**Original Article**

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# To compare the efficacy of progesterone between oral versus vaginal routes of administration in the treatment of first trimester threatened miscarriage

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*[1]Concept, idea and design, acquisition of data, literature Review, final approval and authored the study*
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*[3]Data collection, methodology writing, literature review, drafting and final approval*
*[4]Tabulation of data, bibliography and reviewed the study.*

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**ABSTRACT**

**Objective:** To determine the efficacy of oral versus vaginal progesterone in the treatment of the first trimester threatened miscarriage.

**Methodology:** This randomized controlled trial study was conducted at Gynaecology and Obstetrics Department of Mardan Medical Complex, Mardan from September 2019 to March 2020. A total of 126 women between ages 18-45 years presenting in their first trimester with threatened miscarriage were included. All patients were randomly allocated in two equal groups A and B by lottery method (63 in each group). Patients in group A were given oral progesterone 10 mg bid for one week and group B patients were given vaginal progesterone 400 mg for one week under the supervision of obstetrician. All patients were followed up till 20th week of pregnancy. The efficacy of the drug was evaluated based on the absence of bleeding per vagina and pregnancy proceeding beyond 20 weeks of gestation.

**Results:** A total of 126 women were included. The majority of the patients 64 (50.79%) were between 18 to 30 years of age. The mean age of women in group A was 30.52 ± 4.52 years and in group, B was 30.73 ± 4.23 years. Efficacy of Oral progesterone (group A) was seen in 57 (90.48%) women and of vaginal progesterone (group B) was seen in 46 (73.02%) women. This showed a highly significant difference between the two routes of administration with *p-value* of 0.011.

**Conclusion:** Oral progesterone is more effective than vaginal progesterone in treating first trimester threatened miscarriage in terms of prevention of blood loss and continuing the pregnancy beyond 20 weeks.

**Keywords:** Oral route, Progesterone, Threatened miscarriage, Vaginal Progesterone.

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## Introduction

Threatened miscarriage is the most common complication of pregnancy, occurring in 15-20% of ongoing pregnancy.[1] It is defined as vaginal bleeding and symptoms that suggest that a woman is at increased risk of miscarriage.[2]It is clinically diagnosed when a bloody vaginal discharge or bleeding appears through a closed cervical is during the first half of pregnancy.[3] Ultrasound has modified the diagnosis and approach in the management of miscarriage. For any woman with bleeding in early pregnancy, an ultrasound is offered to ascertain the viability, location of the placenta, and the presence or absence of sub chorionic hematoma which is associated with 4-33% of miscarriage.[4]

Progesterone maintains pregnancy by enhancing uterine quiescence.[5] During early pregnancy, the syncytiotrophoblast secretes human chorionic gonadotropin (hCG), which stimulates progesterone production in the corpus luteum by preventing

regression of this tissue. After seven to nine weeks of gestation, progesterone is directly secreted by the syncytiotrophoblast.[6] Low serum hCG or progesterone levels may predict first trimester abortions. During early pregnancy in women with threatened abortion, progesterone levels were lower in those who had a subsequent miscarriage than in those whose pregnancies continued to fetal viability.[7]

Threatened abortion is diagnosed when vaginal bleeding with or without abdominal pain occurs during the first half of pregnancy. The prerequisites for threatened abortion are a closed cervix and an intrauterine viable fetus.[8] Unfortunately, nearly half of threatened abortions end incomplete miscarriages.[9] Progesterone has been used to treat threatened abortions, but its efficacy remains unclear.[10] The success rate of oral progesterone (10mg bid) in prolonging pregnancy beyond 20 weeks is reported as 84.9%, 56.67%, and 87% in different studies.[11-13] The success rate of vaginal progesterone suppository in the prolongation of pregnancy beyond 20 weeks is reported as 80%.[14]

Although many studies have evaluated the impact of progesterone as a treatment for threatened abortion, only a few randomized studies have been conducted to compare the difference between various routes of administration. The rationale of this study is to evaluate and compare the efficacy of progesterone administered through oral and vaginal routs in pregnant women with the first trimester threatened abortion in preventing miscarriages.

# Methodology

This randomized controlled trial was conducted at Obstetrics and Gynaecology Department of Mardan Medical Complex Teaching Hospital, from 1st January 2020 to 3rd July 2020. The sample size was 126 calculated according to WHO software with 63 patients in each group, with a 95% confidence interval and 80% power of the test. Non-probability, consecutive sampling technique was adopted. Approval from the hospital Ethical and Research Committee was obtained. Written informed consent was taken from all patients after explaining to them the purpose of the study.

All women fulfilling the inclusion criteria i.e. women with threatened miscarriage in their first trimester (up to 12 weeks) were recruited in the study throughout a patient department or emergency department. Women with a history of trauma during pregnancy or bleeding disorders in history were excluded. Detailed history, clinical examination, and routine investigations were done for the confirmation of threatened miscarriage. Patients were randomly allocated into two groups (A and B) by the lottery method with 63 patients in each group. Patients in group A were given tablet progesterone, 10 mg twice daily through oral route, and patients in group B were given vaginal progesterone, 400 mg for one week duration under the supervision of an expert obstetrician. Information like age, parity was recorded on pre designed proforma. Confounders and other biases were controlled by strictly following exclusion criteria. After the intervention, all patients were followed up till 20th week of pregnancy. The efficacy of the rout of administration of progesterone was evaluated based on the absence of vaginal bleeding and pregnancy proceeding beyond 20 weeks of gestation.

Data was collected and analyzed by SPSS version 22. Mean and standard deviation calculated for quantitative variables like age. Frequency and percentages were calculated for categorical variables like parity. Efficacy was compared in two groups. Chi square test was applied. Data was stratified with age and parity. P-value of ≤0.05 was considered statistically significant.

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# Results

A total of 126 women were included in this randomized control trail. Patients were equally divided into two groups, A and B. Majority of patients 64 (50.79%) were between the 18 to 30 years age group. The mean age of women in group A was 30.52 ± 4.52 years and in a group, B was 30.73 ± 4.23 years (TableI). Stratification of efficacy concerning age & parity in both groups is also compared A statistically very significant difference is seen with p-value of 0.008 in age group between 31-45 years. In multiparous women, there is also a significant efficacy seen with a *p-value* of 0.016 as compared to primiparous, with a p-value 0.387.

Efficacy was defined as the absence of bleeding per vagina and pregnancy proceeding beyond 20 weeks of gestation. It is evaluated for both drugs (Table-II).

In group A, efficacy of oral progesterone was 90.48% which was highly significant with *p*-value 0.011 while in vaginal progesterone group B, the efficacy was 73.02%.

Stratification of efficacy with respect to age & parity in both groups is also compared (Table III). A statistically very significant difference is seen with p-value of 0.008 in age group between 31-45 years. In multiparous women, there is also a significant efficacy seen with a p-value of 0.016 as compared to primiparous, with a p-value 0.387.

**Table I: Demographic Characteristics (n=126)**

| Demographic variable | | Group-A(n=63) N(%) | Group-B(n=63) N(%) |
|---|---|---|---|
| **Age (years)** | **18- 30** | 35(55.56) | 29(46.03) |
| | **31-45** | 28(44.44) | 34(53.97) |
| **Parity** | **Primiparous** | 06(9.52) | 05(7.94) |
| | **Multiparous** | 57(90.48) | 58(92.06) |

# Discussion

**Table II: Efficacy of Drugs in both groups. (n=126)**

| Efficacy | Group A (n=63) N (%) | Group B (n=63) N (%) | *P value* |
|---|---|---|---|
| **Yes** | 57(90.48) | 46(73.02) | **0.011** |
| **No** | 06(9.52) | 17(26.98) | |

**Table III: Stratification of efficacy with respect to Age & Parity in both groups. (n=126)**

| Variables | | Group A (n=63) Efficacy | | Group B (n=63) Efficacy | | *p-value* |
|---|---|---|---|---|---|---|
| | | Yes | No | Yes | No | |
| Age (years) | 18-30 | 31 | 04 | 24 | 05 | 0.505 |
| | 31-45 | 26 | 02 | 22 | 12 | 0.008 |
| Parity | Primiparous | 05 | 01 | 03 | 02 | 0.387 |
| | Multiparous | 52 | 05 | 43 | 15 | 0.016 |

Progestogens have been used to treat threatened miscarriage for many years. Some recent studies suggest that the use of progestogens are associated with reduction in the risk of miscarriage in women with threatened miscarriage.[15-17]

It has been suggested that progesterone potentially maintains the survival of the embryo by shifting the immune system towards the production of non-inflammatory T-helper 2 cytokines and by increasing nitric oxide (NO) production, thus improving blood flow and oxygen supply.[18,19] A recent Cochrane review assessing the efficacy and safety of progestogens in threatened miscarriage identified four trials, comparing progesterone with either placebo or no medications.[20]Progesterone treatment for threatened miscarriage reduced the risk of miscarriage by 47 % with a confidence interval consistent with a risk reduction of 21 to 65 %. The success rate of oral progesterone (10mg twice daily) in prolonging pregnancy beyond 20 weeks is reported up to 87%.[14] The success rate of vaginal progesterone suppository in the prolongation of pregnancy beyond 20 weeks is reported as 80%.[15]

In our study, efficacy with oral progesterone (group A) was seen in 90.48% which is statistically highly significant (p-value 0.011). In group B (vaginal progesterone), the efficacy was seen in 73.02% women which was not so significant. This finding is highly supported by Abrar S,in a local study. In this study oral progesterone was effective in 90% of patients while vaginal progesterone was effective in 71% of patients. [21] This finding is almost similar to our results.

The route of administration may influence the efficacy of progesterone therapy during pregnancy.[22, 23] Progesterone can be administered orally, vaginally and intramuscularly. Oral and vaginal administration routes are noninvasive, whereas intramuscular administration is invasive. Additionally, the oral and vaginal routes of administration are associated with acceptable and minimal adverse effects.[24] Oral synthetic progestational agents, including dydrogesterone, have been developed to eliminate issues related to the variable bioavailability of natural oral progesterone formulations.[25] Lee et al collected data from nine randomized trials and reported that the incidence of miscarriage was significantly lower in the oral dydrogesterone group than in the control group (11.7% vs 22.6%; OR 0.43; 95% CI 0.26–0.71; P = 0.001; I2 0%).[26] Similar findings were reported by Wahabi et al that oral progestogens (dydrogesterone and micronized progesterone) were found to reduce the rate of miscarriage compared with no treatment (risk ratio [RR] 0.57; 95% CI 0.38–0.85).[27]Xio-Xue Wang et al pooled data from eight randomized controlled trials in women with threatened miscarriage reported that women receiving dydrogesterone were at a lower risk of miscarriage (RR 0.49, 95% CI 0.33–0.75) than women on natural progesterone (RR 0.69, 95% CI 0.40–1.19). Furthermore, women treated with oral progestogens demonstrated a lower risk of miscarriage (RR 0.55, 95% CI 0.38–0.79) than those on vaginal progestogens (RR 0.58, 95% CI 0.28–

1.21).[28] A more recent study by L Li, Y Zhang, and colleagues also supported that progestogens reduced the risk of miscarriage (RR 0.73, 95% CI 0.59–0.92), with benefit only seen with oral progestogens and not with vaginal progesterone.[29] Similarly in PRISM trail, Vaginal progesterone therapy in the first trimester of pregnancy did not result in a significantly higher rate of live births among women with threatened miscarriages.[30] In terms of safety, no intrauterine deaths, congenital abnormalities or pregnancy-related complications were reported with dydrogesterone.[16,17]

# Conclusion

Oral progesterone is more effective than vaginal progesterone in treating threatened miscarriage of first trimester in terms of prevention of blood loss and reaching the pregnancy beyond 20 weeks. These benefits appear to be statistically significant. Therefore, we recommend that oral progesterone should be a first line treatment option for first trimester threatened miscarriage.

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