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REVIEW ARTICLE

Effect of Intrahepatic Cholestasis of Pregnancy (ICP) on Neonatal Outcome

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Abstract

Intrahepatic cholestasis of pregnancy is a condition unique to pregnancy characterized by pruritus and elevated serum bile acids and/or aminotransferase levels. It usually manifests during second or third trimester of pregnancy and improves after delivery. But neonates are at increased risks of still birth, prematurity, respiratory distress syndrome and metabolic problems. Timely identification and appropriate intervention can reduce the adverse neonatal outcomes.

Keywords: *Obstetric cholestasis, neonatal outcome, effects.*

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy related liver disease.[1] It is typically a reversible cholestatic disease presenting in the second to third trimester of pregnancy and is characterized by pruritus in the absence of a skin rash with abnormal liver function tests. There are elevated serum aminotransferases and/or elevated serum bile acid levels (>or = 10micromol/L) with spontaneous relief of laboratory abnormalities and symptoms promptly after delivery but no later than one month postpartum.[2] Untreated ICP carries potential risks for mothers and their newborn infants. It is associated with adverse obstetrical outcomes, which includes stillbirth, spontaneous preterm delivery, respiratory distress syndrome, meconium aspiration syndrome and fetal asphyxia.[3] It is important to have a clear idea about this cholestatic condition in pregnancy. A brief knowledge on its various effects in fetus and neonates, can guide physicians to diagnose timely as well as to eliminate the risks in the newborn infants during the perinatal and postnatal period. So, this narrative review has been planned to enlighten obstetricians and neonatologists with a detail information on this topic.

Incidence and Epidemiology

Different epidemiologic surveys have found significant regional variation in the incidence of ICP. It varies from 0.1 to 1.5% of pregnancies in Europe and 1 to 5% in China.[4] In comparison with the overall prevalence of ICP which is 0.7%, the white population has a low occurrence of 0.62%, while this number is 1.46% in the Pakistani population and 1.24% in the Indian population.[5] Neonatal risks have also been demonstrated in many clinical studies which revealed that, ICP may lead to preterm delivery in 19-60%, fetal distress in 27-33% and fetal loss in 0.2-4.1% of patients.[6]

Etiopathogenesis

There is still much to be explored about the exact causes of ICP and its manifestation, but it is thought to be multifactorial, including genetic, hormonal and environmental factors.[7] The causes are likely to be due to a number of different factors, including:

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- **Genetic predisposition** - The exact mechanisms causing intrahepatic cholestasis during pregnancy are still unknown; but two adenosine triphosphate binding cassette genes *(ABCB4* and *ABCB11*) have been identified as contributors in some women.[8] Certain genetic mutations, and certain unknown factors, cause a rise in serum bile acids.[9]
- **Hormones** - Pregnancy hormones such as estrogen and progesterone have an effect on the liver's ability to transport certain chemicals, including bile acids. The flow of bile acids is significantly reduced and leads to the bile acids building up in the blood that causes the symptoms. Women carrying multiples, women who have IVF treatment and women who have prior liver diseases also appear to have a higher risk of cholestasis.[10]
- **Environment -** More women were diagnosed as Intrahepatic Cholestasis of Pregnancy (ICP) during the winter months. Although the exact reason is not clear, it is suggested that there is an environmental trigger for the condition, such as reduced exposure to sunlight or change in diet.[11]

Identifying pregnant women with ICP

The symptoms of Intrahepatic cholestasis of pregnancy (ICP) can vary based on its severity and type. But commonly encountered features are itching all over, but often more severe on palms and soles of the feet. The itching can be recurrent or constant. Many women find that it is worse at night and it disturbs their sleep. Dark urine and/or pale stools (grayish in color), jaundice (rare) may also be present. Risk factors may be present in some cases like family history of obstetric cholestasis, multiple pregnancy, carriage of hepatitis C and presence of gallstones etc. During searching the cause behind this, elevated liver enzymes and bile acids can also favor the diagnosis of ICP.[12]

Current guidelines state that a diagnosis of ICP can be made if serum bile acid levels are above 10 mmol/L. When levels reach 40 mmol/L, the case is considered severe and risk of adverse outcomes is increased.[13,14] When levels reach 100 mmol/L, the risk of adverse fetal outcomes is increased further, with a 3.44% risk of stillbirth.[15] Although the diagnostic criteria are focused on bile acid levels, other liver function parameters such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin are used to obtain a complete picture and to rule out the cases in which other liver diseases are present.[16]

Effect of ICP on Mother and Newborn

Maternal

The maternal and fetal consequences in ICP have been studied in different populations. A study done in Sweden showed that women with ICP have almost 3 times more chances of developing gestational diabetes, pre-eclampsia, and preterm labor.[17] Whereas, other studies showed a benign maternal outcome with increased postpartum hemorrhage. Vitamin K deficiency is found only in severe persistent ICP with high levels (>40 μmol/L) of circulating bile acids.[18]

Neonatal

Some neonatal conditions are strictly associated with maternal ICP. The fetal complications includes fetal distress, meconium staining of amniotic fluid at delivery, preterm delivery meconium aspiration syndrome, pneumonia, respiratory distress, major congenital anomalies, hyperbilirubinemia, sepsis and still birth.[19] ICP have influence on long term effects on babies like obesity and diabetes. The findings add strong evidence that the environment that the babies are exposed to in the womb is a major cause of metabolic disease in adults.[20]

Evidences with effect of ICP on neonatal outcomes

Respiratory Distress Syndrome

Maternal intrahepatic cholestasis increases the risk for Respiratory Distress Syndrome. In studies, RDS rate was found three times higher among neonates of the cholestasis group. Zecca et al, in a case-control study (matching on gestational age) showed a risk of RDS in newborns of ICP mother is 2.5 times higher than in control infants (28.6% vs 14%), regardless of BA level.[21] The elevated bile acids are thought to interfere with the formation of surfactant which allows the lungs to expand after birth.[21] Hypothesis to explain increased neonatal morbidity among case infants include a direct effect of bile acid on neonatal lung, which could be induce a "bile acid pneumonia".[21]

Fetal Distress

Placenta plays a major role in protecting the fetus from the adverse effects of potentially toxic endogenous substances such as bile acid.[22] Increased levels of bile acid in maternal circulation, enhances placental transport and facilitate the generation of certain placental hormones which leads to significant constriction among chorionic vessels and resulting fetal distress.[23]

Meconium Aspiration

Sometimes meconium is expelled into the amniotic fluid prior to birth, or during labor due to stress. Meconium may also pass earlier in cholestasis due to increased motility of fetal colon with increased bile acid level. If the baby then inhales the contaminated fluid, respiratory problems may occur. In pregnancies affected by cholestasis, meconium is often passed prior to birth.[24]

Preterm labor

There is an increased risk of spontaneous preterm labor, as many as 60% of deliveries in some studies, however with active management most studies report rates of 30%-40%. This is due to high level of bile acid make the uterus more sensitive to oxytocin that causes uterine contractions· Earlier presentations of Intrahepatic Cholestasis of Pregnancy (ICP) seem to carry an even greater risk of preterm labor, as well as twin or triplet pregnancies.[25]

Stillbirth

Stillbirth tends to occur in the last few weeks of pregnancy. The reason this occurs is not completely understood although it is thought to be due to a cardiac arrhythmia caused by the elevated bile acids. With bile acids remaining under 100 µmol/L, the risk is less than 0.28% and similar to a normal pregnancy. When bile acid level is over 100, the risk of stillbirth increases to over 3%.[26]

Metabolic diseases

Increase in fats and excessive cholesterol transport in placenta from mothers with cholestasis, consistent with a disruption in the metabolism of fats. The researchers propose that this shift in the nutrients supplied by the mother is likely to affect the energy balance in the unborn baby, something that could continue after the baby is born, resulting in an altered metabolism in adult life that could give rise to diseases such as obesity and diabetes. The exact mechanisms of how the increase in bile salts in the mothers' blood programs the unborn baby towards metabolic disease not exactly known yet but it seems likely that epigenetics plays a role.[12] A study done in Sweden showed that women with ICP have almost 3 times more chances of developing gestational diabetes, pre-eclampsia, and preterm labor.[13] However, other studies predict a benign maternal outcome with increased postpartum hemorrhage and vitamin K deficiency only in severe persistent ICP with high levels (>40 ìmol/L) of circulating BA.[14]

Others

A study done by Mullally and Hansen showed that congenital malformations and abortions had no association with ICP, and birth weight of babies born to such mothers was also sufficient.[27] Maternal bile acid especially above 40 ìmol/L, increases the chances of preterm delivery, IUFD, poor Apgar score, and NICU admissions significantly. A large case-control study in the UK showed that women with severe ICP (based on BA levels) had significantly high chances of preterm delivery (OR 5.3, 95% CI: 4.1-6.9), still birth (OR 2.5, 95% CI: 1.0-6.4), and NICU admissions (OR 2.6, 95% CI: 1.9-3.6**)**.[26]

Ways for improving neonatal outcomes

Since the disease is relatively rare and symptoms are often nonspecific, it is important for healthcare practitioners to be aware of the signs and symptoms of the disease to help reduce or prevent adverse outcomes. Following measures can be taken in this regard:

- Women should be informed of the increased risk of perinatal morbidity and maternal morbidity
- Women should be followed up to provide appropriate counseling and to ensure that liver function test returned to normal.
- The current standard of care for ICP patients is a combination of ursodeoxycholic acid by mouth and early delivery between weeks 34 and 38, depending on peak bile acid levels and individual patient circumstance, as the risk of stillbirth due to ICP increases in the last weeks of pregnancy.[28] Ursodeoxycholic acid (UDCA) improves pruritus and liver function in women with obstetric cholestasis. It displaces of more hydrophobic endogenous bile salts from the bile acid pool. This protects the hepatocyte membrane from the

damaging toxicity of bile salts, enhance bile acid clearance across the placenta from the fetus. The results of a meta analysis also suggest that UDCA therapy is beneficial for fetal outcome. No side effects of UDCA have been reported for mothers or babies.[29]

- The other part of management is with proper timing of delivery. Delivery recommendations are based on bile acid levels as risks increase as bile acids become more elevated. For bile acids greater than 100 μmol/L, delivery is at 36 weeks. There is consideration for earlier delivery in these cases with other factors. For levels under 100 μmol/L, delivery is recommended at 36 -39 weeks with delivery earlier in the window if levels reach 40 μmol/L.[30]
- Antenatal corticosteroid administration to mothers who are at risk of preterm delivery is also required to reduce the incidence as well as to reduce the detrimental effects of respiratory distress syndrome (RDS) in newborns.
- Reassurance to parents about the lack of long-term sequelae for mother and baby and discussion of the high recurrence rate (45-90%) and the increased incidence of obstetric cholestasis in family members.[31]
- Team work is required with the neonatologists before and during delivery, so that early intervention can be provided for complications of newborns soon after birth.

Conclusion

Intrahepatic cholestasis of pregnancy is not uncommon. Rather it is associated with adverse maternal and neonatal outcome. There is no specific method of antenatal fetal monitoring for the prediction of fetal death. Therefore, appropriate diagnosis, timely treatment and delivery of the pregnant women with ICP may eliminate the risks in the newborn infants during the perinatal and postnatal period. So, a combined effort is needed between the obstetricians and the neonatologists.

References

1. Brady CW. Liver disease in pregnancy: what's new? *Hematology Communications* 2020;**4**:145-56.
2. Michelle R, Juan V, Aaron C, Peter B, Philip R, Laura B, et al. Fetal Outcomes in Pregnancies Complicated by Intrahepatic Cholestasis of Pregnancy in a Northern California Cohort. *Plos One* 2012;**7**: e28343.
3. Chloe A, Caroline D, Henri L, Vincent D, Emmanuel S, Franck P, et al. Perinatal outcomes of intrahepatic cholestasis during pregnancy:An 8-year case-control study. *Hal Inrae* 2020; https://doi.org/10.1371/journal.pone.0228213.
4. Wang XD, Yao Q, Peng B, Ai Y, Liu SY, Liu SY. Clinical characteristics of 1241 cases of intrahepatic cholestasis of pregnancy. *Chinese Journal of Hepatology* 2007;**15**:291-93.
5. Abedin P, Weaver JB, Egginton E. Intrahepatic cholestasis of pregnancy: prevalence and ethnic distribution. *Ethn Health* 1999;**4**:35-37.
6. Wang XD, Peng B, Yao Q, Zhang L, Xing AY, Xing HL, et al. Perinatal outcomes of intrahepatic cholestasis of pregnancy: analysis of 1210 cases. *Zhonghua Yi Xue Za Zhi* 2006;**86**:446-49.
7. Kondrackiene J, Kupcinskas L. Intrahepatic cholestasis of pregnancy- current achievements and unsolved problems. *World J Gastroenterology* 2006;**14**:5781-88.
8. Dixon PH, Sambrotta M, Chambers J, Harris PT, Syngelaki A, Nicolaides AS, et al. An expanded role for heterozygous mutations of ABCB4, ABCB11, ATP8B1, ABCC2 and TJP2 in intrahepatic cholestasis of pregnancy. *Scientific Reports* 2017;**7**:11823.
9. Wood AM, Livingston EG, Hughes BL, Kuller JA. Intrahepatic cholestasis of Pregnancy: a review of diagnosis and management. *Obstet Gynecol Surv* 2018;**73**:103-109.
10. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. *Obstet Gynecol* 2014;**124**:120-33.
11. Feng C, Li WJ, He RH, Sun XW, Wang G, Wang LQ. Impacts of different methods of conception on the perinatal outcome of intrahepatic cholestasis of pregnancy in twin pregnancies. *Scientific Reports* 2018;**8**:1-8.
12. Senocak GNC, Yilmaz EPT. Maternal and fetal outcomes in pregnancies complicated by intrahepatic cholestasis. *Eurasian J Med* 2019;**51**:270.
13. 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**:180-87.
14. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. *Hepatology* 2004;**40**:467-74.

15. Ovadia C, Seed PT, Sklavounos A, Geenes V, Ilio CD, 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. The *Lancet* 2019;**393**:899-909.

16. Sasamori Y, Tanaka A, Ayabe T. Liver disease in pregnancy. *Hepatol Res* 2020;**50**:1015-23.

17. Wikström SE, Marschall HU, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis of pregnancy and associated adverse pregnancy and fetal outcomes: a 12-year population-based cohort study. *BJOG* 2013;**120**:717-23.

18. Ozkan S, Ceylan Y, Ozkan OV, Yildirim S. Review of a challenging clinical issue: intrahepatic cholestasis of pregnancy. *World J Gastroenterol* 2015;**21**:7134.

19. 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**: e0228213.

20. Papacleovoulou G, Hayyeh SA, Nikolopoulou E, Briz O, Owen BM, Nikolova V, et al. Maternal cholestasis during pregnancy programs metabolic disease in offspring. *Journal of Clinical Investigation* 2013;**123**:3172-81.

21. Zecca E, De LD, Marras M, Caruso A, Bernardini T, Romagnoli C. Intrahepatic cholestasis of pregnancy and neonatal respiratory distress syndrome. *Pediatrics* 2006;**117**:1669-72.

22. Marin JJ, Macias RI, Serrano MA. The hepatobiliary-like excretory function of the placenta: A review. *Placenta* 2003;**24**:431-38.

23. Meng LJ, Reyes H, Palma J, Hernandez J, Ribalta J, Sjovall J. Progesterone Metabolism in Normal Human Pregnancy and in Patients with Intrahepatic Cholestasis of Pregnancy. In: Reyes HB, Leuschner U, Arias IM, editors. Pregnancy sex hormones and the liver. New York: Kluwer; 1996. p. 91-100.

24. Estiú MC, Frailuna MA, Otero C, Dericco M, Williamson C, Marin JJG, et al. Relationship between early onset severe intrahepatic cholestasis of pregnancy and higher risk of meconium-stained fluid. *PloS One* 2017;**12**:e0176504.

25. Germain AM, Kato S, Carvajal JA, Valenzuela GJ, Valdes GL, Glasinovic JC. Bile acids increase response and expression of human myometrial oxytocin receptor. *Am J Obstet Gynecol* 2003;**189**:577-82.

26. Geenes V, Chappell LC, Seed PT, Steer PJ, Knight M, Williamson C. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. *Hepatology* 2014;**59**:1482-91.

27. Mullally BA, Hansen WF. Intrahepatic cholestasis of pregnancy: review of the literature. *Obstet Gynecol Surv* 2002;**57**:47-52.

28. Henderson CE, Rezai S, Mercado R. 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;**213**:593.

29. Bacq Y, Sentilhes L, Reyes HB, Glantz A, Kondrackiene J, Binder T, et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta analysis. *Gastroenterology* 2012;**143**:1492-1501.

30. Lo JO, Shaffer BL, Allen AJ, Little SE, Cheng YW, Caughey AB. Intrahepatic cholestasis of pregnancy and timing of delivery. *J Matern-Fetal Neonatal Med* 2015;**28**:2254-58.

31. Obstetric Cholestasis. Royal College of Obstetricians and Gynecologists. Developing a Green-top Guideline. London: RCOG; 2011. https://www.rcog.org.uk/guidance/browse-all guidance/ green-top- guidelines/obstetric-cholestasis-green-top-guideline-no-43/