels of bile acids in the bloodstream can be toxic to both the mother and fetus**.** In the mother, bile acids can contribute to liver dysfunction, leading to elevated liver enzymes (AST, ALT). In the fetus, increased bile acids may lead to fetal distress**,** preterm birth**,** and stillbirth due to impaired placental function and possible fetal hypoxia. [15,16]

5. Immune and Environmental Factors: Other contributing factors may include an immune response or environmental influences, though these are less clearly understood. Some studies suggest that autoimmune mechanisms or interactions between pregnancy hormones and environmental factors could further impair liver function and bile secretion. [17]



DIAGNOSIS OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY

The diagnosis of intrahepatic cholestasis of pregnancy (ICP) involves a combination of clinical symptoms, laboratory tests, and exclusion of other conditions. Here's an overview of the diagnostic process:

1. Clinical Evaluation

- Symptoms: The main symptom of ICP is pruritus (itching), especially on the palms of the hands and soles of the feet. This often occurs whole body without a rash, typically in the third trimester of pregnancy.
- Other Symptoms: Dark urine, light-colored stools, and jaundice (yellowing of the skin or eyes) can also be present, though not always. [18]

2. Laboratory Tests

- Bile Acid Levels: The key diagnostic marker for ICP is elevated bile acids in the blood, often above 10 µmol/L. This is a critical indicator of cholestasis.
- Liver Function Tests: Elevated liver enzymes, especially AST (aspartate aminotransferase) and ALT (alanine aminotransferase), may be present but are not always elevated. A mild increase in liver enzymes is common. [19]
- Total Bilirubin: Levels of total bilirubin may be mildly elevated in some cases, but significant jaundice is not common.

3. Exclusion of Other Causes

- Ultrasound: An ultrasound may be used to rule out other conditions that can cause similar symptoms, such as gallstones or hepatic diseases unrelated to pregnancy.
- Rule out other causes of itching: It is essential to exclude other potential causes of itching, such as allergic reactions, eczema, or other liver diseases (e.g., hepatitis). [20]

4. Monitoring

- Regular fetal monitoring (non-stress tests, biophysical profiles) to assess fetal well-being and detect any signs of fetal distress due to elevated bile acids.

MANAGEMENT OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Management of Intrahepatic Cholestasis of Pregnancy (ICP) focuses on relieving symptoms, improving maternal liver function, and minimizing risks to the fetus. Here's an overview of the treatment approach:

1. Medications

- Ursodeoxycholic Acid (UDCA): This is the first-line treatment for ICP. It helps lower bile acid levels, improves liver function, and reduces pruritus (itching). UDCA is considered safe during pregnancy and is effective in reducing the risk of complications such as preterm birth and stillbirth.
- Antihistamines: These can be used to manage itching, though they may be less effective in controlling bile acid-related pruritus. Non-sedating antihistamines (like loratadine) are preferred. [21]
- Topical treatments: Calamine lotion or steroid creams can provide symptomatic relief for itching, although their effectiveness is limited.

2. Monitoring

- Fetal Monitoring**:** Regular monitoring of the fetus is crucial. This can include non-stress tests**,** biophysical profiles**,** or ultrasound to assess fetal health and detect signs of fetal distress or preterm birth.
- Liver Function Tests**:** Frequent monitoring of liver enzymes (AST, ALT) and bile acid levels to track the progression of the disease and guide treatment decisions. [22]

3. Management of Complications

- Vitamin K Supplementation**:** Since liver dysfunction can lead to impaired vitamin K absorption, supplementation may be recommended to ensure proper blood clotting before delivery.
- Early Delivery**:** If bile acid levels remain elevated, or if fetal well-being is compromised, early delivery may be considered. Most women with ICP are delivered at 37 weeks or earlier to reduce the risks of stillbirth and fetal distress**.** [23]

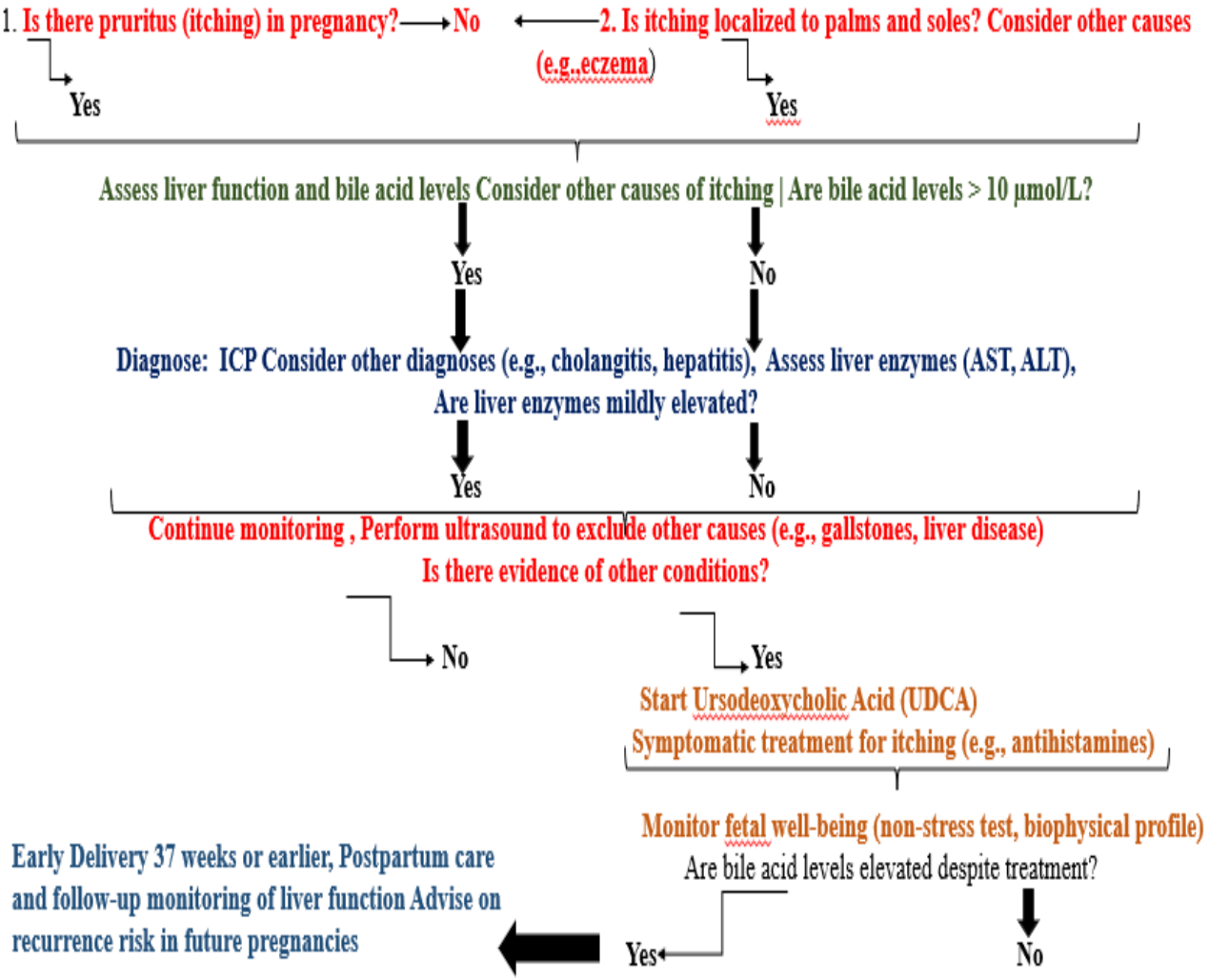
4. Postpartum Care

- Postpartum Monitoring**:** ICP typically resolves within a few days after delivery, but women may require follow-up to monitor liver function.
- Risk of Recurrence: Women who have had ICP in a previous pregnancy are at higher risk of developing it in subsequent pregnancies. Close monitoring is recommended in future pregnancies. [24]

5. Lifestyle Modifications

- Dietary Changes: Some patients may benefit from a low-fat diet to reduce liver strain, although this is not universally recommended.
- Rest and Stress Management: While not a direct treatment, managing stress and ensuring proper rest can help alleviate symptoms. [25]
- Cool baths or cold compresses: May help reduce itching.
- Oatmeal baths or mild anti-itch lotions (check with a doctor before using any topical treatments).
- Loose cotton clothing: may sometime reduces irritation from fabric and sweat.
- Regular prenatal visits: Frequent liver function and bile acid tests are crucial.
- Medication compliance: Ursodeoxycholic acid (UDCA) is often prescribed to reduce bile acid levels.
- Fetal monitoring: Non- stress tests and ultrasounds may be done more frequently to monitor the baby's well-being
- Avoid supplements or medications not approved by your doctor as they may affect liver function.
- Be cautious with herbal remedies—many are not safe during pregnancy or for liver health

ALGORITHM



SIGNIFICANCE

The significance of cocaine-induced mesenteric ischemia lies in its potential for life-threatening complications, the challenges associated with its early diagnosis and management**,** and its growing relevance in the context of rising cocaine abuse worldwide. Early recognition, prompt medical intervention, and a multi-disciplinary approach are essential to improving outcomes. The significance of this condition has grown with the ongoing global issue of cocaine abuse**,** and the increasing prevalence of related health complications. [26,27] Despite its devastating potential, early diagnosis and intervention can significantly improve patient outcomes, particularly when management is multidisciplinary and includes fluid resuscitation**,** vasopressors**,** anticoagulation, and, in severe cases, surgical revascularization **or** bowel resection**.** [28]

Additionally, enhancing public awareness, improving healthcare provider education, and conducting further research are vital steps toward addressing this serious and often fatal condition. [29,30]

CONCLUSION

Cocaine-induced mesenteric ischemia is a serious and potentially life-threatening condition that occurs when cocaine's vasoconstrictive effects reduce blood flow to the intestines, leading to ischemia, bowel infarction, and systemic complications. The condition represents a significant challenge due to its rapid progression**,** often presenting with nonspecific symptoms such as abdominal pain**,** nausea**,** and signs of shock**,** which can delay diagnosis and treatment.

However, challenges remain in terms of recognition**,** timely diagnosis**,** and effective treatment**,** particularly given the condition's subtle onset and the need for advanced imaging and multidisciplinary expertise. Public health initiatives aimed at reducing cocaine use, along with better educational efforts for both healthcare providers and the general public, are essential to decrease the burden of cocaine-induced mesenteric ischemia.

Ultimately, cocaine-induced mesenteric ischemia highlights the significant cardiovascular risks associated with illicit drug **use**, and its management underscores the importance of prompt, coordinated care to prevent irreversible damage and improve patient survival. Continued research into its pathophysiology, improved diagnostic tools, and treatment strategies are necessary to further optimize outcomes for individuals affected by this severe condition**.**

REFERNCES

1. *Williamson C, Geenes V.* Intrahepatic cholestasis of pregnancy. *Obstet Gynecol*. 2014 Jul;124(1):120-133.

2. *Turunen K, Helander K, Mattila KJ, Sumanen M.* Intrahepatic cholestasis of pregnancy is common among patients' first-degree relatives. *Acta Obstet Gynecol Scand.* 2013 Sep;92(9):1108-10.

3. *Pataia V, Dixon PH, Williamson C.* Pregnancy and bile acid disorders. *Am J Physiol Gastrointest Liver Physiol.* 2017 Jul 01;313(1):G1-G6.

4. *Batsry L, Zloto K, Kalter A, Baum M, Mazaki-Tovi S, Yinon Y.* Perinatal outcomes of intrahepatic cholestasis of pregnancy in twin versus singleton pregnancies: is plurality associated with adverse outcomes? *Arch Gynecol Obstet.* 2019 Oct;300(4):881-887.

5. *Hepburn IS, Schade RR.* Pregnancy-associated liver disorders. *Dig Dis Sci.* 2008 Sep;53(9):2334-58.

6. *Williamson C, Hems LM, Goulis DG, Walker I, Chambers J, Donaldson O, Swiet M, Johnston DG.* Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group. *BJOG.* 2004 Jul;111(7):676-81.

7. *Marathe JA, Lim WH, Metz MP, Scheil W, Dekker GA, Hague WM.* A retrospective cohort review of intrahepatic cholestasis of pregnancy in a South Australian population. *Eur J Obstet Gynecol Reprod Biol.* 2017;218:33–38.

8. *Rook M, Vargas J, Caughey A, Bacchetti P, Rosenthal P, Bull L.* Fetal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy in a Northern California cohort. *PLoS One.* 2012;7:3–8.

9. *Puljic A, Kim E, Page J.* The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age. *Am J Obstet Gynecol*. 2015;212

10. *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.

11. *Khurana S, Singh P.* Rifampin is safe for treatment of pruritus due to chronic cholestasis: a meta-analysis of prospective randomized-controlled trials. *Liver Int.* 2006 Oct;26(8):943-8.

12. *Geenes V, Williamson C.* Intrahepatic cholestasis of pregnancy. *World J Gastroenterol.* 2009 May 07;15(17):2049-66.

13. *Floreani A, Gervasi MT.* New Insights on Intrahepatic Cholestasis of Pregnancy. *Clin Liver Dis*. 2016 Feb;20(1):177-89.

14. *Marschall HU, Wikström Shemer E, Ludvigsson JF, Stephansson O.* Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: a population-based cohort study. *Hepatology.* 2013 Oct;58(4):1385-91.

15. *Fairweather DV.* Nausea and vomiting in pregnancy. *Am J Obstet Gynecol*. 1968;102:135–175.

16. *Kallen B.* Hyperemesis during pregnancy and delivery outcome: a registry study. *Eur J Obstet Gynecol Reprod Biol.* 1987;26:291–302.

17. *Goodwin TM, Hershman JM, Cole L.* Increased concentration of the free beta-subunit of human chorionic gonadotropin in hyperemesis gravidarum. *Acta Obstet Gynecol Scand.* 1994;73:770–772.

18. S*ibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA.* Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol*. 1993;169:1000–1006.

19. *Martin JN Jr, Blake PG, Perry KG Jr, McCaul JF, Hess LW, Martin RW.* The natural history of HELLP syndrome: patterns of disease progression and regression. *Am J Obstet Gynecol.* 1991;164:1500–1509;

20. *Estiu MC, Monte MJ, Rivas L, et al.* Effect of ursodeoxycholic acid treatment on the altered progesterone and bile acid homeostasis in the mother-placenta foetus trio during cholestasis of pregnancy. *Br J Clin Phramacol* 2015; 79:316–329.

21. *Wei J, Wang H, Yang X, et al.* Altered gene profile of placenta from women with intrahepatic cholestasis of pregnancy. *Arch Gynecol Obstet* 2010; 281:801–810.

22. *Lee NM, Brady CW.* Liver disease in pregnancy. *World J Gastroenterol* 2009; 15:897–906.

23. *Williamson C, Geenes V.* Intrahepatic cholestasis of pregnancy. *Obstet Gynecol* 2014; 124:120–133.

24. *Than NN, Neuberger J.* Liver abnormalities in pregnancy. *Best Pract Res Clin Gastroenterol* 2013; 27:565–575.

25. *Allen AM, Kim WR, Larson JJ.* The epidemiology of liver diseases unique to pregnancy in a US community: a population-based study. *Clin Gastroenterol Hepatol.* 2016;14:287–294.

26. *Marathe JA, Lim WH, Metz MP, Scheil W, Dekker GA, Hague WM.* A retrospective cohort review of intrahepatic cholestasis of pregnancy in a South Australian population. *Eur J Obstet Gynecol Reprod Biol.* 2017;218:33–38.

27. *Samuelsson AM, et al.* Diet-induced obesity in female mice leads to offspring hyperphagia, adiposity, hypertension, and insulin resistance: a novel murine model of developmental programming. *Hypertension.* 2008;51(2):383–392.

28. *Sheau-Fang N, Lin RC, Laybutt DR, Barres R, Owens JA, Morris MJ.* Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring. *Nature.* 2010;467(7318):963–966.

29. *Burns SP, et al.* Gluconeogenesis, glucose handling, and structural changes in livers of the adult offspring of rats partially deprived of protein during pregnancy and lactation. *J Clin Invest.* 1997;100(7):1768–1774.

30. *Dixon PH, et al.* Contribution of variant alleles of ABCB11 to susceptibility to intrahepatic cholestasis of pregnancy. *Gut.* 2009;58(4):537–544