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A Retrospective Analysis of Fetal and Maternal Outcome in Patients with Intrahepatic Cholestasis of Pregnancy

Nadia Khurshid[1], Farhana Fayaz[2], Insha Jan Khanyari[3]*

[1]Consultant, Department of Obstetrics and Gynaecology, Ujala Cygnus Hospital, Srinagar, Jammu and Kashmir, India.
Email: khurshidnadia@gmail.com,
Orcid ID: 0000-0003-1522-3314
[2]Consultant, Department of Obstetrics and Gynaecology, Sub-district Hospital, Chadora, Jammu and Kashmir, India.
Email: farhana.fayaz.10@gmail.com,
Orcid ID: 0009-0007-4466-0878
*[3]Consultant , Department of Obstetrics and Gynaecology, District Hospital, Ganderbal, Jammu and Kashmir, India.
Email: 0000-0002-7757-6636,
Orcid ID: faizshera@gmail.com

*Corresponding author

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Abstract

Background: Introduction: Intrahepatic cholestasis of pregnancy (ICP), is the most common liver disease specific to pregnancy. Previous studies of fetal effects have suggested that ICP is associated with a higher rate of adverse neonatal outcomes including preterm birth, neonatal respiratory distress syndrome (RDS), meconium-stained amniotic fluid, neonatal intensive care unit admission, and stillbirth. **Material & Methods:** This was a 4 year retrospective observational study including 43,344 female who delivered in our hospital out of which 1126 cases of ICP were identified, who were compared with 1136 age and parity matched controls. **Results:** : Previous history and family history of ICP was significant in the ICP group. Gestational diabetes and preterm labour were more frequent in the ICP group. Mean birth weight was lower in the ICP group, rate of small for gestational age foetuses was not significantly different. Cesearean section and post-partum haemorrhage was more frequent in the ICP group. Adverse neonatal outcomes i.e. respiratory distress syndrome (RDS) and need for NICU admission were more in the ICP group. **Conclusion:** ICP is associated with increased rate of preterm delivery, post-partum hemorrhage and increased neonatal morbidity. Management of patients with ICP should be individualized based on the severity of symptoms and associated medical complications.

Keywords:- Intrahepatic cholestasis of pregnancy, Bile acid, hepatitis, liver disease, pruritis

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP), is the most common liver disease specific to pregnancy.[1] The global incidence of ICP is likely to vary from 1% to 27.6%, depending on the geographic variations, differences in sensitivity between ethnic groups and environmental factors.[2,3,4] Intrahepatic cholestasis of pregnancy is a multifactorial condition. Exact etiology is not well-known, but probably depends on the genetic predisposition, hormonal and environmental factors. It is characterised by pruritus in the absence of a primary skin condition, with abnormal maternal bile acid concentrations. The onset of symptoms is most common in the third trimester, but can be earlier in pregnancy.[4] Pruritus and raised bile acid concentrations should return to normal after birth. Alternative diagnoses (such as pre-eclampsia, viral hepatitis, autoimmune liver disease, drug reactions, allergic reactions, and urticaria etc.) should always be considered before a diagnosis

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of ICP is made; it is also possible for other conditions to co-exist. It is associated with adverse perinatal outcomes including stillbirth, preterm labour and neonatal unit admission. An increase in preterm birth is seen with serum bile acid concentrations above 40 µmol/L, and the risk of stillbirth is increased in women when peak serum bile acid (BA) concentrations are 100 µmol/L or more.[5]

The diagnosis of ICP should be considered in pregnant women who have itching in skin of normal appearance and raised peak random total bile acid concentration of 19 micromol/L or more. If the itchy skin looks normal, or there is only skin trauma due to scratching, the diagnosis may include gestational pruritus, or ICP; measurement of bile acid concentrations and liver function tests should be undertaken. Raised bile acid concentration of 19 micromol/L or more in pregnancy supports diagnosis of ICP. The diagnosis is more likely if it is confirmed that itching and raised bile acids resolve after birth.

New onset pruritus in pregnant women, if associated with rash is unlikely to be ICP. If the itchy skin looks abnormal (other than excoriations) then another cause should be considered. Clinicians should be aware however, that skin conditions (e.g. eczema) and ICP can co-exist.

There is now increasing evidence that in singleton pregnancies, most liver function tests do not reflect risk of fetal demise and that only maternal total bile acid concentrations results are associated with the risk of stillbirth. All women with itching and an initial raised bile acid level, should have a second bile acid measurement repeated around 1week later before any diagnostic or care decisions are determined, as it is common for women with bile acid levels over 100micromol/L and 40–100micromol/L to have subsequent bile acid concentrations that are much lower.[6]

The care of women and pregnant people with ICP is driven by concern from women and from healthcare professionals over the potential increased risk of stillbirth. Previous studies of fetal effects have suggested that ICP is associated with a higher rate of adverse neonatal outcomes including preterm birth, neonatal respiratory distress syndrome (RDS),[7] meconium-stained amniotic fluid,[8] neonatal intensive care unit admission, and stillbirth. No strong evidence exists regarding the association between ICP and adverse pregnancy outcomes.

Aims and Objectives

The aim of the study was to study the fetal and maternal outcome in females with ICP and compare the same with a low risk control group.

MATERIAL AND METHODS

It is a retrospective study in which the maternal and fetal outcomes in women diagnosed with ICP between January 2017 and December 2020 were collected and compared with the control group. During the study period around 43,344 female delivered in our hospital. Out of these around 1126 females were diagnosed with ICP. These were compared with 1136 females with low risk pregnancy which were matched for age and parity. The diagnosis of ICP was based on history, clinical examination and laboratory tests. ICP was diagnosed in females with generalized pruritus in otherwise normal appearing skin (except for excoriations

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following scratch marks) and with BA levels ≥19µmol/L .

All women included in the study had generalized pruritus in the absence of any dermatological condition, viral hepatitis, hypertensive diseases of pregnancy and other hepatobiliary diseases and all symptoms related with ICP had regressed as clinically or laboratory at post-delivery period.

Exclusion Criteria

1. Pregnancies complicated by congenital malformations, consisting of chromosomal abnormalities and/or multiple congenital anomalies.
2. Multiple pregnancies.
3. Patients with chronic liver diseases, skin diseases, allergic disorders, symptomatic cholelithiasis, and ongoing viral infections affecting the liver (hepatitis A, B and C virus, cytomegalovirus, herpes simplex virus, and Epstein-Barr virus).

The study was approved by Institutional Ethical Committee.

Women suspected of having ICP had a routine investigation and follow-up period. Initially, all of the women with ICP underwent liver function tests (LFTs), such as serum aspartate transferase (AST), serum alanine transferase (ALT), direct/indirect bilirubin, lactate dehydrogenase, alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase tests, viral hepatitis serology and abdominal ultrasound. All women were administered ursodeoxycholic acid, emollient and antihistamines if needed.

Statistical Analysis

The demographic data and pregnancy and fetal outcome measures were analysed. The SPSS 19.0 software was used for statistical analysis of the data. The measurement data, such as normal distribution, were described by the mean ± standard deviation . If the distribution was skewed in accordance with the median, then the median was used. Comparison between groups was carried using the unpaired t-test, Chi-squared test and Fisher's exact test.

RESULTS

The maternal and foetal outcomes in 1126 women with ICP during the study period were assessed and compared with 1136 low risk patients. Out of 43,344 deliveries that occurred during the study period,1126 were diagnosed with ICP. The incidence of ICP in our population was around 2.5%. Maternal characteristics were compared and are illustrated in Table 1. No significant difference was seen in terms of age, parity. Previous history and family history of ICP was significant in the ICP group (p value of <0.00001). Hypertensive disorders were more in the ICP group compared to the control group but the difference was not statistically significant. Patients in the ICP group had increased incidence of gestational diabetes (18.9%) compared to the control group (0.7%).

The obstetric outcomes are presented in Table 2. There was statistically significant difference in gestational age at birth between the two groups. The mean birth weight was 3082 g (2825–3370 g) in the case population and 3350 g (3050–3610 g) (P <0.001) in the control population. The rate of small-for-gestational-age (SGA) fetuses did not differ between the groups. Preterm delivery was more in the ICP group. The difference in the incidence of meconium stained liquor was not significant.

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Maternal outcomes has been illustrated in Table 3. Active management resulted in induction of labour in 79% compared to 19% in control group. C-section rate was more in ICP group . Postpartum hemorrhage was also more frequent in the case group (p value 0.00026) with increased need of blood transfusion 3.5% compared to 1.1% in control group.

Neonatal outcomes are presented in Table 4. During the three year study there was no increased stillbirth rate in the ICP group. Neonates exposed to cholestasis had a greater risk of having a RDS in comparison with controls (18.7% vs. 4.6%; P<0.001). Need for mechanical ventilation was more in the cholestasis group. The rates of admission to neonatal intensive care units was approximately four times higher in the cholestasis than the control group (P <0.001).

Table 1: Maternal characteristics within the study population

Maternal characteristics	**ICP (1126)**	**Control (1136)**	**P value**
Maternal age, years (median IQR)	28[23-35]	28[23-35]	1
Nulliparous n %	502[44.6]	522[45.9]	0.513
Previous history of ICP n %	276[24.5]	8[0.7]	<.00001
Family history of ICP n %	42[3.7%]	1	<.00001
Gestational diabetes n%	213[18.9%]	79[6.9%]	<.00001
Hypertensive disorder n%	62[5.5%]	38[3.3%]	0.0124

Table 2: Obstetric outcome within the study population

Obstetric outcome	**ICP (1126)**	**CONTROL(1136)**	**P value**
Gestational age at birth (median IQR)	38(37-38)	40(39-40)	<0.001
Preterm delivery before 37wks n (%)	191(16.9%)	56(4.9%)	<.00001
Meconium stained liquor n (%)	247(22%)	227(20%)	0.2536
Male n (%)	586(52%)	582(51.2%)	0.6998
Birth wt, gm median(IQR)	3082(2825-3370)	3350(3050-3610)	<0.001
Small for gestational age (n%)	82(7.3%)	78(6.8%)	0.6994

Table 3: Maternal outcome within the study population

Maternal outcome	**ICP (1126)**	**Control(1136)**	**P value**
Induction of labour n (%)	890(79%)	218(19%)	<.00001
Vaginal delivery n(%)	429(38%)	788(68.4%)	<.00001
Cesarean section during labour n (%)	258(23%)	156(13.7%)	<.00001
Planned Cesarean section n (%)	439(39%)	192(16.9%)	<.00001
PPH n (%)	247(21.9%)	181(15.9%)	0.00026
Blood transfusion n (%)	40(3.5%)	13(1.1%)	0.00015

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Table 4: Neonatal outcome within the study population.

Neonatal outcome	ICP	Control	P value
5min Apgar score <7 n(%)	47(4.2%)	14(1.2%)	0.00015
RDS n(%)	211(18.7%)	52(4.6%)	<.00001
Mechanical ventilation or intubation n(%)	36(3.2%)	11(1%)	0.0002
Stillbirth n(%)	4(0.4%)	3(0.26%)	0.6963
Need for NICU admission n(%)	36(3.2%)	8(0.7%)	<0.001

DISCUSSION

The maternal and foetal demographic data and outcomes of women with ICP and control were assessed and compared. Most of the women delivered at ≤38 weeks' gestation. The preterm delivery (<37 weeks' gestation) and spontaneous preterm delivery rates were high. Meta-analyses of data from the systematic review showed that, compared with controls, women with intrahepatic cholestasis of pregnancy had a higher risk of spontaneous preterm birth (OR 3·47 [95% CI 3·06–3·95;] and iatrogenic preterm birth (OR 3·65 [1·94 to 6·85]).[5] The mechanism of preterm birth, which is one of the important complications of ICP, still remains unclear.[9,10,11] A study stated that a cholic acid-mediated increase in oxytocin receptor expression might lead to preterm birth by increasing oxytocin sensitivity in the myometrium.[12]

The incidence of foetuses with SGA was low; however, the number of foetuses with low birth weight was more, resembling the high preterm delivery rate. A higher proportion of women with intrahepatic cholestasis of pregnancy had pre-eclampsia and gestational diabetes than those without intrahepatic cholestasis of pregnancy. These results were consistent with the result from large meta-analysis including around 23 studies.[5]

Our study found a higher rate of RDS and neonatal morbidity among neonates of the cholestasis group which was consistent with the other studies. Arthius et al, in a case-control study showed a risk of RDS in ICP newborns 3 times higher than in control infants (17.1% vs 4.6%).[13] Our study also found a significant difference in intensive care unit admission rates among case infants. Overall morbidity in the ICP cases was higher than in the control group. Hypothesis to explain increased neonatal morbidity among case infants include a direct effect of BA on neonatal lung, which could be induce a "bile acid pneumonia".[7,14] BA have been found detectable in the bronchoalveolar lavage fluid of case neonates affected by RDS, some authors have speculated that BA inhibits surfactant activity.[14] There was no significant difference in meconium staining during labor, contrary to other studies.[15]

Mothers with ICP had more postpartum hemorrhages than control women, and required more blood transfusions probably related to their higher rates of cesarean delivery and of oxytocin-induced labor.[16]

During the 3-year study period, there was no significant difference in stillbirths between the two groups. The reported stillbirth rates vary between 0.4% and 7% in patients with ICP.[17,18] The risk of stillbirth seems to increase after 37 weeks and is rare before 34 weeks. It also

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increase with BA level,[15] when serum bile acids concentrations are of 100 µmol/L or more.[5] Two recent large retrospective cohort studies conducted in Sweden and Australia reported favorable outcomes associated with ICP.[3,19] They reported a higher incidence of gestational diabetes, preeclampsia and/or spontaneous preterm labour in women with ICP compared to the general population but no increased risk of stillbirth associated with ICP.[20] These high rates of preterm delivery but not of stillbirths should be considered in the management of ICP. Authors of both cohort studies have argued that no increase in stillbirth rate was likely secondary to proactive medical management. Although the American College of Obstetricians and Gynecologists recommends active management,[21] it does not define an ideal term for childbirth. Similarly, the Royal College of Obstetrics and Gynecology does not recommend systematic active management.[20] Our results support individualized delivery plan taking other associated condition into consideration. It concludes that if ICP is associated with stillbirth, which it does not consider statistically proven, the risk is clinically insignificant.[22]

Our study nonetheless has some limitations. It was a retrospective study with potential bias. ICP was not categorized into mild, moderate and severe.

CONCLUSIONS

ICP is associated with increased rate of preterm delivery, post-partum hemorrhage and increased neonatal morbidity. Management of patients with ICP should be individualized based on the severity of symptoms and associated medical complications.

REFERENCES

1. Clinical Updates in Women's Health Care Summary: Liver Disease: Reproductive Considerations. Obstet Gynecol. 2017;129(1):236. doi: 10.1097/AOG.0000000000001858.
2. Reyes H, Gonzalez MC, Ribalta J, Aburto H, Matus C, Schramm G, et al. Prevalence of intrahepatic cholestasis of pregnancy in Chile. Ann Intern Med. 1978;88(4):487-93. doi: 10.7326/0003-4819-88-4-487.
3. Wikström Shemer E, 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(6):717-23. doi: 10.1111/1471-0528.12174.
4. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol. 2009;15(17):2049-66. doi: 10.3748/wjg.15.2049.
5. 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. doi: 10.1016/S0140-6736(18)31877-4.
6. 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):1066-1075. doi: 10.1111/1471-0528.16567.
7. Zecca E, De Luca D, Marras M, Caruso A, Bernardini T, Romagnoli C. Intrahepatic cholestasis of pregnancy and neonatal respiratory distress syndrome. Pediatrics. 2006;117(5):1669-72. doi: 10.1542/peds.2005-1801.
8. 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(4):e0176504. doi: 10.1371/journal.pone.0176504.
9. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile

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acid levels and fetal complication rates. Hepatology. 2004;40(2):467-74. doi: 10.1002/hep.20336.
10. Kondrackiene J, Beuers U, Zalinkevicius R, Tauschel HD, Gintautas V, Kupcinskas L. Predictors of premature delivery in patients with intrahepatic cholestasis of pregnancy. World J Gastroenterol. 2007;13(46):6226-30. doi: 10.3748/wjg.v13.i46.6226.
11. Pata O, Vardarelı E, Ozcan A, Serteser M, Unsal I, Saruç M, et al. Intrahepatic cholestasis of pregnancy: correlation of preterm delivery with bile acids. Turk J Gastroenterol. 2011;22(6):602-5. doi: 10.4318/tjg.2011.0427.
12. 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(2):577-82. doi: 10.1067/s0002-9378(03)00545-3.
13. 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. doi: 10.1371/journal.pone.0228213.
14. Zecca E, De Luca D, Baroni S, Vento G, Tiberi E, Romagnoli C. Bile acid-induced lung injury in newborn infants: a bronchoalveolar lavage fluid study. Pediatrics. 2008;121(1):e146-9. doi: 10.1542/peds.2007-1220.
15. Kawakita T, Parikh LI, Ramsey PS, Huang CC, Zeymo A, Fernandez M, et al. Predictors of adverse neonatal outcomes in intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol. 2015;213(4):570.e1-8. doi: 10.1016/j.ajog.2015.06.021.
16. Khireddine I, Le Ray C, Dupont C, Rudigoz RC, Bouvier-Colle MH, Deneux-Tharaux C. Induction of labor and risk of postpartum hemorrhage in low risk parturients. PLoS One. 2013;8(1):e54858. doi: 10.1371/journal.pone.0054858.
17. 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(4):1482-91. doi: 10.1002/hep.26617.
18. 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(7):676-81. doi: 10.1111/j.1471-0528.2004.00167.x.
19. 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. doi: 10.1016/j.ejogrb.2017.09.012.
20. Paus TC, Schneider G, Van De Vondel P, Sauerbruch T, Reichel C. Diagnosis and therapy of intrahepatic cholestasis of pregnancy. Z Gastroenterol. 2004;42(7):623-8. doi: 10.1055/s-2004-813165.
21. ACOG Committee Opinion No. 764: Medically Indicated Late-Preterm and Early-Term Deliveries. Obstet Gynecol. 2019;133(2):e151-e155. doi: 10.1097/AOG.0000000000003083.
22. Bolukbas FF, Bolukbas C, Y Balaban H, Aygun C, Ignak S, Ergul E, et al. Intrahepatic Cholestasis of Pregnancy: Spontaneous vs in vitro Fertilization. Euroasian J Hepatogastroenterol. 2017;7(2):126-129. doi: 10.5005/jp-journals-10018-1232.

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