J Nepal Health Res Counc 2021 Apr-Jun;19(51): 321-6

DOI: https://doi.org/10.33314/jnhrc.v19i2.3455

Prevalence and Pregnancy Outcomes of Intrahepatic Cholestasis of Pregnancy

Deekshanta Sitaula,[1] Santosh Timalsina,[2] Basant Sharma,[1] Bandana Pokharel,[1] Rohit Thapa[1]

ABSTRACT

Background: Intrahepatic cholestasis of pregnancy is a common pregnancy-specific liver disease associated with increased risk of adverse fetal and maternal outcomes. We sought to determine its prevalence, risk factors and feto-maternal outcomes.

Methods: A retrospective review of data of 164 pregnant women diagnosed with intrahepatic cholestasis of pregnancy at Chitwan Medical College, Nepal from August 2018 to September 2020 was done. Socio-demographic data, clinic-laboratory profile and feto-maternal outcomes were obtained from clinical audit books and electronic records. A multivariate logistic regression analysis was used to evaluate the predictors of adverse neonatal outcome.

Results: The prevalence of intrahepatic cholestasis of pregnancy was 2.5% (164 out of 6539 deliveries). The mean age was 27.5 $\pm$ 4.4 years and 51.2% were multigravida. The preterm delivery rate was 15.2% and Caesarean delivery rate was 69.5%. 22% of the neonates needed intensive care admission out of which Respiratory Distress Syndrome or Transient Tachypnea of Newborn was seen in half of them. There were 2 cases of Intrauterine Fetal Death. In multivariate analysis, delivery <34 weeks of gestation was only found to be a significant independent predictor of adverse neonatal outcome

Conclusion: The prevalence of intrahepatic cholestasis of pregnancy among pregnant women is significant in our setting which is associated with adverse fetal outcome. Early diagnosis and timely intervention is necessary in order to reduce associated perinatal morbidity.

Keywords: Intrahepatic cholestasis of pregnancy; liver function tests; neonatal outcome; obstetric cholestasis

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is a common pregnancy-specific liver disease, which is characterised by pruritus, typically of the palms and soles during the third trimester along with deranged liver function and elevated serum bile acid levels that normally resolves following delivery.[1]

ICP has been reported to be common in South Asia (1.26 to 3.1%), South America (2.4%) and Scandinavia (2%).[2-7] In Nepal, it has been reported upto 1.15%.[8] This condition has been found to be particularly associated with increased risk of adverse fetal outcomes such as spontaneous and iatrogenic preterm delivery, Respiratory Distress Syndrome (RDS), Intra Uterine Growth Restriction (IUGR), low APGAR score, Meconium Stained Liquor, still birth and neonatal demise.[1,2,9-11]

The objective of this study was to assess the prevalence of ICP among pregnant women in a tertiary care centre in Nepal, explore the associated risk factors and analyze the feto-maternal outcomes.

METHODS

We performed a retrospective review of records of all women who delivered at Chitwan Medical College Teaching Hospital (Chitwan, Nepal) with a diagnosis of ICP within a period of two years (August 2018 to September 2020). Ethical approval was taken from Institutional Review Committee (CMC-IRC). Women with diagnosis of ICP were identified through the clinical audit books and electronic database in the hospital. ICP was diagnosed as per RCOG guideline i.e. the presence of otherwise unexplained pruritus and abnormal liver function tests (LFTs) [AST >31IU/L and ALT>32 IU/L] and/or raised bile acids [>14 micromoles/L] occurring in the pregnant women and both resolving after delivery.[12] However, at our institute, presence of pruritus and

Correspondence: Dr Deekshanta Sitaula, Department of Obstetrics and Gynecology, Chitwan Medical College, Bharatpur, Chitwan, Bagmati Province, Nepal, Email: drdeekshanta@gmail.com, Phone: +9779861056601.

abnormal LFTs were used as diagnostic criteria for ICP as the measurement of serum bile acids could not be done due to resource constraints. Pregnant women with viral hepatitis, hepatic complications of Gestational Hypertension and gallstones were excluded. . Women diagnosed as ICP that did not deliver at this institute (i.e. with no obstetric records) were also excluded. The convenient sampling technique was used. A previous study on feto-maternal outcomes in intrahepatic cholestasis of pregnancy from Nepal reported a prevalence of 1.15%. Assuming the same prevalence of 1.15%, with a 1.5% margin of error and 95% confidence interval, the sample size was calculated to be 195 by using openepi.com, a web base statistical operating system using the formula, $N=Z^2pq/e^2$,where critical value Z=1.96 for 95% confidence interval.

Information on maternal demographics, medical comorbidities, serum biochemical parameters and feto-maternal outcomes were collected for evaluation. The patients were managed by following institutional protocol. All of them were treated with Ursodeoxycholic acid (starting from 300mg thrice a day) from diagnosis upto delivery. Liver Function Tests (LFTs) were monitored twice a week. Induction of labour was planned routinely at 38 weeks or earlier if symptoms became more severe. Dexamethasone was administered prior to delivery. Elective Caesarean Section was planned only in case of maternal or fetal indications. After delivery, the women were observed until the day of discharge for the relief of symptoms of ICP and postnatal complications. However, we could not retrieve any data regarding follow up and postnatal monitoring of LFT.

Feto-maternal outcomes that included delivery gestational age, spontaneous preterm delivery, iatrogenic preterm delivery, birth-weight, mode of delivery, oligohydramnios, intrauterine growth restriction, placental abruption, pre-labour rupture of membrane (PROM), fetal distress (Non reassuring fetal status), chorioamnionitis, postpartum hemorrhage, stillbirth, neonatal intensive care unit (NICU) admission, hyperbilirubinemia, hypoglycaemia, meconium-stained liquor, RDS or Transient Tachypnea of Newborn (TTN) were ascertained. An adverse neonatal outcome was defined as any of the following: NICU admission, hypoglycaemia, hyperbilirubinemia, RDS, TTN, prematurity and low birth weight. Non reassuring fetal status (NRFS) was defined by fetal tachycardia or bradycardia, reduced FHR variability, decelerations and absence of accelearations. PROM was defined as spontaneous rupture of the membranes any time beyond 28th week of pregnancy but before the onset of labour. Hyperbilirubinemia was defined by neonatal hyperbilirubinemia which required phototherapy. Hypoglycemia was defined by neonatal hypoglycaemia that required intravenous infusion of glucose. Diagnosis regarding RDS and TTN were made by the managing neonatologist/paediatrician and based on standard clinical guidelines.

Statistical analysis was done using SPSS v20.0. Categorical variables were expressed as frequency number and percentage (%). Normally distributed scale variables were expressed as mean ± SD, whereas non-normally distributed variables were presented as medians and ranges. The information was illustrated in tabular formats. Both univariate and multivariate logistic regression analyses were done to evaluate the association of different clinical predictors (maternal age, liver enzyme levels, delivery gestational age and preterm birth <37 weeks) with adverse neonatal outcome.

RESULTS

Out of 6539 pregnant women who delivered at Chitwan Medical College within the span of 2 years, ICP was diagnosed in 164 women, with a prevalence of 2.5%. The demographic and laboratory characteristics of the women with ICP are presented in Table 1 and 2. The mean age was 27.5 ± 4.4 years (Range 19-38 years), with 80 (48.8%) primigravida and 84 (51.2%) multigravida. Out of 164, 99 (60.4%) patients were Brahmins. The commonest co-morbidity with ICP was pre-eclampsia (19, 11.6%) followed by GDM (16, 9.7%). All the pregnant women presented with history of itching. The median level of ALT and AST were 128 U/L (15-668) and 103 U/L (13-480) respectively.

Pregnancy outcomes are shown in Table 3. Out of 164 deliveries, 25 (15.2%) were preterm deliveries, the majority of which were iatrogenic (19, 11.5%). More than two-third (69.5%) had Caesarean Section (CS). The emergency CS rate was 48.8%, the frequent most indication being non reassuring fetal status (43.7%) followed by meconium stained amniotic fluid (35.0%).. There were 2 cases of IUFD. Thirty (18.7%) neonates had Low Birth Weight (<2500gm). Thirty-six (22%) neonates were admitted to NICU. The common causes for NICU admission were RDS or TTN (18, 50%), Neonatal sepsis (10, 27.8%), Meconium stained amniotic fluid (4, 11.1%), prematurity with LBW (4, 11.1%) and hyperbilirubinemia (3, 8.3%).

In univariate analysis, maternal age, liver enzyme levels (SGPT and SGOT) and preterm birth (<37 weeks) were found to be associated with adverse neonatal outcome.

Birth weight, gravida status and ethnicity were not related with adverse neonatal outcome. In multivariate analysis, only delivery at <34 weeks POG was the significant independent predictor of adverse neonatal outcome in women with ICP [aOR: 88.2 (95% CI: 2.4 - 3167.0, P = 0.01] when compared to deliveries that occurred at ≥ 37 weeks.

Table 1.Socio-demographic data and pregnancy comorbidities of the study population. (n=164).

Demographic variables	Frequency	%
Maternal age (years)		
<25	43	26.2
25 - 34	107	65.2
≥ 35	14	8.5
Ethnicity		
Brahmin	99	60.4
Chhetri	23	14.0
Newar	6	3.7
Janajati	36	22.0
Gravida		
Primigravida	80	48.8
Multigravida	84	51.2
Past history		
Bad obstetric history	2	1.2
Cholelithiasis	1	0.6
Subfertility (1^0 or 2^0)	9	5.5
CPD	4	2..4
Prior history of ICP	0	0.0
Gestational diabetes	16	9.7
Preeclampsia	19	11.6
Co-existing thyroid disorder	13	7.9

Table 2. Laboratory parameters of the study population. (n=164).

Laboratory parameters	Median value	Range
Hb (g/dl)	11.5	7.5 - 14.5
Platelets (per cu. mm)	170000	75000 - 377000
ALT (IU/L)	128	15 - 668
AST (IU/L)	103	13 - 480
RBS(mg/dl)	98	58 - 158

Table 3.Pregnancy outcomes of patients with ICP. (n=164).

Variables	Frequency (%)	%
Gestational age (weeks)		
<34 wk	5	3.0
34 - <37 wk	19	11.6
≥ 37	140	85.4
Preterm delivery	25	15.2
Preterm delivery type(n=25)		
Spontaneous	6	3.7
Iatrogenic	19	11.5
Birth weight group*		
<2500	30	18.7
2500 - 4000	128	80.0
>4000	2	1.3
Mode of delivery		
Vaginal	47	28.7
Instrumental vaginal	3	1.8
Caesarean section	114	69.5
Emergency CS rate	80	48.8
Oligohydramnios	15	9.1
IUGR	15	9.1
PROM	10	6.1
Nonreassuringfetal status (NRFS)	35	43.7
IUFD	2	1.2
Stillbirth	0	0.0
NICU admission	36	22.0
Reasons for NICU admission†		
RDS or TTN	18	50.0
Sepsis	10	27.8
Meconium stained liquor	4	11.1
Hyperbilirubinemia	3	8.3
Prematurity and LBW	4	11.1
Mortality	0	0.0

**Out of 160 patients, † Out of 36 neonates who were admitted in NICU (same neonate may have more than one diagnosis)*

DISCUSSION

ICP is a common pregnancy-specific hepatic disease

which has a complex etiology with genetic, endocrine and environmental components.[13] Mutations in gene (ABCB4) encoding hepatobiliary transporter proteins (MDR3) responsible for transporting phosphatidylcholine into bile, and abnormal metabolites (estrogen, progesterone and associated metabolites) impairing hepatobiliary carriers may be responsible for the pathogenesis of ICP.[14]

The prevalence of ICP in our study was higher than that previously reported from Nepal (1.15%),[8] but is consistent with the findings from India (2.4%) and South America (2.4%).[4,6] However, this prevalence is lower in comparison to the studies reported in China (6.06%) and Pakistan (3.1%).[2,5] The variations in prevalence of ICP might be due to ethnicity, differences in food habit and nutrition, geographical variation, level of available facilities and variations in diagnostic criteria.[2] The mean age of our patients was lower compared to those reported in Australia (30.0 years) and China (37.5 years) but was higher than that reported in a prior study from Nepal (26.59 years).[2,15,16] Advanced maternal age as a risk factor for ICP as suggested by Gao et al was not exemplified in this study.[2]

Sixteen (9.7%) women with ICP had GDM which is higher than that (6.9%) reported by Celik et al but almost similar to the finding (9.74%) by Gao et al.[2,17] A 12-year population based cohort in Sweden reported an increased risk of gestational diabetes in women with ICP in comparison to normal pregnant women.[18] However, Gao et al indicated that there was no significant difference in gestational diabetes between the two groups.[2] The CS rate was higher than previous two studies reported from Nepal.[8,16] The possible reasons could be the institutional policy of either routine induction or elective LSCS of ICP patients after 38 weeks of gestation. As per literature, almost one-thirds among those undergoing induction had failed induction and underwent CS.[8] It has also been reported that the risk of fetal death in ICP increases by each additional week of expectant management and continues to rise by week of gestation beyond 36 weeks.[19]

There were 25 (15.2%) preterm deliveries out of which 3.7% were spontaneous and 11.5% were iatrogenic. The rate of preterm deliveries in previous studies done by Celik et al. and Shemrer et al. were respectively 22.4% and 13.1%. In literature, it has been shown that women with ICP have higher odd ratios of preterm delivery.[9] ICP is associated with increased risk of premature birth especially iatrogenic, usually as a result of a medical decision to deliver the baby rather than spontaneous onset of labour.[20] Spontaneous preterm deliveries may be explained due to dose dependent effect of bile acid on myometrial contractibility. Studies have demonstrated that serum bile acids, particularly colic acid, enhance the expression of oxytocin receptor and myometrial responsiveness to oxytocin.[17,21]

Thirty six (22%) neonates were admitted to NICU with the most frequent cause being RDS or TTN in 50% of the admitted neonates followed by neonatal sepsis in 27.8%. The rate of NICU admission was lesser than that previously reported from Nepal by Pokhrel et al in which meconium stained liquor (32.5%) was the main reason for NICU admission.[8] Bile acids are known to cause an increase in colonic motility, which could be a possible explanation for meconium passage. Alternatively, bile acids may lead to fetal distress and subsequent meconium passage.[10] The predictors of adverse perinatal outcomes as reported by previous studies were gestational age (< 30 weeks), raised serum total bile acids (TBA) level, increased AST and alkaline phosphatise (ALP).[22,23] In our study, only delivery at <34 weeks POG was the significant independent predictor of adverse neonatal outcome. However, the adverse neonatal outcome of prematurity and that due to ICP can be overlapping as prematurity itself is the cause of various adverse neonatal outcomes. So, we cannot conclude that adverse neonatal outcomes among neonates delivered before 34 weeks of gestation could solely be attributed to ICP.

The major limitation in our study was that we could not report the measurements of serum bile acids in patients with ICP. In addition, the gestational age at which ICP was diagnosed in each patient could not be reported due to missing data in significant number of cases during the retrospective study. The laboratory findings of each patient including LFTs were of pre-delivery admission time. So, the women who were already diagnosed as ICP and started medication could have lower values of LFT than the actual values during the time of diagnosis. Even though RCOG has recommended post-natal monitoring of LFT on a follow up basis, we couldn't retrieve any data regarding follow up in our study.

CONCLUSIONS

The significant prevalence of ICP among pregnant women in our setting needs timely special attention. As this could be a cause of adverse pregnancy outcomes, early diagnosis and timely intervention is required to reduce the perinatal morbidity associated with ICP.

ACKNOWLEDGEMENTS

Department of Obstetrics and Gynecology, Chitwan Medical College, Chitwan, Nepal

Author Affiliations

[1]Department of Obstetrics and Gynecology, Chitwan Medical College, Bharatpur, Chitwan, Bagmati Province, Nepal

[2]Department of Biochemistry, Chitwan Medical College, Bharatpur, Chitwan, Bagmati Province, Nepal

Competing interests: None declared

REFERENCES

1. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol. 2014;124(1):120-33. [PubMed][Article]
2. Gao XX, Ye MY, Liu Y, Li JY, Li L, Chen W, et al. Prevalence and risk factors of intrahepatic cholestasis of pregnancy in a Chinese population. Sci Rep. 2020;10(1):16307. [PubMed] [DownloadPDF] [Article]
3. Abedin P, Weaver JB, Egginton E. Intrahepatic cholestasis of pregnancy: prevalence and ethnic distribution. Ethn Health. 1999;4(1-2):35-7. [PubMed][Article]
4. Sharma N, Panda S, Singh AS. Obstetric Outcome During an Era of Active Management for Obstetrics Cholestasis. J Obstet Gynaecol India. 2016;66(Suppl 1):38-41. [PubMed][DownloadPDF][Article]
5. Hafeez M, Ansari A, Parveen 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):203-6. [PubMed][DownloadPDF]
6. 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. [PubMed][Article]
7. Berg B, Helm G, Petersohn L, Tryding N. Cholestasis of pregnancy. Clinical and laboratory studies. Acta Obstet Gynaecol Scand. 1986;65(2):107-13. [PubMed][Article]
8. Pokhrel GS, Ghimire A, Jha G, Chhetry M, Kumar M. Feto-Maternal outcomes in Intrahepatic Cholestasis in Pregnancy in a Tertiary Care Centre in Eastern Nepal. JoNMC [Internet]. 23Sep.2016 [cited 10Oct.2020] (5(1)):20-5. [Article][DOI]
9. 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 (London, England). 2019;393(10174):899-909. [PubMed][PMC][Article]
10. 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 (Baltimore, Md). 2014;59(4):1482-91. [PubMed][DownloadPDF] [DOI]
11. Fisk NM, Storey GN. Fetal outcome in obstetric cholestasis. Br J Obstet Gynaecol. 1988;95(11):1137-43. [PubMed] [Article]
12. Bicocca MJ, Sperling JD, Chauhan SP. Intrahepatic cholestasis of pregnancy: Review of six national and regional guidelines. Eur J Obstet Gynecol Reprod Biol. 2018;231:180-7. [PubMed][Article]
13. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol. 2009;15(17):2049-66. [PubMed][DownloadPDF] [Article]
14. Pusl T, Beuers U. Intrahepatic cholestasis of pregnancy. Orphanet J Rare Dis. 2007;2:26. [PubMed] [DownloadPDF] [Article]
15. Gardiner FW, McCuaig R, Arthur C, Carins T, Morton A. The prevalence and pregnancy outcomes of intrahepatic cholestasis of pregnancy: A retrospective clinical audit review. Obstet Med. 2019;12(3):123-8. [PubMed] [DownloadPDF] [DOI]
16. Shrestha NS, Panta S. Pregnancy outcome in obstetric cholestasis of pregnancy with active management. Nepal Journal of Obstetrics and Gynaecology. 2017;12(2):32-5. [Article]
17. Çelik S, Çalışkan CS, Çelik H, Güçlü M, Başbuğ A. Predictors of adverse perinatal outcomes in intrahepatic cholestasis of pregnancy. Ginekol Pol. 2019;90(4):217-22. [PubMed] [Article]
18. 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 : an international journal of obstetrics and gynaecology. 2013;120(6):717-23. [PubMed][Article]
19. Puljic A, Kim E, Page J, Esakoff T, Shaffer B, LaCoursiere DY, et al. 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(5):667.e1-5. [PubMed] [Article]
20. RCOG. Obstetric Cholestasis. Green-top Guideline No. 43. 2011. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg43/

21. 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.[PubMed] [Article]

22. Mei Y, Gao L, Lin Y, Luo D, Zhou X, He L. Predictors of adverse perinatal outcomes in intrahepatic cholestasis of pregnancy with dichorionic diamniotic twin pregnancies. J Matern Fetal Neonatal Med. 2019;32(3):472-6.[PubMed] [Article]

23. 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.[PubMed] [DownloadPDF] [Article]