



Original Article

Challenging the safety of progesterone supplementation: is it associated with early-onset intrahepatic cholestasis of pregnancy

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ABSTRACT

BACKGROUND & OBJECTIVE: Intrahepatic cholestasis of pregnancy (ICP) is a gestational problem causing liver dysfunction characterized by itching, biochemical evidence of raised bile acids, and altered liver enzymes (LFTs). It is associated with serious perinatal outcomes. The objective of the study is to evaluate whether exogenous progesterone use during pregnancy is associated with ICP and adverse perinatal outcomes.

METHODOLOGY: This retrospective case-control study was carried out at Sadiq Abbasi Hospital, Bahawalpur, from February 2021 to December 2023. The cases were pregnant women diagnosed with ICP, and the controls were pregnant women who did not have ICP. Data included demographics, progesterone supplementation, obstetric outcomes, and biochemical markers. Associations were interpreted using Chi-square/Fisher's exact tests and multivariable logistic regression adjusted for maternal age, BMI, parity, and prior ICP.

RESULTS: Women with ICP have received more progesterone than controls (52% vs 20%, $p < 0.001$). Progesterone support in the first trimester was related to an increased risk of ICP (aOR 2.8, 95% CI: 1.9–4.1, $p < 0.001$). The ICP group also delivered a higher incidence of preterm delivery (35% vs 12%, $p < 0.001$), lower birth weight neonates, and increased NICU admissions.

CONCLUSION: Progesterone supplementation, specifically in early pregnancy, is a risk factor for the development of ICP. This emphasizes the need for regular and careful checking of bile acid levels in women using exogenous progesterone, as it may elevate the odds of getting an early-onset ICP leading to obstetric complications.

KEYWORDS: Cholestasis, Intrahepatic, Progesterone, Bile Acids, Preterm Birth, Liver function tests.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder that typically develops during the second half of gestation. It is characterized by intense pruritus, elevated serum bile acid levels, and abnormal liver function tests (LFTs), with symptoms and biochemical abnormalities usually resolving after delivery^[1,2]. ICP is clinically significant because it increases the risk of adverse perinatal outcomes, including preterm birth, meconium-stained amniotic fluid, neonatal respiratory complications, and stillbirth, particularly in pregnancies with markedly elevated bile acid levels^[3]. Its reported prevalence ranges from 0.02% to 2.4% worldwide, with considerable variation across geographical regions and ethnic populations^[4].

The pathogenesis of ICP is multifactorial, involving genetic susceptibility and hormonal influences^[5]. Progesterone

metabolites, particularly sulfated progesterone derivatives, have attracted attention because of their potential role in disrupting bile acid homeostasis. These metabolites may interfere with the farnesoid X receptor (FXR)-mediated regulation of bile acid metabolism, contributing to bile acid accumulation and the development of ICP^[6,7]. This potential mechanism has raised concerns regarding exogenous progesterone supplementation, which is commonly prescribed for luteal support in assisted reproductive technology (ART), recurrent pregnancy loss, threatened miscarriage, and the prevention of preterm birth in selected patients^[8,9].

Emerging evidence suggests that progesterone supplementation, particularly at higher doses during early gestation, may be associated with the earlier onset of ICP, occasionally presenting as early as 15 weeks of pregnancy

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[10–12]. However, the extent to which this association varies by progesterone formulation, route of administration, dose, and duration remains poorly established. Given the potential consequences of ICP for maternal and fetal health, clarifying this relationship is important for optimizing progesterone use while preserving its established benefits in appropriately selected pregnancies [13,14].

Despite the widespread use of progesterone supplementation in obstetric practice, local evidence regarding its association with ICP, particularly early-onset disease, remains limited. Moreover, the influence of progesterone exposure during the first trimester on ICP development and subsequent perinatal outcomes requires further investigation [15,16]. Therefore, this study aimed to investigate the association between exogenous progesterone exposure, particularly during the first trimester, and the occurrence of ICP and adverse perinatal outcomes in our population. The findings may help identify areas requiring further research and inform the development of evidence-based progesterone prescribing strategies.

METHODOLOGY

We conducted a retrospective case-control study at Sadiq Abbasi Hospital/QAMC/Bahawal Victoria Hospital, Bahawalpur, Pakistan, from February 2021 to December 2023. A non-probability consecutive sampling technique was used. The sample size was calculated using an unmatched case-control design with a 1:2 case-to-control ratio. Based on Cendek et al., progesterone use was reported in 21.5% of ICP cases and 5.7% of controls [11]. Using a conservative expected exposure difference of 18% among cases and 7% among controls with a 95% confidence level, 80% power and alpha of 0.05, the minimum required sample size was 100 cases and 200 controls. Therefore, 300 participants were included in the study. Ethics approval was granted by the QAMC/BVH review committee (08/DME/QAMC Bahawalpur; Dated: 23/01/2025), and waiver of informed consent was approved.

Participants were pregnant women who received care and delivered at BVH. Cases had intrahepatic cholestasis of pregnancy defined by pruritus plus non-fasting serum bile acids $\geq 10 \mu\text{mol/L}$ and abnormal liver tests (ALT or AST $\geq 40 \text{ IU/L}$) using one laboratory method throughout. Early-onset ICP was defined as ICP diagnosed before 28 completed weeks of gestation. Controls were healthy pregnant women without ICP. We included singleton pregnancies and recorded progesterone exposure when started in the first or second trimester. Exposure details included route (oral micronized progesterone, vaginal/rectal pessary, intramuscular injection), initiation of use (gestational age, frequency, dose range and duration) as reported in medication charts. Dose was grouped by route of administration, and duration was measured in weeks from initiation to discontinuation.

Due to the lack of complete dose and duration data, the primary exposure variable was progesterone yes/no, with descriptive analyses of timing and route of administration. We excluded multiple gestations, fetal anomalies, pre-

existing liver or biliary disease (viral hepatitis, cirrhosis, autoimmune disease, gallstone disease), chronic conditions such as hypertension, pre-eclampsia, or diabetes, use of hepatotoxic drugs, progesterone initiated only in the third trimester, and pruritic or other dermatologic disorders. Data were abstracted from charts and electronic records, including demographics, obstetric history, biochemistry (peak bile acids, ALT, AST, bilirubin), and perinatal outcomes. Analyses used SPSS v 25.

Continuous variables were summarized as mean $\pm$ SD or median (IQR) after Shapiro–Wilk testing and compared with t-tests or Mann–Whitney U tests. Categorical data were reported as n (%) and compared with chi-square or Fisher's exact tests. We fitted multivariable logistic regression to assess the association between progesterone exposure and ICP, adjusting for maternal age, BMI, parity, and prior ICP. Two-sided $p < 0.05$ indicated statistical significance.

RESULTS

A total of 300 pregnant women were part of this study: 100 women diagnosed with ICP and 200 healthy pregnant women as controls. Analysis was done for the demographic data, progesterone intake, and perinatal outcomes between the two groups, as expressed in the tables below.

Amongst the demographic data as written in Table-I, maternal age and BMI were almost the same in both the ICP and control groups. However, nulliparous women were significantly more common in the ICP group (48%) as compared to the control group (28%) ($p < 0.001$).

Table-I: Demographic characteristics of study participants.

Variables	Categories/ units	ICP Group (n=100)	Control Group (n=200)	P-value
Maternal Age	Years	29.5 $\pm$ 4.2	28.9 $\pm$ 3.8	0.45 *
BMI	kg/m ²	27.4 $\pm$ 3.1	26.9 $\pm$ 2.9	0.31 *
Parity Nulliparous , n (%)	Yes	48 (48.0)	56 (28.0)	<0.001 **
	No	52 (52.0)	144 (72.0)	

***Continuous variables compared with independent samples t-test.**

****Categorical variable compared with chi-square (χ^2) test.**

Table-II demonstrates a significant association between the use of progesterone and ICP. Almost half of the women in the ICP group (52%) received progesterone during pregnancy, compared to only 20% of the control group ($p < 0.001$). Notably, most of the ICP group who received progesterone did so in the first trimester (70%). Of the 52 progesterone-exposed ICP cases, 28 (53.8%) had early-onset ICP compared to 12 of 48 non-exposed ICP cases (25.0%), which indicated that progesterone may increase the risk of early-onset ICP.

Table-II: Progesterone use and timing/route by group.

Variables	Response	ICP Group (n=100) n(%)	Control Group (n=200) n(%)	P-value
Progesterone use	Yes	52 (52.0)	40 (20.0)	< 0.001 (χ^2)
	No	48 (48.0)	160 (80.0)	
Route among those with progesterone	Oral	11 (11.0)	12 (6.0)	—
	Vaginal	23 (23.0)	20 (10.0)	—
	Intramuscular	14 (14.0)	8 (4.0)	—
	Dual	4 (4.0)	0 (0.0)	—
Trimester at initiation	First trimester	36 (36.0)	—	—
	Second trimester	16 (16.0)	—	

Values are n (%). Progesterone use was compared with the chi-square (χ^2) test. Timing and route are descriptive among exposed women only.

Table-III: Obstetric and Neonatal Outcomes.

Outcome	Response	ICP Group (n=100) n(%)	Control Group (n=200) n(%)	P-value
Preterm birth <37 weeks	Yes	35 (35.0)	24 (12.0)	<0.001**
	No	65 (65.0)	176 (88.0)	
NICU admission,	Yes	25 (25.0)	20 (10.0)	0.002**
	No	75 (75.0)	180 (90.0)	
Meconium-stained amniotic fluid	Yes	15 (15.0)	10 (5.0)	0.010**
	No	85 (85.0)	190 (95.0)	
Gestational age at delivery (weeks)	Mean±SD	36.8 ± 1.7	38.4 ± 1.2	<0.001 *
Birthweight (g)	Mean±SD	2900 ± 350	3200 ± 370	<0.001 *

*Continuous variables compared with independent-samples t-test.

** Categorical variables compared with chi-square (χ^2) test.

The medical record lacked complete dose and duration data. Thus, we could not reliably perform a formal dose-response analysis. In women for whom exposure data were available, it was found that progesterone was most commonly started in the first trimester in ICP cases. This finding suggests that the timing of exposure is important. However, larger prospective studies are needed with accurate dose and duration information to determine a dose-response relationship.

Obstetric outcomes, including gestational age at delivery, birth weight, and neonatal intensive care unit (NICU) admissions, are summarized in Table-III. The mean gestational age at delivery was significantly lower in the ICP group (36.8 ± 1.7 weeks) compared to the control group (38.4 ± 1.2 weeks) ($p < 0.001$). The incidence of preterm delivery was higher in the ICP group (35%) compared to the control group (12%) ($p < 0.001$). Additionally, neonates born to women with ICP had lower birth weights (2900 ± 350 g) and a higher rate of NICU admission (25%) compared to the control group (10%) ($p = 0.002$). The occurrence of meconium-stained amniotic fluid was also more frequent in the ICP group (15%) compared to the control group (5%) ($p = 0.01$).

The results of biochemical analyses are summarized in Table-IV, which shows significantly higher serum bile acid levels in the ICP group (mean 21.3 ± 8.7 μ mol/L) compared to the control group (5.2 ± 2.1 μ mol/L) ($p < 0.001$). Liver function tests (ALT and AST levels) were also significantly elevated in the ICP group (ALT: 76.5 ± 21.1 IU/L; AST: 82.3 ± 18.9 IU/L) compared to the control group (ALT: 24.8 ± 9.4 IU/L; AST: 26.2 ± 7.6 IU/L) ($p < 0.001$ for both).

In multivariable logistic regression, progesterone supplementation was independently associated with ICP (OR 2.8; 95% CI 1.9–4.1; $p < 0.001$), adjusting for maternal age, BMI, parity, and prior ICP. Nulliparity was also associated with ICP (OR 1.9; 95% CI 1.3–2.8; $p = 0.002$). Table-V shows the adjusted associations from the multivariable logistic regression for factors associated with ICP.

These results strongly suggest that progesterone supplementation, particularly in the first trimester, is associated with an increased risk of developing ICP. Further research is warranted to establish optimal progesterone dosing and timing to reduce the risk of ICP while still providing benefits for pregnancy maintenance.

Table-IV: Biochemical Markers in ICP and Control Groups..

Biochemical Marker	ICP Group (n=100) Mean $\pm$ SD	Control Group (n=200) Mean $\pm$ SD	P-value
Serum bile acids ($\mu\text{mol/L}$)	21.3 $\pm$ 8.7	5.2 $\pm$ 2.1	< 0.001
ALT (IU/L)	76.5 $\pm$ 21.1	24.8 $\pm$ 9.4	< 0.001
AST (IU/L)	82.3 $\pm$ 18.9	26.2 $\pm$ 7.6	< 0.001

Table-V: Multivariable Logistic Regression for ICP (dependent variable: ICP yes/no).

Variable	OR	95% CI	P-value
Progesterone supplementation	2.8	1.9–4.1	<0.001
Nulliparity	1.9	1.3–2.8	0.002
Maternal age (per year)	1.02	0.99–1.05	0.12
BMI (per kg/m^2)	1.03	0.98–1.08	0.21
Prior ICP	3.2	1.5–6.8	0.003

DISCUSSION

This study demonstrated a significant association between exogenous progesterone supplementation and intrahepatic cholestasis of pregnancy (ICP). Progesterone use was reported in 52% of ICP cases compared with 20% of controls, and the association remained significant after adjustment for maternal age, BMI, parity, and previous ICP (aOR 2.8; 95% CI: 1.9–4.1; $p < 0.001$). Furthermore, early-onset ICP occurred in 53.8% of progesterone-exposed cases compared with 25.0% of non-exposed cases. These findings are consistent with previous research suggesting that progesterone metabolites may contribute to ICP through disturbances in bile acid homeostasis and farnesoid X receptor (FXR) signaling^[11]. However, the retrospective design does not establish a causal relationship.

Biochemical findings further supported the diagnosis of ICP. Mean serum bile acid levels were higher in cases than controls (21.3 $\pm$ 8.7 vs. 5.2 $\pm$ 2.1 $\mu\text{mol/L}$), accompanied by significantly elevated ALT and AST levels. These results are consistent with the established biochemical characteristics of ICP^[1,5]. The study also identified higher rates of preterm birth (35% vs. 12%), NICU admission, meconium-stained amniotic fluid, and lower birth weight among ICP cases. These findings align with previously reported maternal and neonatal complications of ICP^[16]. Nevertheless, these outcomes should be attributed to the observed association with ICP rather than directly to progesterone exposure.

Among progesterone-exposed cases, vaginal administration was the most frequently reported route, followed by intramuscular and oral administration. However, these findings do not establish the relative risk associated with individual routes, doses, or treatment durations. Potential exposure misclassification may have occurred because some patients may have used multiple routes or changed routes during pregnancy. Further multicentre studies incorporating standardized exposure definitions and dose–response analyses are needed to clarify these relationships^[1,8].

Clinical Implications: These findings support careful assessment and monitoring of pregnant women receiving

progesterone, particularly those with a previous history of ICP or liver disease. However, progesterone remains indicated in selected obstetric conditions, and its potential association with ICP should be considered alongside its established clinical benefits. The present results do not justify routinely withholding progesterone, reducing its dose, or changing its route or timing. Prospective studies are needed to determine whether specific regimens or exposure periods are associated with increased ICP risk and to inform evidence-based prescribing and monitoring recommendations.

LIMITATIONS AND FUTURE RESEARCH: This study has some limitations. Firstly, the study design format is retrospective, so it has some default limitations of a retrospective study design, like data loss, recall bias, and misclassification of outcomes. Since this was a single-centre study, the results cannot be generalized. Moreover, not all the participants had exact dose and duration of progesterone; thus, it was not possible to determine a dose-response relationship. A detailed comparison of severity of cases with progesterone-exposed and non-exposed ICP cases based on categories of bile acids was also not done due to incomplete stratified data. To validate these findings and determine progesterone dose, duration, route, indication and ICP severity, larger multicenter prospective studies are required.

CONCLUSION

The study sheds light on a profound association between progesterone supplementation, particularly in the first trimester, and the development of ICP. Women receiving progesterone are at an increased risk of developing ICP, causing adverse obstetric and neonatal prognosis, including preterm delivery and NICU care. Hence, meticulous monitoring of LFT levels, which are tailored according to the history and disease of the patient, is required. The recurrence rates are very high in subsequent pregnancies, so one should have high suspicion and low thresholds for monitoring LFTs. More time and research investment is needed to agree on optimal dose and timings of progesterone administration, especially in the background of ICP.

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Author Contributions:

Saba Nadeem: Substantial contributions to the conception and design of the work.

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Salma Jabeen: Drafting the work.

Samina Mafia: Reviewing it critically for important intellectual content.

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