Impact of Obstetric Cholestasis on Fetomaternal Outcome

Rabiah Anwar, Kashif Razzaq, Nusrat Noor, Asma Ansari, Ayesha Imran

Pakistan Naval ship Shifa Hospital, Karachi Pakistan

ABSTRACT

Objective: To evaluate the impact of obstetric cholestasis on maternal and fetal outcomes.
Study Design: Comparative cross-sectional study.
Place and Duration of Study: Department of Gynaecology and Obstetrics, Pakistan Naval Ship Shifa Hospital Karachi Pakistan, from Jan to Dec 2019.
Methodology: All pregnant women with no comorbid and ladies with symptoms and signs of obstetric cholestasis were included during the study period. Antenatal complications and perinatal outcomes of women having obstetric cholestasis were compared with those of pregnant ladies having no comorbid.
Results: Out of 6932 obstetric patients, 90 (1.29%) had obstetric cholestasis. The cholestatic group had significantly high levels of aminotransferases and alkaline phosphatase. There was higher occurrence of preterm prelabour rupture of membrane (11.11% vs 3.33%, p=0.044), preterm delivery (26.66% vs 4.44%, p<0.001), prelabor rupture of membrane (31.11% vs 13.33%, p=0.004) and emergency cesarean section (16.66% vs 4.44%, p=0.008) in obstetric cholestatic group as compared to control. No difference in the occurrence of postpartum haemorrhage was observed in both groups. Meconium stained amniotic fluid (42.22% vs 8.88%, p<0.001) and neonatal intensive care unit admission (23.33% vs 7.77%, p=0.004) were significantly high in the study group as compared to the control. Whereas occurrences of abnormal cardiotocography, APGAR score at 5 minutes, and intrauterine growth restriction in both groups had no significant difference.
***Conclusion*:** Women with obstetric cholestasis are at increased risk of preterm labour, PPROM, emergency LSCS, and poor neonatal outcome (low APGAR, macrosomia, NICU admission), burdening the health care system; hence early diagnosis with careful clinical examination and biochemical testing is essential.

Keywords: Meconium stained amniotic fluid, Obstetric cholestasis, Pregnancy outcome

How to Cite This Article: *Anwar R, Razzaq K, Noor N, Ansari A, Imran A. Impact of Obstetric Cholestasis on Fetomaternal Outcome. Pak Armed Forces Med J 2022; 72(Suppl-2): S379-393. DOI: https://10.51253/pafmj.v72iSUPPL-2.4954*

INTRODUCTION

Obstetric cholestasis (OC), also known as intrahepatic cholestasis of pregnancy (ICP), is a pregnancy-specific disease characterized by pruritis and elevated serum aminotransferases and bile acid levels. It usually starts in the second or third trimester of pregnancy and resolves spontaneously within two to three weeks postnatally.[1] Bile acids are the end product of the metabolism of cholesterol. In the terminal ileum, their reabsorption occurs, and through the portal vein, they are returned to the liver. Tight regulation of bile acid homeostasis is needed because of their toxicity. Farnesoid X receptor (FXR) is the main hepatic bile acid receptor regulating this process.

Obstetric cholestasis affects 0.1-2% of pregnant women,[2] but there is wide demographic variation, with the highest incidence in South America, e.g. Chile (6-27%) and the lowest in Europe (0.2%).[1] There was an overall incidence of 0.7% in different ethnicities in the UK, but Pakistani and Indian origin have 1.2-1.5%.[3] In Punjab, Pakistan, a frequency of 3.1%.[4]

Both genetic and hormonal factors play an important role. The disease is more common in women with multifetal pregnancies and usually occurs in the third trimester. Some women with a history of ICP develop recurrence of symptoms with oral contraceptive use.[5]

ICP typically presents with pruritis in the third trimester. With the advancement of pregnancy, pruritis deteriorates along with worsening liver function tests. This itching may lead to excoriation marks and abrasions. Women may have dark-coloured urine, pale stool and right upper quadrant pain.

Liver function tests, including serum bile acid levels, should be done in pregnant women presenting with pruritis. Serum bile acids are the most sensitive and specific marker for diagnosing and monitoring ICP. However, the test is not currently available at all places. The Royal College of Obstetricians and Gynaecologists (RCOG) guideline recommends that in the

Correspondence: Dr Rabiah Anwar, Department of Gynaecology and Obstetrics, Pakistan Naval Ship Shifa Hospital, Karachi-Pakistan
Received: 09 Aug 2020; revision received: 25 Nov 2020; accepted: 27 Nov 2020

absence of bile acid testing, ICP may be diagnosed in a woman with typical pruritis and abnormal liver function test provided both resolved after delivery.[3] Women with ICP having steatorrhoea are at risk of malabsorption of fats and fat-soluble vitamins, so their coagulation profile should also be checked them.[6] To exclude other causes of cholestasis, a liver ultrasound should be performed. About 13% of women with intrahepatic cholestasis have gallstones.[7]

The potential risks to the fetus are fetal distress, intrauterine fetal death (IUFD), iatrogenic preterm delivery, meconium stained liquor and low birth weight.[2] Persistent itching and consequent sleep deprivation lead to maternal morbidity.[8,9] ICP can cause vitamin K deficiency, resulting in coagulopathy and postpartum haemorrhage.[4] To reduce maternal and fetal problems, the management of these patients is important. Hydrophilic bile acid (ursodeoxycholic acid (UDCA) is used to treat ICP. It alleviates pruritis and reduces serum aminotransferases and bile acid levels without adverse effects on the mother or fetus.[10] It prevents the accumulation of biliary constituents in the fetus and improves perinatal outcomes by reducing fetal distress and even still birth.[10] Very few studies have been carried out about ICP in our country because of the expected low burden of disease. However, this disease seems common in our population and may be associated with poor fetomaternal outcomes. We aimed to study the fetomaternal outcomes in ICP in our settings.

METHODOLOGY

This comparative cross-sectional study was carried out at the Department of Gynaecology/Obstetrics and Medical Department of Pakistan Naval Ship Shifa Hospital Karachi Pakistan, from January to December 2019. PNS Shifa Karachi is a referral institute and a tertiary care hospital catering to many army and civilian personnel. The Ethical Committee approved the study of the hospital (no. ERC/ 2020/gynae/23). Informed verbal and written consent was taken from all the participants, maintaining their confidentiality. The sample size was calculated using the WHO sample size calculator. Assuming a 3.1% frequency of intrahepatic cholestasis in pregnancy,[11] a minimum sample size of 47 was calculated to provide the study with 80% power in assessing the impact of obstetric cholestasis on the fetomaternal outcome. Non-probability, consecutive sampling technique was used for recruitment.

Inclusion Criteria: Women with obstetrical cholestasis (Group-1) and those with normal, uncomplicated pregnancy (Group-2) who delivered newborns at 28-42 weeks of gestation were included in the study.

Exclusion Criteria: Women who had pruritic skin lesions, viral hepatitis, cholestasis due to other reasons (drugs/gallstones), autoimmune liver disease, coagulopathies, thrombocytopenia and medical disorders (anaemia, hypertension and diabetes mellitus) were excluded from the study.

Detailed evaluation of patients was done. For disease identification, itching, the colour of urine and stool were inquired. Appetite, joint pain, rash and mouth ulcers were inquired about to rule out autoimmune causes. History of symptoms of cholestasis with contraceptive pills, itching during previous pregnancies and family history of intrahepatic cholestasis was explored. Detailed general physical and systemic examination was done. Investigations carried out were complete blood count, urine examination, liver function tests and viral serology like hepatitis B surface antigen (HbsAg) and anti-hepatitis C virus (HCV) antibodies. Abdominal ultrasound was done for any biliary duct dilatation. Serum bile acid could not be checked because of the non-availability of the test. Therefore, we made OC a diagnosis of exclusion after history, examination and investigations. Criteria of raised serum amino transferases (>30IU/L) and alkaline phosphatase (>300IU/L) were used for diagnosis of ICP in patients with pruritis of pregnancy in the absence of any dermatosis, viral hepatitis, cholelithiasis and auto immune liver disorder. All patients with ICP were treated with UDCA. Their demographic, clinical and laboratory parameters were recorded in proforma.

Serum LFTs were carried out every 10-14 days in women with OC during regular antenatal visits. The fetus was monitored by the maternal recording of fetal movements, twice-weekly nonstress test (NST) starting at 34 weeks of gestation, and sonography, including amniotic fluid index after every 7-14 days, depending on the period of gestation. All ICP group patients were given vitamin K from 32 weeks onward. Patients who needed intensive fetomaternal monitoring were hospitalized.

Obstetric complications such as preterm premature rupture of membrane (PPROM) (spontaneous rupture of membrane before the onset of labour in pregnancies <37 completed weeks of gestation) and

preterm deliveries (delivery at <37 completed gestational weeks) were observed. Cardio to cographic findings during fetal surveillance, mode of delivery, the passage of meconium during delivery, and APGAR score at 5 minutes after delivery were carefully noted. For confirmation of resolution of clinical symptoms and laboratory parameters, patients were followed up 42 days after delivery.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Descriptive statistics were used to calculate Mean ± SD for age. Frequency and percentages were calculated for numerical data. Pearson chi-squared test was used for the analysis of categorical variables. The value of $p \leq 0.05$ was considered significant.

RESULTS

During the study period, ninety (1.29%) obstetric patients were diagnosed as ICP out of 6932. The mean age of these women was 25.96 ± 3.94 years. Forty-three were nulliparous, and 47 were multiparous. There was no significant difference in maternal age and parity between the two groups. Table-I showed the demographic characters of ICP and the control group.

Table-I: Demographic characteristics of Intrahepatic cholestasis and control group.

Characteristics	Intrahepatic Cholestasis Group n= 90	Control Group n=90	*p*-value
Parity			
Nulliiparous Multiparous	43 47	47 43	0.55
Mean age, Mean ± SD, Years	25.96 ± 3.49	26.92 ± 3.95	

Table-II showed liver function tests of both groups.

Table-II: Liver function tests in intrahepatic cholestasis and control group.

Parameters	Intrahepatic cholestasis group n= 90	Control Group n=90	*p*-value
Serum bilirubin Mean (SD)	19.94 ± 6.998	12.18 ± 2.10	<0.001
Aspartate aminotransferase Mean (SD)	44.35 ± 19.72	21.00 ± 7.63	<0.001
Alanine aminotransferase Mean (SD)	46.97 ± 17.92	23.34 ± 6.92	<0.001
Alkaline phosphatase Mean (SD)	372.58 ± 96.47	246.94 ± 71.175	<0.001

There was a significant rise in serum bilirubin, aminotransferases and alkaline phosphatase in obstetric cholestasis patients compared to control.

Table-III showed obstetric complications of both the ICP and control group.

Table-III: Obstetric complications.

Complications	Obstetric Cholestasis n= 90 (%)	Control Group n= 90 (%)	*p*-value
Preterm Prelabor Rupture of Membrane (PPROM)	10 (11.11%)	3 (3.33%)	0.044
Preterm Delivery	24 (26.66%)	4 (4.44%)	<0.001
Prelabor Rupture of Membrane (PROM)	28 (31.11%)	12 (13.33%)	0.004
Emergency Cesarean Section	15 (16.66%)	4 (4.44%)	0.008
Postpartum Haemorrhage	1 (1.11%)	1 (1.11%)	1.00

There was significantly higher occurrence of pre-term prelabour rupture of membrane (11.11% vs 3.33%, p=0.044), preterm delivery (26.66% vs 4.44%, p<0.001), prelabor rupture of membrane (31.11% vs 13.33%, p=0.004) and emergency cesarean section (16.66% vs 4.44%, p=0.008) in OC group as compared to control group.

Meconium stained amniotic fluid (42.22% vs 8.88%, p<0.001) and NICU admission (23.33% vs 7.77%, p=0.004) were significantly high in ICP group as compared to control group. Nevertheless, the difference in the incidence of abnormal cardiotocography, APGAR score at 5 minutes, and IUGR was not significant in both groups, as shown in Table-IV.

Table-IV: Perinatal outcomes.

Parameters	Obstetric Cholestasis n= 90(%)	Control Group n= 90(%)	*p*-value
Meconium Stained Amniotic Fluid	38 (42.22%)	8 (8.88%)	<0.001
Abnormal Cardiotocography	15 (16.66%)	7 (7.77%)	0.069
APGAR score<7 at 5 minutes of Delivery	5 (5.55%)	1(1.11%)	0.097
Intrauterine Growth Restriction	2 (2.22%)	0 (0%)	0.155
Neonatal Intensive Care Admission	21(23.33%)	7 (7.77%)	0.004

DISCUSSION

This study described the fetomaternal outcome of obstetric cholestasis in tertiary care hospital PNS Shifa Karachi Pakistan. We found the frequency of 1.29% of obstetric cholestasis, which is comparable to a study done by Sultana and her colleagues.[11] However, Hafeez *et al*, observed a 3.1% frequency.[4] A very low incidence of 0.4% had been shown by a local study done in Rawalpindi.[12]

It is said that advanced age (>35years) women have an increased risk of developing OC.[13] Never the less, the mean age of ladies with obstetric cholestasis in our study was 25.96 years (ranging from 21-36 yrs), and maternal age or parity had no difference among both groups. Padmaja *et al*, observed mean age of 28.7 with no significant difference in parity between the two groups.[14] Singh *et al*, also had similar findings.[15]

Generalized pruritis worsening at night was the main symptom observed in all women with cholestasis. The palms and soles were most affected by pruritis in these ladies. We observed a significant rise in serum bilirubin, amino transferase and alkaline phosphatase levels. On average, serum amino transferase was raised two to three times and alkaline phosphatase levels by three to four times above the control in most pregnancies. Serum bile acid levels have more sensitivity and specificity in diagnosing and monitoring OC.[2] We could not determine the levels in our patients due to the non-availability of tests.

It is believed that biliary constituents cause fetal distress and even stillbirth.[1] UDCA may improve perinatal outcomes by preventing their accumulation. We prescribed UDCA to all patients with ICP. We also prescribed antihistamine (Chlorpheniramine) and topical emollients (aqueous cream with menthol) for symptomatic relief.

We observed a significantly higher incidence of PPROM in the OC women group than in the control group (11.11% vs 3.33%). Padmaja observed PPROM in 8.9% of the ICP group compared to 1.1% in the control group.[14] In contrast, one study found PPROM in 6.25% of cases of obstetric cholestasis.[8]

We observed that 26.66% of ladies in the ICP group had preterm deliveries compared to 4.44% of the control group. Preterm delivery in ICP may be due to increased response of myometrial strips to oxytocin and increased oxytocin- receptor expression to cholic acid.[15] A previous study observed that 18.7% of obstetric cholestasis ladies had preterm deliveries.[8] Padmaja observed that 24.4% of deliveries in the ICP group resulted in preterm deliveries compared to 15.6% in the control group [14]. Geenes *et al*,[16] observed the same. Metaanalysis by Mohan also showed an increased preterm birth rate. This included spontaneous and itrogenic preterm birth due to intervention associated with OC.[17] Older studies of ICP demonstrated increased stillbirth associated with OC at 37-39 weeks of gestation. To avoid this risk elective, early delivery was suggested.[18,19]

In our study, 16.66% of cases had emergency cesarean in the study group as compared to 4.44% cases in the control group. Padmaja *et al*, also observed a higher cesarean section rate in the ICP group (93.3% vs 76.7%), but it was not statistically significant ($p>0.05$).[14] Higher elective cesarean section (76.2% vs 65.2%) was the main reason for the higher cesarean sec tion rate. This may be due to increased preterm birth and higher intrapartum meconium events.

In our study, there was one case of PPH in either group. Furrer *et al*, observed no statistical difference in postpartum blood loss in both groups.[20]

We observed meconium-stained amniotic fluid in 42.22% cases of OC as compared to 8.88% cases of the control group. In comparison, Padmaja *et al,* observed meconium staining of amniotic fluid in 17.8% cases of ICP and 1.1% cases of the control group.[14] Kawakita *et al*, observed that with increasing serum bile acid levels, the incidence of meconium-stained amniotic fluid also increases.[21]

We observed abnormal cardio-tocography in 16.66% of cases of ICP as compared to 7.77% of cases of control. In our study, 5.55% of neonates in the study group had APGAR scores <7 at 5 minutes compared to 1.11% of neonates of the control group, which was statically non-significant.

We observed that 23.33% of the newborn in the OC group had NICU admission compared to 7.77% of the newborn in the control group. A similar finding was observed by many previous studies.[21,22]

STUDY LIMITATIONS

The major limitation of our study was the non availability of bile acid levels. However, we diagnosed ICP by clinical features and liver function test and excluded other causes as we are doing in our routine practice. The significant contribution of this study is to make awareness about this disease which will help our obstetric patients.

CONCLUSION

Women with obstetric cholestasis are at increased risk of preterm labour, PPROM, emergency LSCS, and poor neonatal outcome (low APGAR, macrosomia, NICU admission), burdening the health care system; hence early diagnosis with careful clinical examination and biochemical testing is essential.

Conflict of Interest: None.

Author's Contribution

RA: Main author, conception, main work, KR: Co-author, Conceotion, analysis, NN: Study conduction, AA: Critical review, AI: Facilitation.

REFERENCES

1. Geenes V, Williamson C, Chappell LC. Intrahepatic cholestasis of pregnancy. Obstet Gynaecol 2016; 18(4): 273-281.
2. 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.
3. Royal College of Obstetrician and Gynaecologists. obstetric cholestasis rcog green top guidelines. No 43 April 2011. [Internet] Available at: https://www.rcog.org.uk/en/guid-elines-research-services/guidelines/gtg43
4. Hafeez M, Ansari A, Perveen S, Salamat A, Aijaz A. Frequency of intrahepatic cholestasis of pregnancy in Punjab Pakistan: A single centre study. J Pak Med Assoc 2016; 66(2): 203-206.
5. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol 2014; 124(1): 120-133.
6. 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 Clin Anesth 2014; 26(8): 623-627.
7. Marschall HU, WikströmShemer E, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: a population based cohort study. Hepatol 2013; 58(4): 1385-1391.
8. Ghimire SP, Ghimire A, Jha GS, Chhetry M, Kumar M. Fetomaternal outcomes in intrahepatic cholestasis in pregnancy in a tertiary care centre in eastern Nepal. J Nobel Med Coll 2016; 5(1): 20-25.
9. Chappell LC, Chambers J, Thornton JG, Williamson C. Does ursodeoxycholic acid improve perinatal outcomes in women with intrahepatic cholestasis of pregnancy? BMJ 2018; 360: k104.
10. Herrera CA, Manuck TA, Stoddard GJ, Varner MW. Perinatal outcomes associated with intrahepatic cholestasis of pregnancy. J Matern Fetal Neonat Med 2018; 3(14)1: 1913-1920.
11. Sultana R, Sarwar I, Fawad A, Noor S, Bashir R. Neonatal outcome in obstetric cholestasis patient at Ayub teaching Hospital Abbottabad J Ayub Med Coll Abbottabad 2009; 21(4): 76-78.
12. Rasheed S, Afghan S, Mazhar SB. Fetomaternal Outcome in Patients with Obstetric Cholestasis. Ann Pak Inst Med Sci 2009; 5(4): 211-215.
13. Arrese M, Reyes H. Intrahepatic Cholestasis of Pregnancy.A past and present riddle. Ann Hepatol 2006; 5(3): 202-205.
14. Padmaja M, Bhaskar P, Kumar GJ, Seetha R, Mahasweta C. A study of Obstetric Cholestasis. J Obstet Gynaecol India 2010; 60(3): 225-231.
15. Singh G, Sidhu K. Cholestasis of Pregnancy. A prospective study. Med J Armed Forces India 2008; 64(4): 343–345.
16. Geenes V, Chappell LC, Seed PT, Steer PJ, Knight M. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population based case ncontrol study. Hepatolo 2014; 59(4): 1482-1491.
17. Mohan M, Antonios A, Konje J, Lindow S. Akobeng A. Stillbirth and associated perinatal outcomes in obstetric cholestasis: a systematic review and meta-analysis of observa-tional studies. Eur J Obstet Gynecol Reprod Biol X 2019; 3: 100026.
18. Martineau M, Raker C, Powrie R. Intrahepatic cholestasis of pregnancy is associated with an increased risk of gestational diabetes. Eur J Obstet Gynecol Rep Bio 2014; 176(1): 80-85.
19. 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(06): 341-345.
20. Furrer R, Winter K, Schäffer L, Zimmermann R, Burkhardt T, Haslinger C. Postpartum blood loss in women treated for intrahepatic cholestasis of pregnancy. Obstet Gynecol 2016; 128(5): 1048-1052.
21. Kawakita T, Parikh LI, Ramsey PS, Huang CC, Zeymo A,. Predictors of adverse neonatal outcomes in intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2015; 213(4): 570.
22. Sosa S, Valenzuela A, Pacheco J, Damián R. Intrahepatic cholestasis of pregnancy: evaluation of risk factors and predictive factors. Internet J Gynecol Obstet 2009; 12(2): 1-4.