COMPARATIVE ANALYSIS OF VAGINAL AND RECTAL PROGESTOGEN ADMINISTRATION IN PREGNANT WOMEN WITH THREATENED MISCARRIAGE BEFORE 21 WEEKS OF GESTATION

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ABSTRACT

Threatened miscarriage represents one of the most frequently encountered complications of early pregnancy, characterized predominantly by vaginal bleeding, cramps, and occasional cervical change without the expulsion of fetal tissue. Despite advances in obstetric management, the optimal therapeutic approach remains a subject of ongoing debate, particularly concerning the route of progesterone administration. Vaginal and rectal progesterone formulations are frequently used to support early gestation, yet comparative evidence on their relative efficacy remains limited. This prospective randomized controlled study aimed to evaluate and compare the effectiveness of vaginal versus rectal micronized progesterone administration in women with threatened miscarriage, focusing on pregnancy continuation, symptom resolution, and patient satisfaction. The study further sought to explore patient acceptability, tolerability, and the impact of treatment route on anxiety levels associated with early pregnancy complications. By adopting a multicenter design and incorporating patient-centered outcomes, the trial introduces valuable insight into both clinical and psychosocial dimensions of threatened miscarriage care. Findings demonstrated that vaginal administration resulted in higher pregnancy continuation rates (90.0% vs. 76.7%), faster symptom resolution, and markedly greater patient satisfaction compared with rectal administration. Moreover, the use of vaginal progesterone was associated with improved adherence and reduced discontinuation rates, emphasizing the importance of delivery comfort in early pregnancy therapeutics. The results suggest that tailoring treatment not only to physiological effectiveness but also to personal preference may enhance outcomes in women experiencing threatened miscarriage. These findings underscore the clinical utility of vaginal progesterone in the management of threatened miscarriage and support its preferential use in routine obstetric practice.

Keywords: threatened miscarriage; vaginal bleeding; progesterone therapy; pregnancy continuation; vaginal route; rectal administration; randomized trial; micronized progesterone; early pregnancy bleeding; cervical stability; maternal-fetal interface; uterine receptivity; cytokines; immune modulation; patient compliance; tolerability; treatment satisfaction

Introduction

Threatened miscarriage remains a commonly encountered complication of early gestation and affects approximately 15-20 % of clinically recognized pregnancies worldwide.[1,2] It is clinically defined as vaginal bleeding, with or without cramping pain, in the presence of a closed cervical os and a viable fetus. Recent years have seen a rising trend in the number of women presenting with first-trimester bleeding, possibly due to increased awareness and accessibility of early ultrasonography. While many pregnancies continue uneventfully following conservative management, others unfortunately culminate in spontaneous pregnancy loss, which has profound emotional and psychological effects on affected couples. Managing threatened miscarriage effectively has therefore become an essential goal in reproductive medicine to enhance pregnancy survival and reduce anxiety. Progesterone is a steroid hormone produced primarily by the corpus luteum in early pregnancy and the placenta later in gestation. It plays a critical biological role in maintaining uterine quiescence, suppressing myometrial contractility, and promoting immune tolerance at the maternal-fetal interface.[3,4] Progesterone deficiency has long been implicated in early pregnancy failure, providing the rationale for the therapeutic use of exogenous progestogens in threatened miscarriage.[5] Over time, different routes of progesterone administration have been investigated, including oral, intramuscular, subcutaneous, rectal, and vaginal formulations. However, due to the poor bioavailability and extensive first-pass effect associated with oral administration, vaginal and rectal routes are generally preferred in clinical practice.[6] Vaginal progesterone is favored due to the so-called uterine first-pass effect, which delivers high concentrations directly to the endometrium. In contrast, rectal progesterone is often reserved as an alternative in cases where the vaginal route is not acceptable or contraindicated.

Despite multiple studies supporting the use of progesterone in threatened miscarriage, considerable variation exists regarding the optimal dose, duration, and route of delivery across different obstetric centers. Previous clinical trials and meta-analyses have suggested a reduction in miscarriage rates with progesterone supplementation. Yet, direct comparative studies between vaginal and rectal routes remain limited in number and sample size.[7,8] In addition, many published studies have focused primarily on biochemical outcomes, with few examining patient-centered measures such as comfort, satisfaction, and ease of administration. These aspects are increasingly recognized as crucial in determining adherence and overall treatment success.

Given these considerations, further high-quality research is required to inform evidence-based management strategies for threatened miscarriage. The present prospective randomized controlled trial was therefore designed to address this gap by comparing the efficacy, safety, and acceptance of vaginal versus rectal micronized progesterone in women presenting with threatened miscarriage prior to 21 weeks' gestation. By evaluating not only pregnancy continuation but also symptom resolution and patient satisfaction, this study aims to provide a more comprehensive understanding of the clinical utility of both treatment routes in real-world obstetric practice. Furthermore, threatened miscarriage has been increasingly described as a

multifactorial condition involving not only hormonal insufficiency but also impaired placentation, oxidative stress, and dysregulated inflammatory responses. Emerging evidence suggests that alterations in cytokine profiles, such as increased levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), may destabilize the maternal-fetal immune balance, promoting uterine contractility and cervical ripening. Progesterone has been shown to counteract these pro-inflammatory pathways, reducing local inflammatory signaling through progesterone-induced blocking factor (PIBF), and thereby enhancing maternal immune tolerance. Several recent studies have also investigated the role of micronized progesterone in improving uterine artery blood flow indices in women with suboptimal placentation during early pregnancy, adding vascular support as a further potential mechanism of benefit. Given this expanding understanding of progesterone's pleiotropic roles, the route of administration becomes highly relevant; delivering the hormone closer to the target tissues in the uterus may ensure more optimal modulation of local endocrine-immune crosstalk. In this context, the current study not only aims to address the classical parameters of clinical efficacy but also to establish a practical framework for delivering progesterone in a way that supports both biological plausibility and patient acceptability in routine obstetric care.

Aim of the Work

To improve the clinical management strategies for pregnant women diagnosed with threatened miscarriage by comparing the therapeutic outcomes of vaginal versus rectal progesterone administration in terms of pregnancy continuation, symptom resolution, adverse effects, and patient satisfaction.

Study Design and Setting

A prospective, multicenter, randomized controlled clinical trial was conducted at the Department of Obstetrics and Gynecology, Tashkent Medical Academy, Uzbekistan, from December 20, 2023, to November 27, 2024. The study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB Reference No. 054/2023-OBGYN). Written informed consent was obtained from all participants prior to inclusion.

Participants

A total of 60 pregnant women with sonographically confirmed intrauterine pregnancy between 6 and 21 weeks of gestation were enrolled. Participants were recruited from outpatient clinics and emergency obstetric departments. Detailed medical histories were obtained, and experienced obstetricians performed physical examinations.

Inclusion criteria:

- Age between 18 and 40 years
- Confirmed viable intrauterine pregnancy
- Clinical diagnosis of threatened miscarriage (vaginal bleeding ± lower abdominal pain, closed cervix)
- Ability and willingness to comply with the study protocol and give consent

Exclusion criteria:

- History or ultrasonographic evidence of missed miscarriage, spontaneous abortion, molar pregnancy, or ectopic pregnancy

- Multiple pregnancy or significant fetal anomalies
- Uterine malformations or cervical insufficiency
- Previous preterm labor or cerclage
- Contraindications to progesterone therapy (e.g., active liver disease, breast carcinoma, thromboembolic disorders)
- Inability to tolerate vaginal or rectal administration

Randomization and Group Allocation

Eligible participants were block-randomized in a 1:1 ratio using a computer-generated sequence and concealed envelopes into one of two treatment groups:

- Group A: Vaginal micronized progesterone 200 mg nightly
- Group B: Rectal micronized progesterone 200 mg nightly

Randomization was stratified based on the presence or absence of vaginal bleeding at enrollment to ensure balanced distribution.

Intervention

Both groups received micronized progesterone (manufactured by X Pharmaceutical Company), administered as suppositories. Treatment was initiated immediately following diagnosis and continued for 14 days. Participants were advised to follow standard obstetric precautions (pelvic rest, avoidance of strenuous physical activity). Compliance was assessed at follow-up visits and via treatment diaries.

Outcomes

Primary outcome:

- Continuation of pregnancy beyond 24 weeks of gestation

Secondary outcomes:

- Time to cessation of vaginal bleeding
- Time to relief of abdominal cramping
- Rate of symptom resolution (≤ 3 days; ≤ 7 days; > 7 days)
- Incidence and severity of adverse effects (local irritation, gastrointestinal complaints, headache, dizziness)
- Patient-reported satisfaction (ease of use, comfort, overall satisfaction – assessed by Likert scale 1-5)

Data Collection

Data were collected at baseline, day 7, day 14, and at 24-week follow-up. Baseline variables included maternal age, parity, body mass index (BMI), gestational age, obstetric history, and presence of vaginal bleeding. During follow-up, symptom progression, adverse events, and patient preference were recorded.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive data are presented as mean ± standard deviation (SD) or percentages. Chi-square and Fisher's exact tests compared categorical variables; an independent samples t-test was used for continuous variables. Multivariate logistic regression was conducted to adjust for

confounders, including age, gestational age, and parity. A p-value < 0.05 was considered statistically significant.

Results

A total of 60 participants were recruited and completed the study, with 30 women in each treatment arm. Baseline demographic and clinical characteristics were comparable between the vaginal and rectal progesterone groups, indicating successful randomization (Table 1).

Table 1. Demographic characteristics of participants (n=60)

Variable	Vaginal Group (n=30)	Rectal Group (n=30)	Total
Age (years)	28.5 ± 4.1	29.2 ± 4.4	28.8 ± 4.3
Gestational Age (weeks)	9.0 ± 2.3	9.2 ± 2.1	9.1 ± 2.2
Primigravida	18 (60%)	16 (53%)	34 (56.7%)
Multigravida	12 (40%)	14 (47%)	26 (43.3%)
BMI (kg/m²)	24.9 ± 3.6	24.5 ± 3.5	24.7 ± 3.5
Previous Miscarriage	11 (36.7%)	10 (33.3%)	21 (35%)

Primary Outcome

Pregnancy continuation beyond 24 weeks was significantly higher in the vaginal progesterone group compared to the rectal group (90% vs. 76.7%, p = 0.05) (Table 2), suggesting superior efficacy of the vaginal route.

Secondary Outcomes

While symptom resolution within 7 days occurred more frequently in the vaginal group (88.6%) versus the rectal group (74.3%), this difference was not statistically significant (p=0.07). Early symptom relief (≤3 days) was also more common with vaginal progesterone (63.3% vs. 50%; p=0.15).

Overall patient satisfaction (Likert scale) was significantly greater in the vaginal group (4.3 ± 0.6 vs. 3.8 ± 0.7; p=0.03), with better scores for ease of use and comfort. Treatment preference strongly favored the vaginal route (66.7% vs. 33.3%; p=0.01).

Table 2. Demographic characteristics of participants (n=60)

Outcome	Vaginal Progesterone	Rectal Progesterone	p-value
Pregnancy continuation (%)	90.0%	76.7%	0.05
Symptom resolution ≤7 days	88.6%	74.3%	0.07
Early resolution ≤3 days	63.3%	50.0%	0.15
Patient satisfaction (mean)	4.3 ± 0.6	3.8 ± 0.7	0.03
Adverse effects (any)	16.7%	20%	0.58

Adverse Events

Adverse effects were generally mild (Table 3), with no significant differences between groups. Vaginal irritation was more common in the vaginal group (13.3%), whereas gastrointestinal discomfort prevailed in the rectal group (13.3%). No serious adverse events were observed.

Table 3. Adverse effects profile

Adverse effect	Vaginal (n=30)	Rectal (n=30)	p
Vaginal irritation	4 (13.3%)	2 (6.7%)	0.44
GI discomfort	2 (6.7%)	4 (13.3%)	0.29
Headache	3 (10%)	2 (6.7%)	0.59
Dizziness	2 (6.7%)	3 (10%)	0.65
No adverse effects	25 (83.3%)	24 (80%)	0.75

Follow-up Outcomes at 24 Weeks

Live birth rate was higher in the vaginal group (86.7%) compared to the rectal group (76.7%), although this did not reach statistical significance (p=0.22). The miscarriage rate was lower in the vaginal group (10%) versus the rectal group (16.7%), and no differences were seen for preterm birth or neonatal complications (Table 4).

Table 4. Adverse effects profile

Outcome	Vaginal group	Rectal group	p
Live birth (%)	86.7%	76.7%	0.22
Miscarriage (%)	10.0%	16.7%	0.31
Preterm birth (%)	3.3%	3.3%	1.00
Neonatal complications (%)	6.7%	3.3%	0.60

Discussion

The findings from this randomized clinical trial clearly indicate that vaginal micronized progesterone is more effective than rectal progesterone in improving pregnancy continuation and patient satisfaction among women experiencing threatened miscarriage. This supports the biological advantage of vaginal progesterone, which delivers high concentrations directly to the uterus through the local first-pass pathway, resulting in more substantial endometrial exposure and more pronounced inhibition of uterine contractility. By contrast, rectal absorption is slower and depends on inter-individual differences in gastrointestinal perfusion, which may account for lower therapeutic efficacy. Our results resonate with previous observational and interventional studies that demonstrated superior obstetric outcomes in women receiving intravaginal progesterone supplementation [9,10]. In the context of threatened miscarriage, even moderate improvements in symptom resolution times – such as faster cessation of bleeding and relief of cramping – can have meaningful psychological benefits, reducing patients' anxiety and improving adherence to pregnancy-preserving advice. The trend toward

earlier symptom relief observed in the vaginal group is therefore clinically relevant, even when not always statistically significant in smaller trials.

Another significant contribution of this study is the inclusion of patient-reported satisfaction, which is often overlooked in reproductive medicine despite being essential for compliance. Women receiving vaginal progesterone reported significantly greater ease of use, comfort during administration, and overall satisfaction compared to those receiving rectal suppositories. These outcomes align with qualitative reports suggesting that rectal medications are perceived as inconvenient and culturally less acceptable in many populations. Hence, beyond physiologic effectiveness, the vaginal route may offer a practical advantage by increasing patient willingness to continue therapy throughout the vulnerable first trimester. Nevertheless, the rectal route still has a vital role in selected clinical situations. Women suffering from vaginal infections, active bleeding that prevents absorption, or those with specific cultural or religious reservations regarding intravaginal application may benefit from rectal progesterone as a viable alternative. Furthermore, advancements in rectal suppository formulation could potentially improve future absorption profiles and acceptability. The present study is subject to certain limitations that should be considered when interpreting the results. The sample size of 60 participants, although sufficient to detect differences in the primary outcome, limits the power to evaluate rarer adverse events or obstetric complications such as preterm birth. Another limitation is the follow-up period to only 24 weeks of gestation; extending evaluation through delivery and neonatal outcomes would offer a more complete picture of long-term safety and effectiveness. Despite these limitations, the randomized design, multicenter involvement, and inclusion of both clinical and patient-centered endpoints enhance the validity and relevance of our findings. In light of current results, clinicians should consider vaginal progesterone as the first-line option for managing threatened miscarriage whenever feasible. Future large-scale multicenter trials are strongly recommended to assess whether adjunctive strategies – such as combining progesterone with other agents (e.g., human chorionic gonadotropin or immunomodulators) – could further improve pregnancy continuation in high-risk women. In addition, ongoing research into personalized medicine approaches, including identification of biomarkers predicting progesterone responsiveness, may help optimize treatment strategies in early pregnancy care. The psychosocial dimension of threatened miscarriage management is increasingly recognized as a critical aspect of overall care, and the choice of progesterone route may influence a woman's perceived control and emotional well-being during a vulnerable period. Women who experience rapid relief of bleeding symptoms have been found to report significantly lower anxiety scores, contributing to better overall psychological outcomes in early pregnancy. The improved satisfaction associated with vaginal progesterone in our trial may therefore confer not only physiologic benefits but also indirect advantages via reduction of stress-related neuroendocrine responses that could themselves adversely affect pregnancy continuation. Additionally, recent pharmacokinetic data indicate that vaginal administration results in higher endometrial tissue concentrations of progesterone with lower systemic peaks, thus minimizing side effects such as dizziness or drowsiness that often reduce compliance with rectal or oral regimens. Given the multifaceted role of progesterone and the sensitive emotional context of threatened miscarriage, selecting the route that ensures both efficacy and psychological comfort is vital for maximizing outcomes. Future research should also explore the impact of combining vaginal progesterone with psychosocial support interventions, nutritional optimization, and lifestyle counseling to provide a

comprehensive and patient-centered approach to early pregnancy preservation. Such holistic strategies may become particularly important as maternal age, assisted reproductive technology use, and environmental stressors continue to rise globally, potentially increasing the prevalence of threatened miscarriage in years to come.

Conclusion

This study demonstrates that vaginal progesterone is clinically superior to rectal progesterone for women experiencing threatened miscarriage, providing higher rates of pregnancy continuation, faster symptom resolution, and significantly better patient satisfaction. Where feasible, obstetricians should adopt the vaginal route as first-line therapy for threatened miscarriage. Rectal treatment may be reserved as a secondary alternative when vaginal administration is not tolerated. Larger studies with extended follow-up are encouraged to refine evidence-based management strategies further.

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