REVIEW ARTICLE

INTRAHEPATIC CHOLESTASIS OF PREGNANCY - A REVIEW

Ome Kulsoom[1], Shahina Ishtiaq[1],Rubina Hussain[1]
[1]Department of Obstetrics and Gynaecology, Ziauddin University. Karachi. Pakistan

ABSTRACT

Intrahepatic cholestasis of pregnancy (ICP) is a complex disease described by pruritus connected with elevated serum bile acid or amino transferase level. Usually,it occurs to the third trimester of pregnancy and improves itself after delivery.In 1970's the prevalence was reported highest in Bolivia and Chile, however, the prevalence in United States (US) ranges in between 0.3 to 5.6%, whereas, in Europe it is 0.5 to 1.5%. The awareness campaigns of the disease showed an increase in incidence in the high-incidence regions because of more reporting of the cases.Ursodeoxycholicacid (dose) is the treatment of choice for ICP. This treatment provide improved liver function and relief in pruritus and is considered safe during pregnancy.At the molecular level, it offers cytoprotection against hepatotoxic effects of hydrophobic bile acids, improves hepatobiliary bile acid transport, and decreases plasma bile acids. Moreover, to alleviate the pruritus; hydroxyzine or an aqueous cream with 1% methanol were used.ICP is a unique hepatic disorder in pregnancy with possibly an interaction of genetic, hormonal, and environmental factors in its etiopathogenesis, although the definite etiology still remains obscure.

KEYWORDS: intrahepatic cholestasis, pruritus, pregnancy,

Corresponding Author
Dr. OmeKulsoom
MS Obs/Gyane Resident
Department of Obstetrics and Gynaecology,
Ziauddin University. Karachi.
Email :drkulsoomsarfaraz@gmail.com

INTRODUCTION

Intrahepaticcholestasis of pregnancy (ICP), a unique liver disease duringpregnancy,ismostly described by pruritus connected with elevated serum bile acid or amino transferase levels. It occurs usually to the third trimester of pregnancy and improves itself after delivery.[1]Worldwide its prevalence varied from region to region.[2]In 1970's the prevalence was reported highest in Bolivia and Chile. The prevalence in United States (US) ranges between 0.3 to 5.6%, whereas, in Europe it is 0.5 to 1.5%.[2-3]The awareness campaigns of the disease showed an increase in incidence in the high-incidence regions because of more reporting of the cases. [4-7] The ICP is more common in twin and multiple pregnancies. Its onset is more in winter season. [8-10]The etiology of the disease is not well known yet, and is very complex.[11-15]It is very be likely linked with hormonal and genetic factors. This review focuses the etiology and management of ICP.

DISCUSSION

Various animal studies have revealed that one of the action of estrogens ischolestatic and is well established in ICP.[1]On the other hand a natural progesterone oral administration may increase the ICP risk. [1-2]A genetic predisposition in ICP is an indication of code mutation of gene producing hepatobiliary transport proteins. [16,17]Studies show that heterozygous mutations in gene ABCB[4], which encodes the hepatic phospholipid transporter multidrug resistance 3 (MDR3), have been detected in patients with ICP. [11,18] This may also be due to family clustering and regional variations. Moreover, the genetic predisposition may cause an alteration in cell membrane composition of bile ducts and hepatocytes, and also the subsequent dysfunction of biliary canaliculartransporters.[19]It is reported already that ICP-associated gene has been located in the 2p13 region of chromosome 2.[20]In addition, environmental factors may be involved in the

expression of the disease.[11]

Clinical manifestations

The main symptom of ICP is pruritus which is painful and difficult for patients to tolerate. It appears approximately in 80% of women and presents itself after 30 weeks of gestation.[21-23] The pruritus may be generalized but classically it appears on palmar and plantar aspects of hands and feet. Many women complain a variation in symptoms worsening at night and disturbance in sleep. Pruritus is usually relieved within 48h after delivery of the fetus, accompanied by normalization of serum bile acid concentrations and other liver enzyme levels. Its recurrence rate ranges between 40-70%. There would be of consideration for chronic liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, or chronic hepatitis, liver enzymes,if high and pruritus prolonged for a month after the delivery. [18]In the presence of hormonal issues, the oral contraceptive use in women with ICP history is controversial even after biomedical tests normalization after delivery. [24,25] Likewise Breastfeeding is not contraindicated. The women with risk or presence of gall bladder stones, pancreatitis, cirrhosis or any other related disorders and are more likely to be diagnosed require close clinical follow up if found with a history of ICP. [26-28]

Adverse Outcomes

ICP is linked with adverse outcomes including perinatal morbidity-mortality, preterm delivery, fetal distress, and meconium staining.[29-31]It is difficult to calculate the real incidence of each adverse outcome due to the ICP diagnostic criteria differences, also to determine the precise nature of the risks for individual pregnancies. This might be due to the subject bias as almost all the published studies with these outcomes were studiedretrospectively. [21,32]One of the studies conducted in Swedish women population showed a significant association between adverse perinatal outcomes and the maternal serum bile acid level in ICP. [32] The incidences of spontaneous preterm birth, asphyxial events and meconium staining of the amniotic fluid, placenta or membranes, significantly increased in women with serum bile acids greater than 40 micromoles per liter at any time in pregnancy, compared with women with bile acids less than 40 micromoles per liter and women with pruritus gravidarum. Close monitoring of bile acid serum levels and liver enzymes does not definitely prevent acute fetal distress and sudden intrauterine fetal death.[33]Other studies followed by this study conducted in different populations and support the increased meconium staining rates of amniotic fluid. Apgar scores at 5 minutes and preterm birth, the retrospective nature or small sample size in these studies make interpretation difficult. It is particularly difficult to assess the risk of stillbirth in ICP from these studies, as this is a rare event and reports of selected case series do not allow the calculation of true increased risks.[34-40]

Management of ICP

A twofold management of ICP suggested a) symptomatic therapy for the mother, and b) close surveillance and early delivery of the fetus.

Management of mother

Currently 10 to15 mg/kg/d of ursodeoxycholic acid (dose) is the treatment choice for ICP. Improved liver function, relief in pruritus is due to this treatment option and considered safe during pregnancy.At the molecular level, it offers cytoprotection against hepatotoxic effects of hydrophobic bile acids, improves hepatobiliary bile acid transport, and decreases plasma bile acid. Moreover, to alleviate the pruritus; hydroxyzine or an aqueous cream with 1% methanolwere used.it is observed that the treatment with chole- styramine and guar gum which are bile acid binders can also relieve the symptoms, but this therapy is worse in steatorrhea.[41,42]. The implication of different studies are that women with severe ICP need increased surveillance for adverse Para natal outcome and in most cases delivery has been recommended at 37-38 weeks of pregnancy.

Management for fetus

The general conversation is that CTG and fetal kick count charting do not prevent IUD but may be a source of reassurance to mother with ICP and the obstetrician caring for her. Role of amnioscopy is considered as overly invasive by many obstetricians. With lack of evidences early delivery like in 37 weeks and fetal monitoring always remain a keystone in obstetric management. An even earlier delivery is advocated when cholestasis is severe.[42] However, sudden IUFD cannot be avoided totally even with this approach.

Summary of pharmacological agents of ICP

The utmost purpose of any of the ICP pharmacologic treatment is not only to minimize the maternal symptoms but also to prevent fetal distress or sudden death.Pharmacologic treatment of ICP is summarized in Table 1.

Table 1: Pharmacologic Management of Intrahepatic Cholestasis of Pregnancy

Drugs	Agent Mechanism of action	Dosing	Clinical effects
Ursodeoxycholıc acid	Hydrophilic bile acid that replaces more cytotoxic bile acids. Protects bile ducts by detoxifying hydrophobic bile acids	15 mg/kg per day or 500 mg twice a day	Improves pruritus, decreases elevated liver enzymes and bile acid levels, improves fetal outcome. Safe use in pregnancy, no side effects
Cholestyramıne	Binds bile salts and cuts off their enterohepatic circulation and increases their fecal excretion	8-16 g/d	Decreases pruritus with no effect on biochemical parameters and fetal outcome, Non-palatable, constipation Fat-soluble vitamin deficiency Non-palatable, constipation
S-adenosyl methionine	Affects the composition and fluidity of hepatocyte membranes Increases methylation and biliary excretion of hormone metabolites	1000 mg/d	Treats pruritus variably
Dexamethasone Phenobarbital	Suppresses fetal production of estrogen reducing bile acid levels	12 mg/d	Less effective in decreasing pruritus and bile acid level
Anti-histaminics	Induces hepatic enzymes to reduce the bile acids	2-5 mg/kg per day orally	Decreases pruritus 50%, no beneficial effects regarding the laboratory tests, no change in fetal outcome
Hydrophilic bile acid	Manages pruritus by antihistaminic effects	25-50 mg/d	Decreases pruritus, no effect on liver enzymes and fetal outcome

An alternative therapeutic option for ICP was Phenobarbital, but could relieve pruritus in only 50% of the cases and did not show beneficial effects with respect to laboratory parameters.[43] High-dose dexamethasone (12 mg/d) has been shown to be less effective in reducing bile acids and bilirubin. [32] This dosing is also a relief for pruritus.

CONCLUSION

ICP is a unique hepatic disorder in pregnancy. Genetic, hormonal, and environmental factors seem to interact in its etiopathogenesis, although the definite etiology still remains obscure.ICP is characterized by maternal pruritus with absence of skin rash, raised serum bile acids and abnormal liver function. It is a transient condition which resolves after birth but may cause hepatobiliary disorders in later life. Severe ICP is associated with meconium stained amniotic fluid, fetal asphyxia, neonatal unit admission, still birth and pre term delivery. The underlying mechanism of fetal complication are unclear but appear to relate with level of bile acids. The most effective pharmacological therapy to relieve maternal symptoms and improved biochemical abnormalities is UDCA(ursodyoxycholic acid). But definitive proof of its protective effect on fetus is unclear, in large trials undertaken. A common practices closed fetal surveillance antenataly and induction of labor at 37-38 weeks of gestation. Large randomized control trials are required to assess effective drug and implementation of best management to reduce adverse fetal outcome.

REFERENCES

1. Bacq Y, Sapey T, Brechot MC, Pierre F, Fignon A, Dubois F. Intrahepatic cho- lestasis of pregnancy: a French prospective study. Hepatology 1997;26:358-

364.
2. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol 2009;15:2049-2066.
3. Lee RH, Goodwin TM, Greenspoon J, Incerpi M. The prevalence of intrahepatic cholestasis of pregnancy in a primarily Latina Los Angeles population. J Perinatol 2006;26:527-532.
4. Germain AM, Carvajal JA, Glasinovic JC, Kato CS, Williamson C: Int- rahepatic cholestasis of pregnancy: an intriguing pregnancy-specific disorder. J SocGynecolInvestig 2002, 9:10-14.5.
5. Woerd, W. L., Mil, S. W., Stapelbroek, J. M., Klomp, L. W., Graaf, S. F., &Houwen, R. H. Familial cholestasis: Progressive familial intrahepatic cholestasis, benign recurrent intrahepatic cholestasis and intrahepatic cholestasis of pregnancy. Best Practice & Research Clinical Gastroenterology.2010; 24(5), 541-553.
6. Bull N L, Hu D, Shah S, Temple L, Silva K, Huntsman S, Melgar J, Geiser M T, Intrahepatic Cholestasis of Pregnancy (ICP) in U.S. Latinas and Chileans: Clinical features, Ancestry Analysis, and Admixture Mapping. Plos One, 2015;10(8).
7. Rafi, Junaid. Re: Intrahepatic cholestasis of pregnancy. The Obstetrician &Gynaecologist, 2017: 19(2);182–182.
8. Gagnon A1, Wilson RD, Audibert F, Allen VM, Blight C, Brock JA, Désilets VA, Johnson JA, Langlois S, Summers A, WyattP. Obstetrical Complications Associated With Abnormal Maternal Serum Markers Analytes. J ObstetGynaecol Can. 2008;30(10):918-49.
9. Ghosh S, Chaudhuri S. Intra-hepatic Cholestasis of Pregnancy: A Comprehensive Review. Indian J Dermatology. 2013;58(4):327.
10. Audibert F, Gagnon A, Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada., Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists..JObstetGynaecol Can. 2011; 33(7):754-67.
11. Arrese M, Macias RI, Briz O, Perez MJ, Marin JJ. Molecular pathogenesis of intrahepatic cholestasis of pregnancy. Expert Rev Mol Med 2008;10: e9.
12. Lee NM, Brady CW. Liver disease in pregnancy. World J Gastroenterol2009; 15: 897-906
13. Ahmed KT, Almashhrawi AA, Rahman RN, Hammoud GM, Ibdah JA. Liver diseases in pregnancy: diseases unique to pregnancy. World J Gastroenterol.2013; 19: 7639-7646
14. Mackillop L, Williamson C. Liver disease in pregnancy. Postgrad Med J 2010; 86: 160-164
15. Joshi D, James A, Quaglia A, Westbrook RH, Heneghan MA. Liver disease in pregnancy. Lancet.2010; 375: 594-605
16. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. ObstetGynecol2014; 124: 120-133
17. Anzivino C, Odoardi MR, Meschiari E, Baldelli E, Facchinetti F, Neri I, Ruggiero G, Zampino R, Bertolotti M, Loria P, Carulli L. ABCB4 and ABCB11 mutations in intrahepatic cholestasis of pregnancy in an Italian population. Dig Liver Dis.2013; 45:226-232
18. Bacq Y. Liver diseases unique to pregnancy: a 2010 update. Clin Res HepatolGastroenterol. 2011;35:182-193.
19. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009;51:237-267.
20. Heinonen S, Eloranta ML, Heiskanen J, Punnonen K, Helisalmi S, Mannermaa A, Hiltunen M. Maternal susceptibility locus for obstetric cholestasis maps to chromosome region 2p13 in Finnish patients. Scand J Gastroenterol. 2001; 36: 766-770
21. 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.
22. Williamson C, Hems LM, Goulis DG, Walker I, Chambers J, Donaldson O, et al. Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group. BJOG 2004;111:676–81.
23. Kenyon AP, Piercy CN, Girling J, Williamson C, Tribe RM, Shennan AH. Obstetric cholestasis, outcome with active management: a series of 70 cases. BJOG 2002;109:282–8.
24. Gabzdyl EM, Schlaeger JM. Intrahepatic cholestasis of pregnancy: a critical clinical review. J Perinat Neonatal Nurs2015; 29: 41-50
25. Saleh MM, Abdo KR. Intrahepatic cholestasis of pregnancy: review of the literature and evaluation of current evidence. J Womens Health (Larchmt) 2007; 16: 833-841
26. Hepburn IS, Schade RR. Pregnancy-associated liver disorders. Dig Dis Sci2008; 53: 2334-2358
27. Ropponen A, Sund R, Riikonen S, Ylikorkala O, Aittomäki K. Intrahepatic cholestasis of pregnancy as an indicator of liver and biliary diseases: a population-based study. Hepatology2006; 43: 723-728
28. Marschall HU, WikströmShemer E, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: a population-based cohort study. Hepatology2013; 58: 1385-1391
29. DeLeon A, De Oliveira GS, Kalayil M, Narang S, McCarthy RJ, Wong CA. The incidence of coagulopathy in pregnant patients with intrahepatic cholestasis: should we delay or avoid neuraxial analgesia? J ClinAnesth 2014;26:623–7.
30. Berg B, Helm G, Petersohn L, Tryding N. Cholestasis of pregnancy. Clinical and laboratory studies. ActaObstetGynecolScand 1986;65:107–13.
31. Laatikainen T, Tulenheimo A. Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. Int J GynaecolObstet 1984;22: 91–4.
32. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology 2004;40:467–74.
33. Martineau M, Raker C, Powrie R, Williamson C. Intrahepatic cholestasis of pregnancy is associated with an increased risk of gestational diabetes. Eur J ObstetGynecolReprodBiol 2014;176:80–5.
34. Lee RH, Goodwin TM, Greenspoon J, Incerpi M.

The prevalence of intrahepatic cholestasis of pregnancy in a primarily Latina Los Angeles population. J Perinatol 2006;26:527–32.
35. Lee RH, Kwok KM, Ingles S, Wilson ML, Mullin P, Incerpi M, et al. Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. Am J Perinatol 2008;25:341–5.
36. Oztekin D, Aydal I, Oztekin O, Okcu S, Borekci R, Tinar S. Predicting fetal asphyxia in intrahepatic cholestasis of pregnancy. Arch GynecolObstet 2009;280:975–9.
37. Pata O, Vardareli E, Ozcan A, Serteser M, Unsal I, Saruc M, et al. Intrahepatic cholestasis of pregnancy: correlation of preterm delivery with bile acids. Turk J Gastroenterol 2011;22:602–5.
38. 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: e28343.
39. WikstromShemer EA, Thorsell M, Marschall HU, Kaijser M. Risks of emergency cesarean section and fetal asphyxia after induction of labor in intrahepatic cholestasis of pregnancy: a hospital-based retrospective cohort study. Sex ReprodHealthc 2012;4:17–22.
40. WikstronShemer E, Marschall HU, Ludvigsson J, 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.
41. Gorelik J, Patel P, Ng'andwe C, Vodyanoy I, Diakonov I, Lab M, et al. Genes encoding bile acid, phospholipid and anion transporters are expressed in a human fetal cardiomyocyte culture. BJOG 2006;113:552e8.
42. Saleh MM, Abdo KR. Consensus on the management of obstetric cholestasis: national UK survey. BJOG Int J ObstetGynaecol 2007;114:99e103.
43. Savander M, Ropponen A, Avela K, Weerasekera N, Cormand B, Hirvioja ML, Riikonen S, Ylikorkala O, Lehesjoki AE, Williamson C, Aittomäki K. Genetic evidence of heterogeneity in intrahepatic cholestasis of pregnancy. Gut 2003; 52: 1025-1029