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RESEARCH ARTICLE

Maternal and Neonatal Outcomes in Intrahepatic Cholestasis of Pregnancy: A Case-Control Study

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Abstract: ***Background***: The objectives of this study are to evaluate maternal and neonatal outcomes linked to Intrahepatic Cholestasis of Pregnancy (IHCP), a liver disorder unique to pregnancy that usually occurs in the second or third trimester. Characterized mainly by itching and elevated bile acids, IHCP is associated with complications such as preterm birth, fetal distress, and higher cesarean section rates. This case-control study was conducted at Saveetha Medical College and Research Institute and involved 184 pregnant women: 92 with IHCP and 92 controls. Patients were monitored from diagnosis and followed for three weeks postpartum. IHCP was diagnosed based on clinical symptoms and bile acid levels exceeding 10 µmol/L. The IHCP group showed significantly higher liver enzymes, bilirubin, and bile acids. Maternal outcomes included increased preterm births (27.17% vs. 14.13%, p=0.045) and cesarean deliveries. Neonatal complications were also more common in the IHCP group, including fetal distress (25% vs. 13.04%, p=0.035), more NICU admissions (7.61% vs. 3.26%, p=0.045), lower APGAR scores, and unexpectedly higher birth weights. Stratified analysis indicated worse outcomes in women with bile acid levels of ≥40 µmol/L. These findings highlight the importance of early detection and monitoring in IHCP to reduce complications. Bile acid levels are crucial prognostic markers that may reflect metabolic effects on fetal growth, warranting further research to understand these mechanisms and improve outcomes for this high-risk group.

Keywords: Intrahepatic Cholestasis of Pregnancy (IHCP), Maternal and Neonatal Outcomes, Serum Bile Acids, Pregnancy-Related Liver Disorder, Fetal Complications, Obstetric Outcomes.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (IHCP) is a liver disorder that affects pregnancies, approximately 0.5% to 1.5% worldwide [1]. This condition is most commonly observed during the second and third trimesters and is clinically characterized by generalized pruritus (without a rash)—especially on the palms and soles—accompanied by elevated serum bile acid levels and abnormal liver function tests [2]. Although the exact pathogenesis remains unclear, current evidence suggests that a combination of genetic predisposition, hormonal factors, and environmental influences contributes to its development [3]. Notably, elevated levels of oestrogen and progesterone metabolites during late pregnancy may disrupt hepatocellular bile acid transport mechanisms, resulting in cholestasis.

IHCP shows considerable risks to both maternal and fetal health. The condition has been associated with an increased incidence of adverse fetal outcomes such as spontaneous preterm birth, fetal distress, meconium-stained amniotic fluid, and, in extreme cases, fetal demise [4]. Pregnancy complications, including elevated levels of labor induction and cesarean delivery, have been observed to reduce anticipated harm to the fetus [5]. Probably, a direct correlation has been identified between elevated maternal bile acid levels in blood and the severity of fetal complications, underscoring the necessity of early diagnosis, vigilant monitoring, and appropriate obstetric interventions to optimize fetal and neonatal outcomes [6].

Despite the correlations that are currently in place, on outcomes of IHCP in Indian pregnant women, there is minimal data available on the clinical profile. Differences in genetic makeup, environmental exposures, and healthcare practices necessitate region-specific investigations to understand the condition's implications better. Identifying this gap, the study aims to explore differences in maternal liver function parameters and determine how IHCP influences the frequency of preterm births and the mode of delivery compared with controls. Furthermore, it seeks to assess the burden of adverse neonatal outcomes, including NICU admissions, fetal distress, and changes in birth weight. Additionally, the study investigates the relationship between the severity of IHCP, classified based on bile acid concentrations, and maternal and neonatal outcomes.

By addressing these objectives through a well-defined case-control design, this investigation aims to generate clinically relevant insights that can guide antenatal surveillance, risk stratification, and management protocols for IHCP in Indian clinical settings. The findings are expected to enrich the existing body of knowledge while supporting evidence-based strategies aimed at improving outcomes for both mothers and their infants.

MATERIALS AND METHODS

This is a hospital-based, analytical, observational case–control study with cases and controls matched by gestational age and parity in a 1:1 ratio. This comparative case-control study model aimed to assess maternal and neonatal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy (IHCP). The study was conducted in the Department of Obstetrics and Gynaecology at Saveetha Medical College and Research Institute between January 2023 and December 2024. Recruitment of participants, exposure assessment based on biochemical and clinical diagnostic criteria, and prospective perinatal follow-up continued through pregnancy until three weeks postpartum. Data collection included demographic details, clinical history, biochemical investigations, and clinically significant perinatal outcomes.

Pregnant women diagnosed with IHCP based on clinical presentation (pruritus) and elevated bile acid levels (>10 µmol/L) and/or abnormal liver function tests were included as cases. Healthy pregnant women without IHCP, matched for gestational age (±1 week) and parity, were considered controls. Women with pre-existing liver diseases, viral hepatitis, preeclampsia, haemolysis-elevated liver enzymes-low platelet count (HELLP) syndrome, and multiple pregnancies were excluded. A 1:1 matching ratio was followed in this study to control for confounding by gestational age and parity, enhancing internal validity.

The number of factors was examined in this study, which includes neonatal outcomes, including NICU admission, fetal distress, birth weight, and APGAR scores, as well as maternal outcomes such as preterm birth, mode of delivery, and liver function parameters. Predictors such as maternal age, parity, and gestational age at diagnosis were assessed, while risk factors, including maternal BMI, gestational diabetes, and hypertension, were considered. Based on the Bile acid levels, the severity of IHCP is classified into two categories: mild (<40 µmol/L) and severe (≥40 µmol/L) for stratified analysis.

Clinical history was abstracted from standardized patient medical records, and laboratory values were obtained using validated hospital reporting systems. Neonatal parameters were recorded at birth using uniform protocols. Selection bias was minimized through the use of strict inclusion and exclusion criteria, as well as gestational age– and parity–matched recruitment. Information bias was minimized through the use of structured data extraction and standardized biochemical assays. Confounding variables were statistically controlled using conditional logistic regression modelling.

priori power analysis was used to determine the sample size, assuming a 90% confidence level and 65% power. Based on prior data, the expected prevalence of preterm birth in IHCP was estimated at 26% versus 14% in controls. For a total of 184 participants, Standard formulas were used to calculate the required sample size of 92 matched cases and 92 controls.

DATA ANALYSIS:

SPSS version 25.0 was used to conduct data analysis. Based on the data distribution, the student's t-test or the Mann-Whitney U test was used to analyze continuous variables, such as gestational age, liver enzyme levels, and birth weight. By using The Chi-square test or Fisher's exact test as appropriate, Categorical variables, including preterm birth and NICU admission, were compared. Statistically significant is described as a two-tailed p-value <0.05. Considering the severity, the IHCP Subgroup analysis was performed to assess its differential impact on maternal and neonatal outcomes. Sensitivity analyses, including the exclusion of borderline bile acid levels, were conducted to test the robustness of results. Multiple imputation techniques were used to address the Missing values. A reliable assessment of IHCP-associated maternal outcomes and neonatal outcomes was made possible by this precise methodological approach, which provides high internal validity and reduced bias.

RESULTS AND OBSERVATIONS:

After 220 pregnant women were assessed for eligibility, 184 met the inclusion criteria and were enrolled in the study. Out of these, 92 were diagnosed with IHCP (case group), and 92 were healthy pregnant women (control group). Thirty-six women were excluded due to pre-existing liver diseases (n = 12), viral hepatitis (n = 10), preeclampsia (n = 8), or multiple pregnancies (n = 6). All enrolled participants completed follow-up through delivery and the postpartum period, and their data were analysed.

The mean maternal age was 29.89 ± 4.35 years in the IHCP group, whereas the control group had a mean maternal age of 29.70 ± 4.33 years (Table 1). The groups were similar in terms of body mass index (BMI), parity distribution, and gestational age at the time of participation. As compared to the controls, serum bile acid levels and liver function markers were significantly higher in the (IHCP). When comparing IHCP cases to controls Liver function tests indicated significantly elevated bilirubin levels (0.80 ± 0.07 mg/dL vs. 0.40 ± 0.03 mg/dL, p = 0.0001), AST (245.30 ± 137.20 IU/L vs. 39.20 ± 16.10 IU/L, p = 0.0001), ALT (190.30 ± 107.20 IU/L vs. 39.30 ± 9.30 IU/L, p = 0.0001), and serum bile acids (32.00 ± 7.30 µmol/L vs. 15.00 ± 3.20 µmol/L, p = 0.0001) in IHCP cases compared to controls (Table 2). Among the IHCP group, 27.17% experienced preterm delivery compared to 14.13% in the control group. The frequency of cesarean section was

slightly higher in the IHCP group (56.52%) than in controls (45.66%) (Table 3). Neonatal complications, including fetal distress, low birth weight, and NICU admissions, were significantly more common in the IHCP group. Compared to controls (37.24 ± 1.90 weeks) (p = 0.015) the IHCP cases (36.63 ± 2.57 weeks) had been significantly lower in usual gestational age at delivery. The IHCP group probably had a higher risk of preterm birth (p = 0.045), as well as a greater frequency of NICU admissions (7.61% vs. 3.26%, p = 0.045) and fetal distress (25.00% vs. 13.04%, p = 0.035). The ICHP group had significantly reduced mean birth weight (3.30 ± 0.48 kg vs. 3.11 ± 0.33 kg, p = 0.027), and lower APGAR scores at 5 minutes (8.00 ± 0.92 vs. 9.00 ± 0.83, p = 0.018) (Table 4). According to Subgroup analysis severity of IHCP (mild: bile acid levels <40 µmol/L; severe: ≥40 µmol/L) indicated a higher risk of adverse perinatal outcomes in the severe IHCP subgroup susceptibility analyses, excluding borderline bile acid level cases, confirmed the robustness of these findings. The data support a significant association between IHCP and adverse maternal and neonatal outcomes, emphasizing the importance of close monitoring and timely intervention.

Table 1: Age Distribution of IHCP and Control Groups

Group	Count	Mean Age (Years)	Std Dev	Min Age	Max Age
IHCP	92	29.89	4.35	21	40
Control	92	29.7	4.33	21	39

Table 2: Comparison of Liver Function Parameters Between IHCP and Control Groups

Parameter	IHCP (Mean ± SD)	Control (Mean ± SD)	P-value
Bilirubin Levels (mg/dl)	0.80 ± 0.07	0.40 ± 0.03	0.0001
Serum AST (IU/L)	245.30 ± 137.20	39.20 ± 16.10	
Serum ALT (IU/L)	190.30 ± 107.20	39.30 ± 9.30	
Serum ALP (IU/L)	378.50 ± 116.30	127.20 ± 12.30	
Serum Bile Acids (µMol/L)	32.00 ± 7.30	15.00 ± 3.20	

Table 3: Obstetric Outcomes

Parameter	IHCP (n=92)	Control (n=92)	P-value
Mean Gestational Age (Weeks)	36.63 ± 2.57	37.24 ± 1.90	0.015
Preterm Delivery (%)	25 (27.17%)	13 (14.13%)	0.045
Vaginal Delivery (%)	40 (43.48%)	50 (54.34%)	0.089
LSCS (%)	52 (56.52%)	42 (45.66%)	0.089

Table 4: Neonatal Outcomes

Parameter	IHCP (n=92)	Control (n=92)	P-value
Uneventful Outcome (%)	34 (36.96%)	64 (69.57%)	0.0012
NICU Stay (%)	7 (7.61%)	3 (3.26%)	0.045
Preterm Birth (%)	25 (27.17%)	13 (14.13%)	0.045
Fetal Distress (%)	23 (25.00%)	12 (13.04%)	0.035
Mean Birth Weight (kg)	3.30 ± 0.48	3.11 ± 0.33	0.027
APGAR Score (Mean ± SD)	8.00 ± 0.92	9.00 ± 0.83	0.018

DISCUSSION

Applying rigorous 1:1 matching of cases and controls based on gestational age and parity, this hospital-based analytical observational case-control study conducted at Saveetha Medical College and Research Institute aimed to examine maternal and neonatal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy (IHCP). Our findings substantiate the hypothesis that IHCP has significant effects on perinatal health, evidenced by a higher prevalence of adverse maternal and neonatal outcomes in the affected cohort compared to matched controls [1, 4, 6]. The study carefully excluded potential confounders such as viral hepatitis, preeclampsia, HELLP syndrome, and multiple pregnancies, ensuring a focused evaluation of IHCP-related risks [2, 12].

The biochemical profile of women with IHCP showed a significant increase in liver enzymes (AST, ALT, and ALP), serum bilirubin, and bile acids, consistent with the pathophysiology of cholestasis [1, 2, 3, and 16]. These findings describe the hepatic dysfunction inherent to IHCP and support the clinical diagnostic criteria used in the study [14]. The mean serum bile acid levels in the IHCP group (32.00 ± 7.30 µmol/L) were significantly higher than those in controls (15.00 ± 3.20 µmol/L), with this increase accompanied by substantial rises in AST, ALT, and bilirubin, all with strong statistical significance (p < 0.0001). These elevations are not only diagnostic but also clinically important, as shown by their correlation with adverse maternal and neonatal outcomes [4, 7].

Gestational age at delivery was significantly lower in the IHCP group (36.63 ± 2.57 weeks) compared to controls (37.24 ± 1.90 weeks), as shown by maternal outcomes, reflecting an increased risk of medically indicated or spontaneous preterm births [5,6,11]. This was supported by the significantly higher incidence of preterm deliveries in the IHCP group (27.17%) compared to the control group (14.13%; p = 0.045). Although the rate of cesarean section was higher in the IHCP cohort (56.52% vs. 45.66%), this difference did not reach statistical significance (p = 0.089), suggesting that clinical judgment regarding mode of delivery may be influenced by fetal distress or timing of labor induction rather than IHCP alone [9, 8].

The IHCP group experienced a higher range of complications, particularly neonatal outcomes, which were notable. NICU admissions were also higher, 7.61% of IHCP cases versus 3.26% of controls (p = 0.045), and fetal distress was significantly more frequent among neonates born to mothers with IHCP (25.00% vs. 13.04%; p = 0.035) [4, 7, 11]. These findings reinforce the importance of close fetal monitoring in pregnancies complicated by IHCP [17]. Furthermore, the APGAR scores at 5 minutes were significantly lower in the IHCP group (8.00 ± 0.92) compared to the control group (9.00 ± 0.83; p = 0.018), supporting the clinical relevance of intrauterine exposure to elevated bile acids and hepatic dysfunction [3, 4].

One particularly intriguing result was the significantly higher mean birth weight observed in the IHCP group (3.30 ± 0.48 kg) compared to controls (3.11 ± 0.33 kg; p = 0.027 This finding might suggest different fetal growth dynamics in IHCP pregnancies and challenges conventional concerns about fetal growth restriction in cholestasis [6,15]. Our results align with new research suggesting that placental compensation, altered maternal lipid metabolism, or improved nutrient transport may contribute to increased fetal growth in some IHCP cases, despite previous studies showing a risk for small-for-gestational-age neonates [15,18]. This clinical contradiction elevates the need for detailed mechanistic studies, focusing on placental pathology and metabolic interactions between mother and fetus.

Subgroup analysis by disease severity revealed that higher bile acid levels (≥40 µmol/L) were associated with a greater risk of adverse perinatal outcomes, including preterm delivery and NICU admission [4, 6, 7]. This dose-response relationship confirms the prognostic importance of bile acid stratification in clinical management. Moreover, the sensitivity analyses further strengthened the robustness and internal validity of our conclusions, as they excluded borderline bile acid levels, yielding consistent results [7, 10].

The methodological strengths of this study lie in its careful matching strategy, exclusion of confounders, and comprehensive assessment of both maternal and neonatal outcomes. Maternal age, parity, and gestational age. By adjusting these factors and addressing information and selection bias through standardized data collection and laboratory assays, we ensured high data integrity [8, 14]. A more complicated comprehension of IHCP severity and its clinical implications was made possible by the use of conditional logistic regression and subgroup analysis. This method preserved the generalizability to a larger obstetric population while enabling an accurate assessment of relative risk [13].

CONCLUSION

According to the study, IHCP has been estimated to be a serious obstetric disorder associated with elevated risks of adverse maternal and neonatal outcomes. This exhibits higher rates of preterm birth, fetal distress, and NICU admissions, along with significantly altered liver function and bile acid profiles. Pregnancy affected by IHCP highlights the significance of early detection, diagnosis, close follow-up surveillance, and gestation-specific therapeutic intervention.

The marked lower gestational age at delivery and lower APGAR scores observed in the IHCP group emphasize the potential for compromised fetal well-being, which supports the need for intensified antenatal monitoring. Primarily, the observed higher birth weight in the IHCP group presents new research opportunities regarding metabolic and placental adaptations in cholestasis pregnancies. Whether this finding reflects a genuine increase in fetal growth potential or a compensatory response to hepatic dysfunction remains to be determined.

Clinically, this study highlights the significance of bile acid levels not only as a diagnostic tool but also as a predictor of disease severity and risk for newborns. The observed dose-response relationship between bile acid concentration and maternal and fetal outcomes proposes that even minimal elevations necessitate close follow-up and possibly pre-emptive intervention. Furthermore, this study supports the need for individualized delivery planning based on both biochemical and clinical indicators.

Moving forward, research should focus on understanding the mechanistic causes of increased fetal weight in IHCP and examining long-term developmental outcomes in newborns exposed to higher maternal bile acids. Predictive models and management strategies have advanced through multicenter studies that include larger, more diverse populations and placental biomarker assessments. Clinical trials aimed at improving bile acid-lowering treatments and identifying the best timing for delivery could also offer vital guidance to improve maternal and neonatal health.

In conclusion, our findings underscore the importance of recognizing IHCP as a condition with substantial clinical

implications. The data support a preventive approach to diagnosis and management, guided by bile acid levels and maternal liver function, to optimize fetal well-being in pregnancies complicated by cholestasis and to point out the risk of adverse perinatal outcomes.

AUTHOR'S CONTRIBUTIONS

Conceptualization, Design, Data collection, Statistical analysis, Manuscript Preparation, Manuscript Editing, and Data interpretation: J. Lakshmi Samhitha, Nidhi Sharma, Bhargavi Beere, Vinod Kumar Nelson

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CONFLICTS OF INTEREST

The authors declare no conflict of interest among themselves

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REFERENCES

1. Geenes, V., Williamson, C., 2009, Intrahepatic cholestasis of pregnancy. World J Gastroenterol.7; 15(17):2049–66.
2. Lammert, F., Marschall, H. U., Glantz, A., Matern, S., 2000, intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. J Hepatol.33 (6):1012–21.
3. Ovadia, C., Williamson, C., 2016, intrahepatic cholestasis of pregnancy: Recent advances. Clin Dermatol. 34(3):327–34.
4. Glantz, A., Marschall, H. U., Mattsson, L. A., 2004, intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatol Baltim Md. 40(2):467–74.
5. Bacq, Y., Sapey, T., Bréchot, M. C., Pierre, F., Fignon, A., Dubois, F., 1997, intrahepatic cholestasis of pregnancy: a French prospective study. Hepatol Baltim Md. (2):358–64.
6. Geenes, V., Chappell, L. C., Seed, P. T., Steer, P. J., Knight, M., Williamson, C., 2014, Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatol Baltim Md. 59(4):1482–91.
7. Brouwers, L., Koster, M. P. H., Page-Christiaens, GCML, Kemperman, H., Boon, J., Evers, I. M., 2015, intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. A m J Obstet Gynecol. 212(1):100.e1-7.
8. Hagenbeck, C., Hamza, A., Kehl, S., Maul, H., Lammert, F., Keitel, V., 2021, Management of Intrahepatic Cholestasis of Pregnancy: Recommendations of the Working Group on Obstetrics and Prenatal Medicine – Section on Maternal Disorders. Geburtshilfe Frauenheilkd. 81(8):922–39.
9. Lee, R. H., Kwok, K. M., Ingles, S., Wilson, M. L., Mullin, P., Incerpi, M.,2008, Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. Am J Perinatol. 25(6):341–5.
10. Martineau, M., Raker, C., Powrie, R., Williamson, C., 2014, Intrahepatic cholestasis of pregnancy is associated with an increased risk of gestational diabetes. Eur J Obstet Gynecol Reprod Biol.176 (5):80–5.
11. Kawakita, T., Parikh, L. I., Ramsey, P. S., Huang, C. C., Zeymo, A., Fernandez, M., 2015, Predictors of adverse neonatal outcomes in intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol.213 (4):570.e1-8.
12. Ozkan, S., Ceylan, Y., Ozkan, O. V., Yildirim, S., Review of a challenging clinical issue: 2015, Intrahepatic cholestasis of pregnancy. World J Gastroenterol W J G. 21; 21(23):7134–41.
13. Chappell, L. C., Bell, J. L., Smith, A., Linsell, L., Juszczak, E., Dixon, P. H., 2019,Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. Lancet Lond Engl. 7; 394 (10201):849–60.
14. Pillarisetty, L. S., Sharma, A., 2025, Pregnancy Intrahepatic Cholestasis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; [cited 2025 Feb 17]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK551503/
15. Papacleovoulou, G., Abu-Hayyeh, S., Nikolopoulou, E., Briz, O., Owen, BM., Nikolova, V., 2013, Maternal cholestasis during pregnancy programs metabolic disease in offspring. J Clin Invest. 123(7):3172–81.
16. Majsterek, M., Wierzchowska-Opoka, M., Makosz, I., Kreczyńska, L., Kimber-Trojna,r Ż., Leszczyńska-Gorzelak ,B.,2022, Bile Acids in Intrahepatic Cholestasis of Pregnancy. Diagn Basel Switz. 12(11):2746.
17. Kwon, J. Y., Park, I. Y., 2016, fetal heart rate monitoring: from Doppler to computerized analysis. Obstet Gynecol Sci. 59(2):79–84.
18. Kuper, S. G., Abramovici, A. R., Jauk, V. C., Harper ,L. M., Biggio, J. R., Tita ,A . T.,2017, The effect of omega-3 supplementation on pregnancy outcomes by smoking status. Am J Obstet Gynecol. 217(4):476.e1-476.e6.