International Journal of Reproduction, Contraception, Obstetrics and Gynecology
*Chaurasia A et al. Int J Reprod Contracept Obstet Gynecol. 2025 May;14(5):1557-1561*
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20251241

**Original Research Article**

# Progesterone prescription in pregnancy: revisiting rationality

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**Received:** 16 March 2025
**Accepted:** 07 April 2025

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## ABSTRACT

**Background:** Progesterone is widely used in pregnancy for conditions like luteal phase defects and preterm labor prevention. However, irrational use, especially prolonged or with multiple formulations, raises concerns about liver dysfunction and intrahepatic cholestasis of pregnancy (IHCP). This study aimed to assess the impact of progesterone use on liver function tests (LFTs) and IHCP incidence based on duration and type of therapy.
**Methods:** A prospective study of 150 antenatal women categorized into three groups: no progesterone (Group A), progesterone until 16 weeks (Group B), and until 32 weeks (Group C). Liver enzyme levels were measured at baseline, mid, and late pregnancy. IHCP was diagnosed with bile acid levels >20 mmol/l.
**Results:** IHCP incidence was significantly higher in Group C (28%) compared to Group A (4%) and Group B (12%) ($p<0.001$). There was significant reversible rise of liver enzymes in group B which normalised after the stoppage of progesterone while in group C, liver enzymes remain persistently elevated.
**Conclusions:** Prolonged and multiple progesterone formulations led to persistent liver enzyme elevation but these changes are transient and go away quickly when the dose is discontinued or modified. Rational prescribing based on clear indications and appropriate formulations is essential for safe outcomes. Choosing the right patients is the main factor that determines how effective progesterone supplements are.

**Keywords:** Dosage, IHCP, Liver, Preparations, Progesterone

## INTRODUCTION

Progesterone is an age-old drug which has been used in various forms for various indications. Usage during pregnancy has been specifically recommended in cases with Luteal Phase Defect as documented clinically by recurrent first trimester abortions or threatened abortions and in pregnancies conceived with ovulation induction. Another clear recommendation is prevention of Preterm labor in patients vulnerable for it.[1]

Nowadays, sometimes progesterones are being used non-judiciously that too for prolonged periods even when there are no clear cut indications. When exactly indicated, progesterone is really of much help but irrationally used progesterone unnecessarily raises increased cost of treatment as well as progesterones being known to alter liver function test leads to high incidence of development of IHCP.[2,3]

There are variety of progesterone preparations available in the market, such as dydrogesterone, micronized progesterone, and hydroxyprogesterone caproate, and lack of clear cut recommendations for their individual usage create confusion and overlap in prescriptions.[4,5]

In last decade, Intrahepatic cholestasis of pregnancy (IHCP) has indeed become more frequently diagnosed condition, with its incidence ranging from 1%-3% of antenatal women which is definitely due to better diagnostic techniques, but overuse and inappropriate use of progesterones during pregnancy cannot be ignored.[6] This study is done to show alterations in LFT in patients taking progesterone in response to duration of therapy and simultaneous usage of multiple progesterones.

As the landscape of progesterone supplementation in pregnancy continues to evolve, this research brings forward the latest findings on rationality behind progesterone prescription in pregnancy, contributing cutting-edge new knowledge to the ongoing discussions. This study aimed to evaluate and analyse the incidence of altered liver function test and IHCP in women receiving exogenous progesterone.

## METHODS

### *Type of study and place*

This was a prospective observational study concluded at Department of Obstetrics and Gynaecology, Swaroop Rani Nehru Hospital, MLN Medical College, Prayagraj.

### *Study period*

This study was conducted for 1 year (from January 2023 - December 2023).

### *Sample size*

Total 150 patients included in this study.

### *Inclusion criteria*

Antenatal women receiving exogenous progesterone preparations and giving consent to participate in the study.

### *Exclusion criteria*

Women with pre-existing liver dysfunction and women who have not consented to participate in the study.

### *Assessment parameter*

Serum total bilirubin, SGPT and SGOT were done at around 5-6 weeks POG to have the baseline values, and then at 18-20 weeks POG and 30-32 weeks POG in all the groups to demonstrate the impact of Progesterone therapy. Serum bile acid was tested in the patients who developed clinical symptoms of IHCP and the diagnosis of IHCP made at the levels >20 mmol/l.

### *Statistical analyses*

$\chi^2$ and the t-test. P value <0.05 was considered statistically significant.

After approval from Institutional Ethics committee, Patients were enrolled and followed. Study groups were based on usage or non-usage of progesterone with detailing of the preparation used, time of start and duration of therapy, and simultaneous usage of multiple progesterone (were prescribed to the patients with RPL and Recurrent Preterm labor). Patients were allocated to following groups.

Group A- Patients receiving no progesterone preparations (50 patients).

Group B- Patients receiving progesterone preparations till 16 weeks (50 patients).

Group C- Patients receiving progesterone preparations till 32 weeks (50 patients).

Group B and C were further sub classified into B1, B2 and C1, C2 depending upon single or multiple progesterone.

## RESULTS

Table 1 presents the participant's demographic data and revealed a mean age of 28.5 years (±4.2) across all groups, with a majority being multiparous (60%), belonging to middle class (70%). The baseline characteristics, including body mass index (BMI) and gravidity were comparable across the three groups.

**Table 1: Demographic characteristics of participants.**

| Characteristic | | Group A (No progesterone) (n=50) | Group B (Progesterone until 16 weeks) (n=50) | Group C (Progesterone until 32 weeks) (n=50) | Total (n=150) |
|---|---|---|---|---|---|
| **Mean age (years)** | | 28.4 (±4.1) | 28.6 (±4.3) | 28.7 (±4.5) | 28.5 (±4.2) |
| **Parity (multiparous) (%)** | | 30 (60) | 32 (64) | 28 (56) | 90 (60) |
| **Socioeconomic status (%)** | Middle class | 35 (70) | 36 (72) | 34 (68) | 105 (70) |
| | Lower class | 15 (30) | 14 (28) | 16 (32) | 45 (30) |
| **Mean BMI (kg/m²)** | | 24.5 (±3.2) | 24.7 (±3.1) | 24.6 (±3.3) | 24.6 (±3.2) |
| **Gravidity** | | 1.4 (±0.6) | 1.5 (±0.7) | 1.6 (±0.8) | 1.5 (±0.7) |

Figure 1 shows that the incidence of ICP was significantly higher in women receiving long-term progesterone supplementation.

In Group A & B, the incidence of ICP was 4% and 12% respectively while Group C showed a striking 28% incidence (p<0.001).

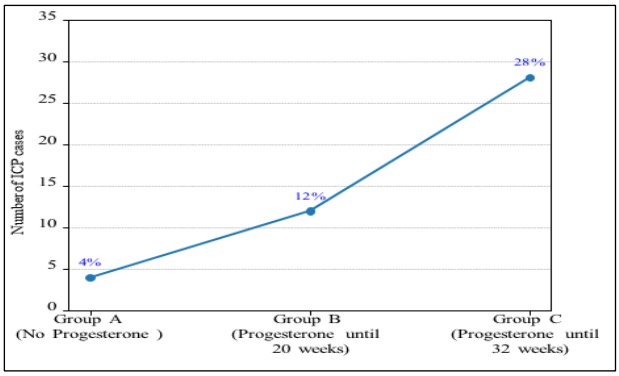


**Figure 1: Incidence of ICP after progesterone supplementation.**

Table 2 presents data comparing three groups of subjects based on their exposure to progesterone during pregnancy and its effects on liver function tests, specifically SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamic pyruvic transaminase), and total bilirubin levels. SGOT levels ranged from 25±5 U/l in Group A to 76±5 U/l in Group C2, while SGPT levels increased from 20±4 U/l in Group A to 72±6 U/l in Group C2. Total bilirubin levels also rose from 0.5±0.1 mg/dl in Group A to 2.6±0.5 mg/dL in Group C2. All p values were <0.001, indicating significant differences across groups suggesting prolonged and higher dose progesterone exposure may affect liver function.

**Table 2: Mean serum levels of liver enzymes across groups.**

| Variable | Group A (No progesterone) | Group B1 (Single progesterone till 16 weeks) | Group B2 (Multiple progesterone till 16 weeks) | Group C1 (Single progesterone till 32 weeks) | Group C2 (Multiple progesterone till 32 weeks) | P value |
|---|---|---|---|---|---|---|
| **SGOT (U/L)** | 25±5 | 62±1 | 64±2 | 75±5 | 76±5 | <0.001 |
| **SGPT (U/L)** | 20±4 | 56±2 | 58±2 | 70±6 | 72±6 | <0.001 |
| **Total bilirubin (mg/dL)** | 0.5±0.1 | 1.2±0.3 | 1.3±0.3 | 2.5±0.5 | 2.6±0.5 | <0.001 |

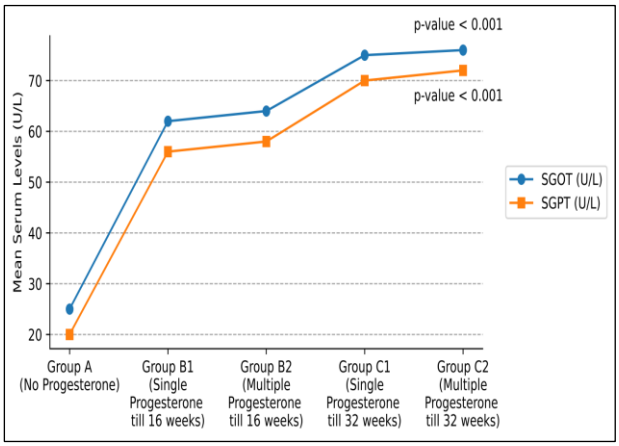


**Figure 2: Mean serum levels of SGOT and SGPT across groups.**

Figure 2 presents comparative data of SGOT and SGPT and Figure 3 represents trends in total bilirubin levels across all groups which demonstrated the significant reversible rise of liver enzymes in group B which normalised after the stoppage of progesterone while in group C, liver enzymes remain persistently elevated.

Table 3 illustrates the correlation between the duration of progesterone therapy and serum SGOT, SGPT and total bilirubin levels across three groups of antenatal women. The multivariable regression analysis indicated that for every additional week of progesterone therapy, there was a corresponding increase in SGOT, SGPT and total bilirubin levels ($\beta$ = 1.6 for SGOT and SGPT; $\beta$ = 0.06 for total bilirubin) suggesting that prolonged exposure to exogenous progesterone exacerbates liver function abnormalities.

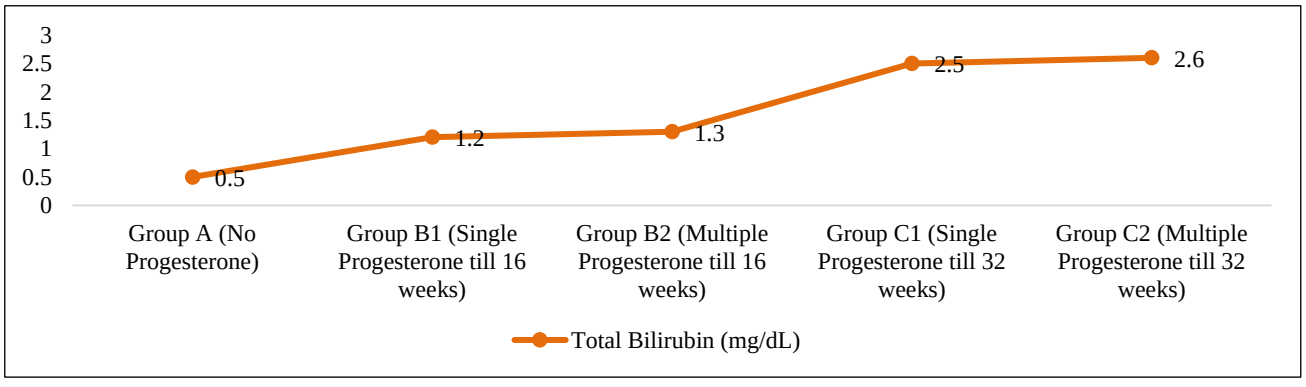


**Figure 3: Mean serum levels of total bilirubin across groups.**

These results provide fresh insights into the field of progesterone prescription in pregnancy by utilizing the most recent datasets available.

**Table 3: Correlation between duration of progesterone therapy and change in liver parameters.**

| Variable | Group A (No progesterone) | Group B (Progesterone until 16 weeks) | Group C (Progesterone until 32 weeks) | Change per week (of progesterone therapy (*β*)) |
|---|---|---|---|---|
| **SGOT (U/L)** | 25±5 | 63±3 | 75±5 | 1.6 |
| **SGPT (U/L)** | 20±4 | 57±2 | 70±6 | 1.6 |
| **Total bilirubin (mg/dl)** | 0.5±0.1 | 1.2±0.3 | 2.5±0.5 | 0.06 |

## DISCUSSION

Nowadays it has become very common to see the prescriptions of pregnant women with multiple progesterone that too without particular indication. Availability of diverse progesterone formulations and unclear recommendations for individual progesterone often leads to overlapping prescriptions, creating potential risks of overuse or drug interactions. Since in our country, antenatal care is being provided by the other health care providers and non-specialists as well, progesterones are being used immensely in irrational ways. Lack of awareness, lack of concern, conscious or unconscious intention to increase pharmacy turnover of individual set ups and impact of robust marketing by medical representatives are definitely playing a major role in irrational prescribing practices and overuse of progesterone.[3,7]

Either being used rationally or irrationally, progesterone leads to altered liver enzymes. Orally used exogenous progesterone modifies hepatobiliary transport mechanism resulting in raised liver enzymes, bile acids and development of ICP. These alterations usually occur after 1 to 2 weeks of start of treatment but thankfully are usually transient and go away quickly when the dose is discontinued or modified. These changes in liver parameters are less obvious with vaginal administration of progesterone because it is absorbed locally and bypasses the first pass metabolism, thus have lesser effect on liver function test.[8]

Our study showed significant difference in liver enzymes across groups. In Groups B1 and B2, liver enzyme elevations normalized after stopping progesterone, while in Groups C1 and C2, liver enzymes remained persistently elevated. In an attempt to compare our results with other studies, we tried to search the relevant articles, but failed to get any such study done in pregnant population. The physiological changes during pregnancy make these women more vulnerable to deleterious effect of oral or parenteral progesterone supplementations. This highlights the importance of careful clinical judgment when prescribing progesterone, ensuring that it's truly indicated and appropriate form is being used that too for appropriate time period. While compiling data, we also noticed that ICP development was more in patients who were started with progesterone in early gestation and continue for longer periods. Usage of multiple progesterone further increased the risk. This study introduces new evidence supporting the appropriate use of progesterones, contributing to the evolving understanding of progesterone prescription in pregnancy.

This study has few limitations. Firstly, small sample size. Secondly, study is single-centre study. Also, comparison with vaginal progesterones were not done.

## CONCLUSION

Choosing the right patients is the main factor that determines how effective progesterone supplements are. When exactly indicated, progesterone is really of much help. Optimal management requires careful consideration of the individual patient's condition, evidence-based guidelines on the appropriate use of each progesterone formulation, and efforts to minimize unnecessary polypharmacy to ensure favourable pregnancy outcomes.

## ACKNOWLEDGEMENTS

Authors would like to thanks all the participants.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Chaurasia A, Singh V, Shweta K, Bajpai S. Progesterone prescription in pregnancy: revisiting rationality. Int J Reprod Contracept Obstet Gynecol 2025;14:1557-61.