Efficacy of oral versus vaginal progestogens for early pregnancy maintenance in women with recurrent miscarriages: a randomized controlled trial

Laiyla Shinwari 1,2, Afrah Aman 1,3, Mehwish Syed 1,4, Rabia Nawaz 1,3, Rehana Rahim 1

ABSTRACT

OBJECTIVE: To compare the effectiveness of oral and vaginal progestogens in the maintenance of early pregnancy in women with recurrent miscarriages.

METHODS: This randomized controlled trial was conducted at Lady Reading Hospital, Peshawar, Pakistan, from April to September 2021. Pregnant women aged 16–40 years with a history of at least three recurrent miscarriages presenting at or before 7 weeks of gestation were enrolled. A total of 108 patients were randomly assigned to two groups: group A received oral progestogens (10 mg twice daily), and group B received vaginal progestogens (200 mg twice daily). Treatment lasted for 12 weeks, with successful outcomes defined as no vaginal bleeding and pregnancy continuing beyond 12 weeks. Data analysis was conducted using SPSS-20 software.

RESULTS: The mean age of patients was 29 ± 3.88 years in group A and 27 ± 3.12 years in group B. Oral progestogens (group A) were effective in 48 (88.9%) patients, whereas vaginal progestogens (group B) were effective in 36 (66.7%) patients (p=0.03). Oral progestogens showed significantly greater efficacy compared to vaginal progestogens in individuals aged 20–30 years (p=0.04) and those with fewer than four previous miscarriages (p=0.03). However, there was no significant difference in efficacy between the two groups for participants aged 31–40 years or those with 4 or more previous miscarriages.

CONCLUSION: Oral progestogens are more effective than vaginal progestogens in preventing recurrent miscarriages, especially in participants aged 20–30 years and with fewer than 4 previous miscarriages. More research is needed to validate and explore underlying mechanisms.

Clinical Trial Registration Number: IRCT202301117057148N1

KEYWORDS: Progestins (MeSH); Fetal Viability (MeSH); Pregnancy (MeSH); Parity (MeSH); Abortion, Habitual (MeSH); Abortion, Spontaneous (MeSH).


INTRODUCTION

Recurrent miscarriage (RM) is the occurrence of three or more consecutive pregnancy losses before fetal viability, presenting a significant challenge in obstetrics and gynecology. It encompasses primary RM, where viable pregnancy has never been achieved, and secondary RM, characterized by a history of live births preceding miscarriages. Secondary RM typically carries a more favorable prognosis for successful pregnancy. The prevalence of RM has been reported to range between 1% and 2%. In India, RM has been observed in 7.46% of women. Approximately 70% of pregnancies are lost before live birth: 30% due to failure to implant, 30% after implantation but before a missed period, and 10% as clinical miscarriage. RM complicates 15-20% of all clinically established pregnancies, with 1-2% of couples experiencing recurrent early loss. Despite extensive research, the pathophysiology of RM remains incompletely understood, with approximately 50% of cases lacking an identified cause. Factors such as inadequate progesterone secretion and delayed endometrial development during implantation may contribute to recurrent miscarriage. Various interventions, including bed rest, avoidance of sexual intercourse, uterine relaxing agents, vitamins, folic acid, human chorionic gonadotrophin, and immunotherapy, have shown ambiguous results in preventing RM. Progesterone therapy is commonly used to maintain early pregnancy, inducing secretory changes necessary for successful implantation. It can be administered orally, intramuscularly, rectally, or vaginally.

The efficacy of progesterone therapy may be influenced by the route of administration, with minimal adverse effects associated with oral and vaginal routes compared to invasive intramuscular injections. However, controversy exists regarding the optimal route of administration, with some studies suggesting oral administration while others find no significant difference among routes.

Further research is needed to evaluate the most effective route for preventing early pregnancy loss in RM. Hence, we...
planned this study to compare the effectiveness of oral and vaginal progestogens in the maintenance of early pregnancy in women with RM. Comparing the effectiveness of oral and vaginal progesterone may provide valuable insights for future research and potentially reduce the financial burden on patients if oral progesterone proves to be more cost-effective.

**METHODS**

This randomized control trial was conducted at the Post Graduate Medical Institute, Lady Reading Hospital Peshawar, Pakistan from April 2021 to September 2021. Ethical approval for this study was obtained from the Ethical Committee of the College of Physicians and Surgeons of Pakistan, reference number: CPSP/REU/OBG-2014-022-6174, dated 03-01-2020. Additionally, the study was registered with the Iranian Registry of Clinical Trials, a Primary Registry in the WHO Registry Network, under IRCT ID: IRCT20230117057148N1. Total sample size calculated was 108. It was calculated using the WHO calculator: P1 proportion of effectiveness of oral progestogens 12 (A) = 87% versus P2 proportion of effectiveness of vaginal progestogens 11 (B) = 63%; power of test = 90%; 95% confidence interval; 5% level of significance; sample size was 54 in each group.

The study enrolled pregnant women aged 16–40 with a history of at least three recurrent miscarriages who presented at or before 7 weeks of gestation. Written consent was obtained from each participant after explaining the procedures, potential effects and side effects of drugs, and ensuring confidentiality. Patients with threatened miscarriage, structural uterine abnormalities distorting the cavity, absence of fetal cardiac activity (missed abortion), contraindications to progestogen use (such as allergy to progesterone or patients with breast carcinoma), chronic medical conditions (including thyroid diseases, diabetes, and hypertension), and inadequate treatment compliance were excluded from the study.

The patients were randomly divided into two equal groups, labeled as group A and group B, using computer-generated numbers. Each group comprised 54 patients. Group A received oral progestogens (dydrogesterone) at a dose of 10 mg twice daily, while group B received vaginal progestogens (micronized natural progesterone) at a dose of 200 mg twice daily for 12 weeks (Figure 1). The efficacy of the treatments was assessed by the continuation of pregnancy beyond 12 weeks. All data were recorded using a pre-designed proforma. Transvaginal ultrasound examinations were conducted at 7, 9, and 12 weeks of gestation to assess the presence of fetal cardiac activity.

After data collection, it was entered and analyzed using SPSS 20 software. Mean and standard deviation were calculated for qualitative variables such as age. Frequency and percentage were calculated for categorical data, such as efficacy for group A and B. The efficacy of drugs between the two groups (A and B) was compared using the chi-square test. Stratification based on age and number of miscarriages was performed, and post-stratification chi-square tests were applied. A p-value ≤ 0.05 was considered significant.

**RESULTS**

This study was conducted on 108 women, with 54 participants in each group, to evaluate the efficacy of oral and vaginal progestogens in preventing recurrent miscarriages during early pregnancy. The mean age in group A was 29±3.88 years, whereas in Group B, it was 27±3.12 years. Additional details and subdivisions concerning age are provided in Table I.

The mean age of participants in Group A was 29±3.88 years, and in Group B, it was 27±3.12 years. The majority of participants in Group A (n=36; 66.7%) and Group B (n=38; 70.4%) belonged to the 31-40 years' age group (Table I).

Regarding efficacy, oral progestogens (Group A) were effective in 48 (88.9%) patients, while vaginal progestogens (Group B) were effective in 36 (66.7%) patients (p-value = 0.03).

Table II illustrates the comparison of oral and vaginal progestogens’ efficacy in preventing recurrent miscarriages based on age and the number of miscarriages.
previous miscarriages. Oral progestogens showed significantly higher efficacy than vaginal progestogens in participants aged 20-30 years (p=0.04) and those with fewer than 4 previous miscarriages (p=0.03). No significant difference was observed in efficacy between the two groups for participants aged 31-40 years or those with 4 or more previous miscarriages.

**DISCUSSION**

The current study aimed to assess the effectiveness of progesterone via oral and vaginal routes. Our findings indicate that treatment with oral progestogens was significantly more effective in preventing RM compared to vaginal progestogens (p < 0.05). Stratification by age and number of miscarriages also revealed significant differences in efficacy between the groups (p < 0.05).

Progesterone, often referred to as the “pregnancy hormone,” plays a crucial role in facilitating the successful implantation of a fertilized egg into the uterine lining. Beyond this primary function, progesterone also contributes to various processes, including the suppression of inflammatory responses, modulation of maternal immune responses, reduction of uterine contractility, support during the luteal phase, and enhancement of uteroplacental circulation. It is suggested that inadequate secretion of progesterone may be a contributing factor in many cases of miscarriages. As a result, gynecologists and obstetricians frequently administer progesterone during the first trimester of pregnancy to prevent spontaneous miscarriage.

Various studies have been conducted to investigate the role of progesterone in maintaining pregnancy, particularly in cases of threatened and recurrent miscarriages. However, controversy persists regarding the optimal route of administration, as evidenced by conflicting results in existing research. In our study, oral progestogens demonstrated superior efficacy, consistent with findings from other research. A study reported by Ghosh et al., in 2014 found oral progesterone (10mg BID) effective in 90% of cases, aligning with our results. Additionally, Ghosh et al., observed higher pregnancy rates (92.0%) in the oral progestogens group compared to the vaginal progestogens group (82.3%). Similarly, Wang et al., reported a lower risk of miscarriage in women treated with oral progestogens compared to those receiving vaginal progestogens. A meta-analysis by Wahabi et al., further supported the superiority of oral progestogens in reducing the incidence of recurrent miscarriages during pregnancy.

A review conducted by a group of obstetricians and gynecologists in Saudi Arabia emphasized the role and route of progestogens in preventing recurrent miscarriage. Their analysis concluded that oral progestogens were well tolerated and more effective in reducing the risk of recurrent miscarriage in at-risk women. Another study by El-Zebdeh and colleagues investigated the effect of oral progestogens in recurrent miscarriage and found that viable pregnancies occurred in 87% of cases beyond 12 weeks. These findings align with the results of our study and are consistent with the majority of the aforementioned studies.

In contrast, Lee et al., conducted a systematic review encompassing 51 articles, comparing the efficacy of oral and vaginal progestogens in preventing RM. While they found no significant difference in the efficacies of oral and vaginal progestogens when compared individually, oral progestogens were slightly more effective than vaginal progestogens when compared to the control group. Similarly, Barbosa et al., conducted another systematic review comparing the efficacy of the two routes in preventing miscarriage. Their analysis concluded that there was no significant difference in miscarriage rates between oral and vaginal progestogens. Additionally, both routes showed similar outcomes in terms of ongoing pregnancies/live births.

### Table I: Comparison of age distribution and efficacy of progestogens in preventing recurrent miscarriages among study groups A and B (n=108)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>Group A (n=54)</th>
<th>Group B (n=54)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>20-30</td>
<td>18 (33.3%)</td>
<td>16 (29.6%)</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>31-40</td>
<td>36 (66.7%)</td>
<td>38 (70.4%)</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>Effective</td>
<td>48 (88.9%)</td>
<td>36 (66.7%)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Not Effective</td>
<td>6 (11.1%)</td>
<td>18 (33.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Group A: received oral progestogens; Group B received vaginal progestogens

### Table II: Comparison of efficacy of oral and vaginal progestogens in preventing recurrent miscarriages based on age and number of previous miscarriages

<table>
<thead>
<tr>
<th>Variables</th>
<th>Efficacy</th>
<th>Group A</th>
<th>Group B</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 - 30</td>
<td>Effective</td>
<td>17 (1.5%)</td>
<td>7 (13%)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Not effective</td>
<td>1 (1.9%)</td>
<td>6 (11.1%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30 - 40</td>
<td>Effective</td>
<td>31 (57.4%)</td>
<td>29 (53.7%)</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Not effective</td>
<td>5 (9.2%)</td>
<td>12 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>No. of miscarriage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 4</td>
<td>Effective</td>
<td>44 (81.5%)</td>
<td>27 (50%)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Not effective</td>
<td>2 (3.7%)</td>
<td>10 (18.5%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 4</td>
<td>Effective</td>
<td>4 (7.4%)</td>
<td>9 (16.7%)</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>Not effective</td>
<td>4 (7.4%)</td>
<td>8 (14.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Group A: received oral progestogens; Group B received vaginal progestogens; # Chi-square test
The effective role of progesterone in maintaining pregnancy may be attributed to its fundamental role in various reproductive processes. Progesterone facilitates secretory changes in the uterine lining, which are crucial for successful embryo implantation. Additionally, progesterone reduces uterine contractility, further supporting the implantation process. Progesterone is also thought to regulate the mother's immune responses, preventing rejection of the embryo. Furthermore, pro-inflammatory cytokines have been linked to miscarriage frequency, while progesterone-induced blocking factor suppresses immunological reactions and promotes a shift from type-1 to type-2 cytokines, ultimately increasing type-2 cytokine levels.

**CONCLUSION**

In conclusion, oral progestogens demonstrate superior efficacy over vaginal progestogens in preventing recurrent miscarriages during early pregnancy. This was evidenced by significantly higher effectiveness rates in the oral progestogens group (88%), compared to the vaginal progestogens group (66%). An important finding of our study was the greater efficacy of oral progestogens among participants aged 20–30 years and those with fewer than 4 previous miscarriages. These results highlight the significance of considering the route of administration when prescribing progestogens to prevent recurrent miscarriages. Further research may be necessary to validate these results and explore the underlying mechanisms.

**REFERENCES.**


AUTHORS’ CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

**LS:** Concept and study design, acquisition, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

**AA, MS & RN:** Acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

**RR:** Concept and study design, analysis and interpretation of data, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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