Original Research Paper

Volume - 15 | Issue - 05 | May - 2025 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Obstetrics & Gynaecology

PROGESTERONE ADMINISTRATION IN EARLY PREGNANCY AND ITS INCIDENCE ON INTRAHEPATIC CHOLESTASIS OF PREGNANCY: A PROSPECTIVE OBSERVATIONAL STUDY

Dr. Himanshi Pareek*	Junior Resident (Third Year), Department of Obstetrics & Gynaecology, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India. *Corresponding Author
Dr. Avneet Kaur Lally	Junior Resident (Third Year), Department of Obstetrics & Gynaecology, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.
Dr. SPS Goraya	Professor and Head of Unit, Department of Obstetrics & Gynaecology, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.
Dr. Komal Bansal	Senior Resident, Department of Obstetrics & Gynaecology, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.

ABSTRACT **Background:** Intrahepatic cholestasis of pregnancy (IHCP) is a liver disorder unique to pregnancy, often associated with adverse maternal and fetal outcomes. The increasing use of progesterone in early pregnancy has been linked to the development of intrahepatic cholestasis of pregnancy (IHCP) in later trimesters. **Objective:** To investigate the association between early pregnancy progesterone therapy and the incidence of IHCP. **Methods:** A prospective observational study was conducted over 18 months at a tertiary care center. A total of 120 pregnant women were divided into two groups: Group A (n=60) received progesterone, and Group B (n=60) did not. IHCP was diagnosed based on clinical symptoms and laboratory markers, including fasting bile acid levels >10 µmol/L. Outcomes such as the incidence of IHCP, meconium-stained liquor (MSL), respiratory distress syndrome (RDS), and preterm birth were compared. **Results:** IHCP incidence was significantly higher in Group A (78.3%) than in Group B (31.7%) ($p<0.001$). MSL was more common in Group A (43.3%) than in Group B (21.7%) ($p=0.012$). However, RDS (11.7% vs. 26.7%; $p=0.037$) and preterm birth (13.3% vs. 31.7%; $p=0.016$) were significantly lower in the progesterone group. **Conclusion:** While early pregnancy progesterone administration is associated with a higher incidence of IHCP, it appears to have a protective effect against RDS and preterm birth. These findings underscore the complex effects of progesterone therapy in pregnancy and warrant further research.

KEYWORDS : Intrahepatic cholestasis of pregnancy, progesterone, bile acids, pruritus

INTRODUCTION

Intrahepatic cholestasis of pregnancy (IHCP) is a liver disorder occurring in 0.2-2% of pregnancies, marked by pruritus and elevated serum bile acids, typically in the second or third trimester. IHCP is linked to adverse perinatal outcomes, including preterm birth, fetal distress, and stillbirth. While its exact cause is unclear, hormonal, genetic, and environmental factors likely contribute.

Progesterone therapy, commonly used to prevent early pregnancy loss, plays a role in maintaining endometrial receptivity and reducing uterine contractility. However, concerns exist about exogenous progesterone potentially inducing IHCP by altering bile acid metabolism and impairing hepatocellular bile acid transport. Its sulfated metabolites can inhibit key transporters like the bile salt export pump (BSEP) and farnesoid X receptor (FXR), impairing bile flow.

This study aims to prospectively evaluate the incidence of IHCP in women receiving early progesterone therapy compared to those without supplementation, clarifying the potential link and informing safer management of high-risk pregnancies.

MATERIALS AND METHODS

Study Design And Population

This prospective observational study was conducted over a period of 18 months (October 2023 to March 2025) at the Department of Obstetrics & Gynaecology, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala. Ethical approval was obtained from the Institutional Ethics Committee (IEC/MMIMSR/23-128) and written informed consent was obtained from all participants.

A total of 120 participants were stratified into two groups:

- **Group A:** 60 antenatal patients who received progesterone in early pregnancy (first trimester).
- **Group B:** 60 antenatal patients who did not receive progesterone.

The progesterone preparation used in Group A was natural micronized progesterone, administered vaginally/orally/intramuscularly at a dose of 300/300/500 mg respectively until 24 weeks of gestation.

Inclusion Criteria

- All antenatal patients visiting the Obstetrics OPD/IPD in their first trimester who were willing to participate in the study.

Exclusion Criteria

1. Patients with pre-existing liver disorders.
2. Patients with obstructive jaundice.
3. Patients with known hypersensitivity to progesterone.
4. Patient with primary or pregnancy related skin diseases.

Study Protocol

All participants underwent baseline assessments, including medical history, physical exam, and routine antenatal tests. Group A received progesterone therapy as per hospital protocol.

Participants were followed throughout their pregnancy with regular antenatal visits. Liver function tests were performed at baseline, 20 weeks, 28 weeks, and 34 weeks of gestation, or whenever clinically indicated. Patients presenting with pruritus underwent additional investigations, including serum bile acid levels.

Diagnostic Criteria for IHCP

Diagnosis of IHCP was established based on the presence of the following:

1. Pruritus predominantly affecting the palms and soles, without primary skin lesions, which resolves after delivery.
2. Elevated liver enzymes: Alanine aminotransferase (ALT) >40 IU/L and/or Aspartate aminotransferase (AST) >40 IU/L.
3. Elevated fasting total bile acid (TBA) levels exceeding 10 µmol/L.
4. Absence of other causes of liver dysfunction.

Outcome Measures

Primary Outcome:

- Incidence of IHCP in both groups.

Secondary Outcomes:

- Incidence of meconium-stained liquor (MSL).

- Incidence of respiratory distress syndrome (RDS) in neonates.
- Incidence of preterm birth (delivery before 37 completed weeks of gestation).

Statistical Analysis

Data were analyzed using SPSS Version 20.0. Continuous variables were expressed as Mean±SD, and categorical variables were summarized as frequencies and percentages. Chi-square tests were used for categorical variables, and independent t-tests were used for continuous variables. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The baseline characteristics of both groups are presented in Table 1. There were no significant differences between the groups regarding age, body mass index (BMI), parity, or baseline liver function tests.

Table 1: Baseline Characteristics Of Study Participants

Characteristic	Group A (Progesterone) (n=60)	Group B (Control) (n=60)	p-value
Age (years)	27.3 ± 4.5	26.8 ± 4.2	0.518
BMI (kg/m²)	24.6 ± 3.2	24.1 ± 3.4	0.417
Nulliparity, n (%)	32 (53.3%)	29 (48.3%)	0.584
Baseline LFT			
- ALT (IU/L)	21.4 ± 6.8	20.8 ± 7.2	0.639
- AST (IU/L)	20.2 ± 5.9	19.7 ± 6.3	0.656
- ALP (IU/L)	82.7 ± 15.6	80.3 ± 16.2	0.415
History of miscarriage, n (%)	18 (30.0%)	12 (20.0%)	0.207

Primary Outcome: IHCP Incidence

IHCP incidence was significantly higher in Group A (78.3%) than Group B (31.7%) (p<0.001).

Table 2: Incidence of IHCP and Laboratory Parameters

Parameter	Group A (Progesterone) (n=60)	Group B (Control) (n=60)	p-value
IHCP incidence, n (%)	47 (78.3%)	19 (31.7%)	<0.001
Gestational age at diagnosis (weeks)	28.6 ± 4.2	31.4 ± 3.8	0.011
Peak TBA (µmol/L)	32.8 ± 18.6	24.7 ± 12.3	0.043
Peak ALT (IU/L)	148.6 ± 72.4	112.3 ± 58.7	0.036
Peak AST (IU/L)	124.2 ± 58.3	92.5 ± 47.2	0.029

Group A with IHCP had earlier symptom onset (28.6 vs. 31.4 weeks; p=0.011) and higher peak bile acids and liver enzymes than Group B.

Clinical Presentation

The most common symptom in both groups was pruritus, particularly affecting the palms and soles. The severity of pruritus, as assessed using a visual analog scale (0-10), was significantly higher in Group A compared to Group B (7.4 ± 1.8 vs. 5.9 ± 2.1; p=0.008).

Secondary Outcomes

Secondary outcomes are compared between the two groups in Table 3.

Table 3: Comparison Of Secondary Outcomes

Outcome	Group A (Progesterone) (n=60)	Group B (Control) (n=60)	p-value
Meconium-stained liquor, n (%)	26 (43.3%)	13 (21.7%)	0.012
Respiratory distress syndrome, n (%)	7 (11.7%)	16 (26.7%)	0.037
Preterm birth, n (%)	8 (13.3%)	19 (31.7%)	0.016
Mean gestational age at delivery (weeks)	38.2 ± 1.6	37.4 ± 2.1	0.019
Mean birth weight (grams)	3124 ± 412	2957 ± 485	0.042
NICU admission, n (%)	9 (15.0%)	14 (23.3%)	0.238

Group A had a higher incidence of meconium-stained liquor (43.3% vs. 21.7%; p=0.012) and a lower incidence of respiratory distress syndrome (11.7% vs. 26.7%; p=0.037). Despite the higher IHCP incidence, Group A had a lower preterm birth rate (13.3% vs. 31.7%; p=0.016) and a higher mean gestational age at delivery (38.2 vs. 37.4 weeks; p=0.019).

DISCUSSION

Progesterone use in early pregnancy was associated with a 2.5-fold increased risk of intrahepatic cholestasis of pregnancy (IHCP). Affected women also showed earlier symptom onset and more severe biochemical changes.

The higher incidence of IHCP in the progesterone group aligns with the known cholestatic effects of progesterone and its metabolites, particularly in genetically susceptible individuals [9]. Progesterone metabolites, especially sulfated metabolites, can impair bile acid transport by inhibiting the bile salt export pump (BSEP) and the farnesoid X receptor (FXR), leading to decreased bile flow and accumulation of bile acids [10].

The increased meconium-stained liquor in the progesterone group likely reflects elevated bile acids in IHCP, which can trigger fetal meconium passage. This underscores the need for close fetal monitoring in such cases.

Despite higher rates of IHCP and MSL, the progesterone group showed lower incidences of preterm birth and respiratory distress syndrome. This may reflect progesterone's role in preventing preterm labor by reducing uterine contractility and supporting fetal lung development and surfactant production.

Progesterone's dual impact on IHCP risk and pregnancy outcomes highlights the need for personalized risk-benefit assessment.

CONCLUSION

Progesterone therapy in early pregnancy demonstrates a dual effect: increasing IHCP risk while reducing preterm birth and respiratory distress syndrome. Clinicians should monitor for cholestasis in high-risk patients. Future studies should investigate genetic predispositions and safer progesterone formulations to optimize outcomes.

Acknowledgments

The authors would like to thank the staff of the Department of Obstetrics & Gynaecology at Maharishi Markandeshwar Institute of Medical Sciences and Research for their support in conducting this study. We also express our gratitude to all the patients who participated in this research.

Conflict of Interest

The authors declare no conflict of interest.

REFERENCES

1. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. *Obstet Gynecol.* 2014;124(1):120-133.
2. Wood AM, Livingston EG, Hughes BL, Kuller JA. Intrahepatic Cholestasis of Pregnancy: A Review of Diagnosis and Management. *Obstet Gynecol Surv.* 2018;73(2):103-109.
3. Ovadia C, Seed PT, Sklavounos A, 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.
4. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. *Cochrane Database Syst Rev.* 2018;10:CD003511.
5. Shah D, Nagarajan N. Luteal insufficiency in first trimester. *Indian J Endocrinol Metab.* 2013;17(1):44-49.
6. Abu-Hayyeh S, Papacleovoulou G, Williamson C. Nuclear receptors, bile acids and cholesterol homeostasis series - bile acids and pregnancy. *Mol Cell Endocrinol.* 2013;368(1-2):120-128.
7. Abu-Hayyeh S, Papacleovoulou G, Lövgren-Sandblom A, et al. Intrahepatic cholestasis of pregnancy levels of sulfated progesterone metabolites inhibit farnesoid X receptor resulting in a cholestatic phenotype. *Hepatology.* 2013;57(2):716-726.
8. Dixon PH, Williamson C. The pathophysiology of intrahepatic cholestasis of pregnancy. *Clin Res Hepatol Gastroenterol.* 2016;40(2):141-153.
9. Bacq Y, Sapey T, Bréchot MC, Pierre F, Fignon A, Dubois F. Intrahepatic cholestasis of pregnancy: a French prospective study. *Hepatology.* 1997;26(2):358-364.
10. Arrese M, Reyes H. Intrahepatic cholestasis of pregnancy: a past and present riddle. *Ann Hepatol.* 2006;5(3):202-205.
11. Bacq Y. Liver diseases unique to pregnancy: a 2010 update. *Clin Res Hepatol Gastroenterol.* 2011;35(3):182-193.
12. Tsur A, Mei-Dan E, Zaltz A, et al. Vaginal progesterone and intrahepatic cholestasis of pregnancy. *Am J Perinatol.* 2023;40(11):1158-1162.
13. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. *Hepatology.* 2004;40(2):467-474.
14. Romero R, Conde-Agudelo A, Da Fonseca E, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. *Am J Obstet Gynecol.* 2018;218(2):161-180.
15. Sfakianaki AK, Norwitz ER. Mechanisms of progesterone action in inhibiting prematurity. *J Matern Fetal Neonatal Med.* 2006;19(12):763-772.
16. Provost PR, Simard M, Tremblay Y. A link between lung androgen metabolism and the emergence of mature epithelial type II cells. *Am J Respir Crit Care Med.* 2004;170(3):296-305.
17. Dixon PH, Sambrotta M, Chambers J, et al. An expanded role for heterozygous mutations of ABCB4, ABCB11, ATP8B1, ABCC2 and TJP2 in intrahepatic cholestasis of pregnancy. *Sci Rep.* 2017;7(1):11823.
18. Keitel V, Dröge C, Häussinger D. Targeting bile acids in the gut-liver axis and beyond with the FXR agonist obeticholic acid. *Hepatol Int.* 2019;13(6):665-673.