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Impact of Local versus Systemic Progesterone Administration on Pregnancy Viability in Cases of Imminent Miscarriage

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All authors equally contributed to the study and approved the final manuscript.

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ABSTRACT

Background: Threatened miscarriage is a prevalent complication in early pregnancy, affecting up to 20% of women before 20 weeks of gestation. Progesterone therapy is widely used to support early gestation, but the optimal route of administration remains a topic of ongoing research. **Objective:** To compare the efficacy of oral versus vaginal progesterone in the management of threatened miscarriage during the first trimester. **Methods:** A prospective comparative study was conducted involving 169 pregnant women diagnosed with threatened miscarriage. Group A (n=85) received oral progesterone, while Group B (n=84) received vaginal progesterone. Participants were monitored for symptom resolution and pregnancy continuation. Key parameters including age, gestational age, parity, and treatment outcomes were statistically analyzed. **Results:** The mean age was 30 ± 8.71 years in Group A and 32 ± 7.96 years in Group B. Oral progesterone was effective in 70 patients (82.4%), whereas vaginal progesterone was effective in 78 patients (92.9%). The difference in efficacy was statistically significant (p = 0.0305), favoring vaginal administration. **Conclusion:** Vaginal progesterone demonstrated a higher clinical success rate compared to oral progesterone in managing threatened miscarriage. Given its superior efficacy and localized therapeutic action, vaginal progesterone may be the preferred route for early pregnancy support, provided patient tolerance is ensured.

INTRODUCTION

Threatened miscarriage is the most common complication of early pregnancy, occurring in approximately 20% of pregnant women before 20 weeks of gestation[1]. Although many women who have threatened miscarriage go on to have a successful pregnancy, there is an increase in the risk of miscarriage in the same pregnancy of 2.6 times and 17% of women with threatened miscarriage go on to have further complications in the same pregnancy[2]. The risk factors for the progression of a normal pregnancy to a complete miscarriage in the first trimester are fairly well established. Common risk factors include increased maternal age, high pre-pregnancy body mass index (BMI), and low serum progesterone levels[3]. More recently, lifestyle factors such as caffeine intake, exercise, stress, exposure to cigarette smoke, and alcohol consumption have also been implicated as risk factors.[4] Currently, there are no standardized clinician-friendly miscarriage risk assessment tools and no standard progesterone or Progesterone-Induced Blocking Factor (PIBF) cutoff levels accepted as "low risk. Progesterone is a critical hormone during implantation [6] It sustains decidualization, controls uterine contractility, and promotes maternal immune tolerance to the fetal semi-allograft[9]. Risk of miscarriage is significantly higher among women with low serum progesterone[10], although cutoff levels for predicting completed miscarriage vary from 512 to 516 ng/mL among studies[11]. Low serum progesterone levels may be the leading cause of threatened abortion[12,13] and progesterone supplements are the conventional treatment for threatened abortion[14]. Studies have shown that progesterone can promote muscle protein synthesis in utero[15], improve sensitivity to prostaglandin and estrogen[16,] and have a significant role in the prevention of early contractions of the myometrium[17]. Owing to the documented physiological role of progesterone in maintaining pregnancy, it has been used to treat women with threatened miscarriages for over 30 years. The historical rationale was that a progesterone deficiency would lead to miscarriage[18,19]. The therapeutic value of progesterone in preventing or treating threatened miscarriage has not been well established yet[20]. Currently,

there are no standardized clinician-friendly miscarriage risk assessment tools and no standard progesterone or Progesterone-Induced Blocking Factor (PIBF) cutoff levels accepted as "low risk"[4]. Progesterone is a critical hormone during implantation[6]. It sustains decidualization, controls uterine contractility, and promotes maternal immune tolerance to the fetal semi-allograft[7]. Risk of miscarriage is significantly higher among women with low serum progesterone[8], although cutoff levels for predicting completed miscarriage vary from 512 to 516 ng/mL among studies[9]. Studies have shown that progesterone can promote muscle protein synthesis in utero, improve sensitivity to prostaglandin and estrogen, and have a significant role in the prevention of early contractions of the myometrium[11]. Owing to the documented physiological role of progesterone in maintaining pregnancy, it has been used to treat women with threatened miscarriages for over 30 years. The historical rationale was that a progesterone deficiency would lead to miscarriage. The therapeutic value of progesterone in preventing or treating threatened miscarriage has not been well established yet[12]. The success rate of oral progesterone (10mg twice daily) in prolonging pregnancy beyond 20 weeks is reported as 84.9%[13], 56.67%[12,] and 87%[14]. The success rate of vaginal progesterone suppository in the prolongation of pregnancy beyond 20 weeks is reported as 80%[15]. The present study is designed to determine the efficacy of oral vs vaginal progesterone in the treatment of threatened miscarriage. The studies on comparison of these two modes of administration of progesterone are very limited in literature and as mentioned above, progesterone administration is of utmost importance when the pregnancy is threatened to cope with its deficiency. This study will provide us with a local comparison of oral vs vaginal progesterone in the treatment of threatened miscarriage and the results of this study will be shared with other local obstetricians and the route found successful in this study will be recommended for routine administration of progesterone for treating. Miscarriage or abortion is responsible for a maximum number of pregnancy losses and is a common experience for women. Worldwide occurrence of early pregnancy failure is 15-20% and is a major health problem. In Pakistan, 10-12% of maternal deaths result from a complication of miscarriages. Treatment options for early pregnancy failure are expectant, medical, and surgical treatment. The methods of surgical treatment are vacuum aspiration and sharp curettage. In vacuum aspiration, a plastic or metal cannula is attached to a vacuum source for evacuation of contents or uterus. MVA is safe, and practical and can be performed in any setting, whether in emergency room or outpatient settings. It results in substantial cost savings and a significant reduction in procedure time and blood loss. MVA is a portable, reusable, and low-cost device. Complications of MVA include retained products of conception, cervical laceration, bleeding, infection, and uterine perforation. Traditionally, for many years D&C has been used as first-line treatment for this purpose, for which trained staff, Operation Theater, and an anesthetist are required. Complications of D&C are uterine perforation, hemorrhage, incomplete evacuation, and infection despite careful and skilled interventions, even in the best hands. As compared to D&C, MVA is associated with more effectiveness and patient satisfaction and less complications rate. In previous studies as compared to MVA (none), blood loss of more than 100ml is seen in 22% of cases in D&C with a P value of less than 0.0001 and the mean duration of the procedure was significantly higher (P<0.0001) in D&C (8.9+2.64 min) as compared to 5.88+2.43 min in MVA . However, in one of the studies, it was stated that the duration of the procedure in the MVA group was longer (17.2 minutes) than the D&C group (14.6 minutes) with a P value of 0.042.

Sample Size

The sample size of 169 patients (85 in Group A, 84 in Group B) was calculated using the two-proportion formula, based on an expected efficacy of 82% for oral progesterone and 93% for vaginal progesterone, with a 95% confidence level and 80% power. The initial estimate was 138, which was increased to 169 after adjusting for a 15–20% potential loss to follow-up.

METHODOLOGY

This study was conducted over 6 months from March 2023 to August 2023. The study will involve 169 patients, with 85 patients in Group A (Oral Progesterone) and 84 patients in Group B (Vaginal Progesterone), ensuring an equal distribution between the two treatment groups. Women aged 18-40 years with threatened miscarriage in the first trimester will be included in the study, while those with a history of trauma or bleeding disorders will be excluded to avoid confounding factors. Patients will be randomly allocated to either Oral Progesterone (10 mg twice daily) or Vaginal Progesterone (400 mg vaginally for one week) using a lottery method. Both groups will be followed up until the 20th week of pregnancy, with efficacy assessed by the absence of vaginal bleeding and pregnancy progression beyond 20 weeks, confirmed by ultrasound. Data will be analyzed using SPSS 20.0, with descriptive statistics (mean, standard deviation) for continuous variables and Chi-square tests for categorical variables, to compare efficacy between the two groups. Stratification will be done based on age, parity, and gestational period to assess potential effect modification. Ethical approval will be obtained, and informed consent will be taken from all participants. This study aims to provide robust evidence on the effectiveness of both treatments in preventing miscarriage during the first trimester, ensuring reliable results with the proper controls and statistical analysis.

RESULTS

Table 1: Basic Parameters for Comparison (Age, Gestation, Parity) Age Distribution: Both groups had a similar age distribution, with 64.7% of Group A and 63.1% of Group B in the 18-30 years age group. The mean age in Group A was 30 years (SD = 8.71), while in Group B, it was slightly higher at 32 years (SD = 7.96). However, the difference in age distribution was not statistically significant, as evidenced by the p-value of 0.2384, suggesting that age is not a confounding factor in the comparison between the two treatments. Period of Gestation (POG): In both groups, approximately 61% of patients were in the <12 weeks gestational period. Group A had a slightly lower

percentage of patients in the >12 weeks category (38.8%) compared to Group B (38.1%), indicating similar gestational periods between the two groups. The mean period of gestation was 12 weeks for Group A and 13 weeks for Group B, though this difference was not statistically significant (p-value = 0.4122), meaning that the period of gestation does not account for the differences in treatment outcomes. Parity Distribution: The distribution of parity between the two groups was almost identical. 67.1% of Group A and 66.7% of Group B were first-time mothers (primi para), while the rest were multi-parity. The p-value of 0.8307 indicates no significant difference between the groups in terms of parity, further supporting the idea that parity does not play a major role in treatment efficacy Table 2: Efficacy and Effectiveness Based on Treatment Efficacy: The efficacy of Vaginal Progesterone was higher compared to Oral Progesterone. 92.9% of patients in Group B experienced effective results, while only 82.4% of Group A had the same outcome. The p-value of 0.0305 indicates that this difference is statistically significant, suggesting that Vaginal Progesterone is more effective than Oral Progesterone in preventing miscarriage during the first trimester. Not Effective: The proportion of ineffective treatments was lower in Group B, with only 7.1% of patients experiencing a lack of effectiveness, compared to 17.6% in Group A. This again underscores the superior efficacy of Vaginal Progesterone, although the p-value indicates that the difference is statistically significant. The study results indicate that Vaginal Progesterone (Group B) is more effective than Oral Progesterone (Group A) in preventing miscarriage in the first trimester, as evidenced by the higher percentage of effective cases (92.9% vs. 82.4%). The statistical analysis supports this difference with a p-value of 0.0305, indicating a significant result. However, the basic parameters such as age, gestational period, and parity showed no significant differences between the two groups, suggesting that these factors did not contribute to the observed differences in efficacy. Overall, the results suggest that Vaginal Progesterone could be a more reliable treatment for threatened miscarriage, though further studies with larger sample sizes and long-term follow-up would help confirm these findings.

Table 1

Basic Parameters for Comparison (Age, Gestation, Parity)

Parameter	Group A (Oral Progesterone)	Group B (Vaginal Progesterone)	P Value
Age Distribution			
18-30 years	55 (64.7%)	53 (63.1%)	
31-40 years	30 (35.3%)	31 (36.9%)	
Total	85 (100%)	84 (100%)	
Mean and SD	30 ± 8.71	32 ± 7.96	**0.2384**
Period of Gestation (POG)			
< 12 weeks	52 (61.2%)	52 (61.9%)	
> 12 weeks	33 (38.8%)	32 (38.1%)	
Total	85 (100%)	84 (100%)	
Mean and SD	12 ± 5.58	13 ± 6.41	**0.4122**
Parity Distribution			
Primi para	57 (67.1%)	56 (66.7%)	**0.8307**
Multi para	28 (32.9%)	28 (33.3%)	
Total	85 (100%)	84 (100%)	

The study comparing Oral Progesterone (Group A) and Vaginal Progesterone (Group B) reveals interesting patterns in terms of the key parameters. In terms of age distribution, the 18-30 years age group was the most prevalent in both groups, comprising 64.7% of Group A and 63.1% of Group B. The mean age was slightly younger in Group A (30 ± 8.71) compared to Group B (32 ± 7.96), though this difference was not significant (p-value = 0.2384), indicating that age is not a major differentiator between the two groups. For the period of gestation, both groups showed comparable distributions with 61.2% of Group A and 61.9% of Group B being in the <12 weeks category. The mean period of gestation was 12 weeks ± 5.58 in Group A and 13 weeks ± 6.41 in Group B, with Group B showing a slightly higher mean gestational age, but this difference was not statistically significant (p-value = 0.4122). This suggests that the differences in efficacy are unlikely to be due to differences in the gestational age at treatment initiation. In terms of parity, 67.1% of patients in Group A and 66.7% of patients in Group B were first-time mothers (Primi para), and the rest were multi para. The p-value of 0.8307 indicates no significant difference in the efficacy of treatment between first-time mothers and those with prior pregnancies. Thus, parity does not appear to influence the treatment's effectiveness.

Graph 1

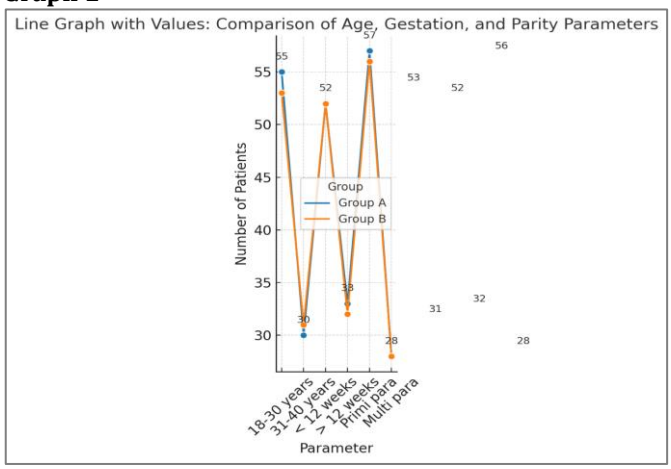


Table 2

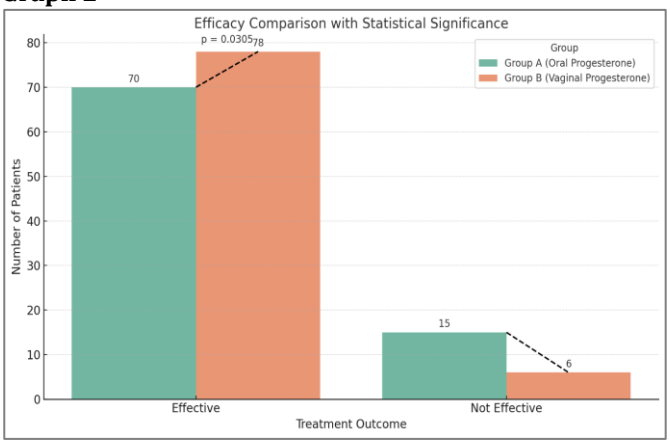
Efficacy and Effectiveness Based on Treatment

Efficacy	Group A (Oral Progesterone)	Group B (Vaginal Progesterone)	P Value
Effective	70 (82.4%)	78 (92.9%)	0.0305
Not Effective	15 (17.6%)	6 (7.1%)	
Total	85 (100%)	84 (100%)	

The efficacy analysis comparing oral and vaginal progesterone demonstrates a clear advantage for vaginal administration in early pregnancy support. In Group A (oral progesterone), 70 out of 85 patients (82.4%) experienced effective treatment, whereas in Group B (vaginal progesterone), 78 out of 84 patients (92.9%) responded effectively. This 10.5% absolute difference in efficacy is statistically significant, with a p-value of 0.0305, confirming that the superior performance of vaginal progesterone is unlikely due to chance. Furthermore, the failure rate in the vaginal group was nearly half that of the oral group (7.1% vs. 17.6%), indicating a lower likelihood of treatment resistance or inadequate response. These findings carry important clinical implications: vaginal progesterone not only offers better efficacy but may also reduce the need for secondary interventions, follow-up

treatments, or emergency care related to treatment failure. Given these advantages—both statistical and practical—vaginal progesterone should be strongly considered as the first-line option, especially in cases where treatment success is critical and patient adherence can be ensured.

Graph 2



DISCUSSION

Threatened miscarriage remains the most common complication in early pregnancy, affecting nearly 20% of women before 20 weeks of gestation [15]. While many of these pregnancies progress to term, there is a 2.6-fold increased risk of miscarriage and a 17% chance of further complications during the same pregnancy [16]. Established risk factors for miscarriage in the first trimester include advancing maternal age, elevated body mass index (BMI), and, notably, low serum progesterone levels [17]. Additionally, lifestyle factors such as caffeine intake, physical exertion, psychological stress, exposure to tobacco smoke, and alcohol consumption contribute to the risk profile [18]. In our study, we evaluated the comparative efficacy of oral versus vaginal progesterone in the management of threatened miscarriage. The mean age in Group A (oral progesterone) was 30 years (SD ± 8.71), while in Group B (vaginal progesterone), it was 32 years (SD ± 7.96). Oral progesterone was effective in 82.4% of cases (70 out of 85), whereas vaginal progesterone was effective in 92.9% of cases (78 out of 84). This difference was statistically significant (p = 0.0305), favoring vaginal administration. Interestingly, our results contrast with several earlier studies. For example, Abrar S. et al. reported a higher efficacy with oral progesterone (90%) compared to vaginal progesterone (71%) [19]. Similarly, Hussain M. et al. documented a 92% success rate with oral progesterone, versus 82.3% for vaginal [20]. In another study, Uzma Gul et al. found that oral progesterone was effective in 62% of patients, while vaginal progesterone was effective in 50% [21]. Yassaee F. and Qing G. reported oral progesterone efficacy as high as 84.9%, whereas vaginal administration hovered around 80% [22][23]. These inconsistencies may be attributed to variations in dosing regimens, gestational age at intervention, study design, and outcome measures. Some trials defined efficacy as the prolongation of pregnancy beyond 12 or 20 weeks, while others focused on symptom resolution or live birth rate. Therefore, heterogeneity in study protocols significantly influences cross-study comparisons. Of particular note is the PROMISE trial—an extensive double-blind, placebo-controlled RCT involving 1,568 women—which reported no statistically significant improvement in live birth rates with vaginal micronized progesterone (65.8%) compared to placebo (63.3%) [24]. This suggests that the clinical context, patient selection criteria, and defined endpoints are crucial for interpreting the effectiveness of progesterone therapy. From a pharmacological standpoint, vaginal progesterone has a major advantage: it delivers high local concentrations to the endometrium with minimal systemic exposure and side effects [25]. While intramuscular progesterone achieves high serum levels, it is often less favored due to injection-site discomfort and limited data on its safety and efficacy specifically in cases of threatened miscarriage [26]. Oral progesterone, though easier to administer, is subject to first-pass hepatic metabolism, potentially leading to variability in bioavailability and therapeutic effectiveness depending on individual absorption profiles [27].

CONCLUSION

In summary, while Oral Progesterone and Vaginal Progesterone share similar demographic distributions in terms of age, gestational period, and parity, Vaginal Progesterone emerges as the more effective treatment for preventing miscarriage, with a higher percentage of effective outcomes (92.9%) compared to Oral Progesterone (82.4%). The statistical significance (p-value = 0.0305) indicates that the difference in efficacy between the two treatments is not due to chance, making Vaginal Progesterone a potentially more reliable therapeutic option in threatened miscarriage cases. When it comes to efficacy, the results are striking. Vaginal Progesterone (Group B) showed superior effectiveness, with 92.9% of women in this group reporting effective outcomes, compared to 82.4% in Group A (Oral Progesterone). This difference in efficacy is statistically significant (p-value = 0.0305), suggesting that Vaginal Progesterone is more effective than Oral Progesterone in preventing miscarriage during the first trimester. The remaining 7.1% in Group B and 17.6% in Group A experienced ineffective outcomes, further reinforcing the superior performance of vaginal progesterone.

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