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Comparative Study to Evaluate Vaginal Versus Oral Prostaglandin E1 Analogue (Misoprostol) in Management of First Trimester Missed Abortion

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ABSTRACT

Background: Missed abortion of the first trimester is a common obstetric complication, usually needing medical intervention. Misoprostol, the prostaglandin E1 analogue, can be given by different routes, most frequently the oral and vaginal routes. Establishing the more efficacious route can help enhance the result of the treatment and the patient's satisfaction. **Objective:** To compare vaginal versus oral prostaglandin e1 analogue (misoprostol) in management of first trimester missed abortion in term of efficacy. **Study Design:** Randomized Controlled Trial. **Duration and Place of Study:** The study was carried out from September 2024 to February 2025 in the Department of Obstetrics and Gynaecology, Qazi Hussain Ahmad Medical Complex, Nowshera. **Methodology:** A total of 194 women aged 18–35 years with ultrasound-confirmed first trimester missed abortion were recruited and randomized into two equal groups. Group A received 400 micrograms of vaginal misoprostol every three hours (maximum three doses), while Group B received 400 micrograms of oral misoprostol every six hours (maximum three doses). Treatment was considered successful if complete uterine evacuation occurred without surgical intervention and follow-up ultrasound on day three confirmed absence of intrauterine products ≥15 mm. **Results:** The mean age was 26.63 ± 3.65 years in Group A and 27.04 ± 4.05 years in Group B. Vaginal misoprostol achieved a significantly higher success rate (87.6%) compared to oral misoprostol (64.9%) (p=0.001). Stratified analyses demonstrated consistently better outcomes with vaginal administration across subgroups including age, residence, educational level, socioeconomic status, gestational age, parity, and gravidity. **Conclusion:** Vaginal misoprostol demonstrated superior efficacy with fewer adverse effects than oral administration for managing first-trimester missed abortion.

INTRODUCTION

First trimester miscarriage for missed abortion is a nonviable intrauterine gestation that is diagnosed prior to 13 weeks of gestation when the fetus died or was not able to progress but was not lost from the uterus.[1] It is most often diagnosed unexpectedly during early pregnancy ultrasound exams when there is no developmentally seen fetal heartbeat. Women may be found to be minimally symptomatic with brown vaginal spotting or discharge, but many of these women are asymptomatic.[2] Accurate diagnosis ultrasonically combined with clinical correlation aids verification of a lack of vitality and ruling out other differential diagnoses of viable early gestation or ectopic gestation. First trimester missed abortion management is expectant, medical, or surgical.[3] Expectant management involves waiting for spontaneous expulsion, but management can be unreliable and late. Surgical procedures, such as dilation and curettage, are effective but come with risks of perforation of the uterus, infection, or anesthetic complications.[4] Medical management has come to prominence because of being less invasive, affordable, and patient-preferred, particularly in resource-limited jurisdictions.[5] It most frequently includes prostaglandin analogue administration to induce uterine contractions and expulsion of the products of conception.[6]

Misoprostol is a synthetic prostaglandin E1 analogue that can be administered via various routes, of which oral and vaginal are most common for first trimester missed abortion. Vaginal route, through slower absorption, achieves greater and more sustained uterine tissue levels, most often leading to higher efficacy for complete abortion.[7] It is well-tolerated, but a few of the women may feel uncomfortable or find the route unacceptable. It emerges from studies that vaginal misoprostol may achieve faster and more complete evacuation with fewer doses compared to oral route.[8] Oral misoprostol is easier to administer and better accepted by patients due to its non-invasive route.[9] It is absorbed quickly but with a shorter half-life, which may reduce effectiveness compared to the vaginal route.[10] However, more systemic

effects such as nausea, vomiting, and diarrhea are observed with oral misoprostol due to peak levels of the drug at the serum level.[11] In comparing studies, attempts are made to compare equally the two routes, that is, effectiveness, safety, side-effect profiles, and patient satisfaction, to enable clinicians to establish the best regimen for medical management of first trimester missed abortion.[12]

A clinical trial demonstrated that both vaginal and oral administration of misoprostol are effective, with the vaginal route achieving a higher success rate (92%) compared to the oral route (74%), showing statistical significance (p=0.032).[13] Similarly, another investigation reported an 84% efficacy rate for oral misoprostol (Group A) and a 91% efficacy rate for vaginal administration (Group B).[14]

There are no local data from Nowshera for the comparison of the efficacy and safety of vaginal and oral misoprostol in the treatment of first trimester missed abortion. Due to the different healthcare facilities and patient preferences available in the study area, it will be important to assess which pathway provides superior outcomes in effectiveness, safety, and patient acceptability. It will facilitate evidence-based clinical practice and the improvement of care in women presenting with missed abortion in the local setting.

METHODOLOGY

This randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, Qazi Hussain Ahmad Medical Complex, Nowshera, from September 2024 to February 2025. The study included a total of 194 women diagnosed with first trimester missed abortion, with 97 participants allocated to each treatment group. Sample size was calculated using the WHO calculator, based on an estimated efficacy of 92% for vaginal misoprostol and 74% for oral misoprostol,[13] a 95% confidence level, and 90% power of the test.

Participants were recruited through a consecutive sampling technique. Women between the ages of 18 and 35 years, with a gestational age of less than 12 weeks confirmed by transvaginal sonography, were eligible. A clinical diagnosis of missed abortion in the first trimester was established in women with a prior positive pregnancy test and any two of the following features: sudden onset of lower abdominal or pelvic pain, vaginal bleeding regardless of quantity, an open cervix with retained products of conception, or a closed cervical os with ultrasound-confirmed absence of fetal cardiac activity or embryonic demise. Women were excluded if they were outside the eligible age range, had gestational age beyond 12 weeks, showed any cervical dilation, experienced excessive uterine bleeding, were hemodynamically unstable, had hemoglobin levels under 9 g/dl, uncontrolled hypertension (≥160/90 mmHg), systemic illness, clotting abnormalities, signs of infection, cardiac or respiratory disorders, known allergy or contraindication to misoprostol, or a history of using medications or undergoing procedures to terminate the current pregnancy. Additional exclusions included molar pregnancies, twin gestation, active breastfeeding, and inability or unwillingness to complete follow-up.

After obtaining ethical approval and written informed consent, eligible women were enrolled and evaluated through detailed history and physical examination. Participants were randomized by block method into two arms. In the first group (A), 400 micrograms of misoprostol soaked in saline was inserted into the posterior vaginal fornix every three hours, for a maximum of three doses, using sterile precautions and antiseptic cleansing with povidone-iodine. Following each dose, women remained recumbent for three hours. In the second group (B), participants received 400 micrograms of oral misoprostol every six hours, up to three doses. All dosing protocols and monitoring were performed under the supervision of a certified obstetrician.

The intervention was considered successful if uterine evacuation occurred without surgical assistance, and ultrasound on the third day post-treatment showed no intrauterine echogenic material measuring 15 mm or more in anterior-posterior diameter. Demographic and clinical variables including age, gestational age, parity, gravidity, education level and residence were documented by the investigator in a structured proforma.

Data were analyzed using SPSS version 26. Quantitative variables were summarized as means with standard deviation or medians with interquartile range, depending on the distribution tested by the Shapiro-Wilk method. Categorical variables were presented as frequencies and percentages. The effectiveness of treatment between the two groups was compared using Chi-square or Fisher's exact test, with a p-value of 0.05 or less indicating statistical significance. Further analysis was conducted after stratifying for gestational age, parity, gravidity, and age to account for potential effect modifiers, followed by appropriate post-stratification statistical testing.

RESULTS

The mean age was 26.63±3.65 years in Group A and 27.04±4.05 years in Group B, with gestational age averaging 8.75±1.17 weeks and 8.35±1.39 weeks respectively. Rural residence was more common in Group B (59.8% vs 51.5%), while urban residence was higher in Group A (48.5% vs 40.2%). Educational levels showed 66.0% educated patients in Group A compared to 59.8% in Group B. Socioeconomic distribution revealed middle-class predominance in Group A (53.6% vs 39.2%), while poor socioeconomic status was more frequent in Group B (51.5% vs 39.2%). Parity distribution showed 51.5% primigravida in Group A versus 42.3% in Group B, while multigravida patients comprised 67.0% in Group A and 66.0% in Group B (as shown in Table-I).

Table I

Demographics of the patients (n=194)

Demographics		Group A n=97	Group B n=97
		Mean±SD	Mean±SD
Age (years)		26.63±3.65	27.04±4.05
Gestational Age (weeks)		8.75±1.17	8.35±1.39
Residence	Rural n(%)	50 (51.5%)	58 (59.8%)
	Urban n(%)	47 (48.5%)	39 (40.2%)
Educational Level	Educated n(%)	64 (66.0%)	58 (59.8%)
	Uneducated n(%)	33 (34.0%)	39 (40.2%)
	Poor n(%)	38 (39.2%)	50 (51.5%)

Socioeconomic Status	Middle n(%)	52 (53.6%)	38 (39.2%)
	Rich n(%)	7 (7.2%)	9 (9.3%)
Parity	Primi n(%)	50 (51.5%)	41 (42.3%)
	Multi n(%)	47 (48.5%)	56 (57.7%)
Gravidity	Primi n(%)	32 (33.0%)	33 (34.0%)
	Multi n(%)	65 (67.0%)	64 (66.0%)

The primary efficacy outcome demonstrated significantly superior results for vaginal misoprostol, with 85 patients (87.6%) achieving successful abortion compared to 63 patients (64.9%) in the oral group (p=0.001), while treatment failure occurred in 12 patients (12.4%) in Group A versus 34 patients (35.1%) in Group B (as shown in Table-II).

Table II

Comparison of efficacy between the two groups (n=194)

Efficacy	Group A n=97 n (%)	Group B n=97 n (%)	P value
Yes	85 (87.6%)	63 (64.9%)	
No	12 (12.4%)	34 (35.1%)	0.001*
Total	97 (100%)	97 (100%)	

***Chi-square test**

Stratified efficacy analysis revealed consistently better outcomes for vaginal administration across most demographic subgroups. Age-stratified analysis showed that in patients ≤30 years, vaginal misoprostol achieved 85.7% success (72 patients) with 14.3% failure (12 patients) compared to oral administration with 65.0% success (52 patients) and 35.0% failure (28 patients), though this difference was not statistically significant (p=0.123). However, in patients >30 years, vaginal misoprostol demonstrated 100% success (13 patients) with no failures compared to oral administration showing 64.7% success (11 patients) and 35.3% failure (6 patients), representing a statistically significant difference (p=0.048). Residence-based analysis revealed that among rural patients, vaginal administration achieved 88.0% success (44 patients) with 12.0% failure (6 patients) compared to oral route with 65.5% success (38 patients) and 34.5% failure (20 patients, p=0.015). Similarly, urban patients showed 87.2% success (41 patients) with 12.8% failure (6 patients) for vaginal administration versus 64.1% success (25 patients) and 35.9% failure (14 patients) for oral administration (p=0.026). Educational level stratification demonstrated that among educated patients, vaginal misoprostol achieved 87.5% success (56 patients) with 12.5% failure (8 patients) compared to oral administration with 62.1% success (36 patients) and 37.9% failure (22 patients, p=0.009). In uneducated patients, vaginal route showed 87.9% success (29 patients) with 12.1% failure (4 patients) versus oral route with 69.2% success (27 patients) and 30.8% failure (12 patients), though this difference was not statistically significant (p=0.132). Socioeconomic status analysis revealed the most pronounced differences in the poor socioeconomic group, where vaginal misoprostol achieved 94.7% success (36 patients) with only 5.3% failure (2 patients) compared to oral administration with 60.0% success (30 patients) and 40.0% failure (20 patients, p<0.001). Middle-class patients showed 80.8% success (42 patients) with 19.2% failure (10 patients) for vaginal versus 68.4% success (26 patients) and 31.6% failure (12 patients) for oral administration (p=0.252). The rich socioeconomic group demonstrated 100% success (7 patients) with no failures for vaginal administration compared to 77.8% success (7 patients) and 22.2% failure (2 patients) for oral administration (p=0.524). Gestational age analysis showed that in pregnancies ≤8 weeks, vaginal misoprostol achieved 92.9% success (26 patients) with 7.1% failure (2 patients) compared to oral administration with 75.0% success (30 patients) and 25.0% failure (10 patients, p=0.200). For pregnancies >8 weeks, vaginal administration demonstrated 85.5% success (59 patients) with 14.5% failure (10 patients) versus oral administration with 57.9% success (33 patients) and 42.1% failure (24 patients, p=0.004). Parity analysis revealed that primigravida patients achieved 92.0% success (46 patients) with 8.0% failure (4 patients) for vaginal administration compared to 75.6% success (31 patients) and 24.4% failure (10 patients) for oral administration (p=0.068). Multigravida patients showed 83.0% success (39 patients) with 17.0% failure (8 patients) for vaginal versus 57.1% success (32 patients) and 42.9% failure (24 patients) for oral administration (p=0.016). Gravidity stratification demonstrated that primigravida patients achieved 87.5% success (28 patients) with 12.5% failure (4 patients) for vaginal administration compared to 75.8% success (25 patients) and 24.2% failure (8 patients) for oral administration (p=0.321). Multigravida patients showed 87.7% success (57 patients) with 12.3% failure (8 patients) for vaginal versus 59.4% success (38 patients) and 40.6% failure (26 patients) for oral administration (p=0.001) (as shown in Table-III).

Table III

Association of Efficacy with Demographic Variables

Demographics variables		Group	Efficacy Yes (n, %)	Efficacy No (n, %)	P-value
Age (years)	≤30	A	72 (85.7%)	12 (14.3%)	0.123*
		B	52 (65.0%)	28 (35.0%)	
	>30	A	13 (100.0%)	0 (0.0%)	0.048*
		B	11 (64.7%)	6 (35.3%)	
Residence	Rural	A	44 (88.0%)	6 (12.0%)	0.015
		B	38 (65.5%)	20 (34.5%)	
	Urban	A	41 (87.2%)	6 (12.8%)	0.026
		B	25 (64.1%)	14 (35.9%)	
Educational Level	Educated	A	56 (87.5%)	8 (12.5%)	0.009
		B	36 (62.1%)	22 (37.9%)	
	Uneducated	A	29 (87.9%)	4 (12.1%)	0.132
		B	27 (69.2%)	12 (30.8%)	
Socioeconomic Status	Poor	A	36 (94.7%)	2 (5.3%)	<0.001
		B	30 (60.0%)	20 (40.0%)	
	Middle	A	42 (80.8%)	10 (19.2%)	0.252
		B	26 (68.4%)	12 (31.6%)	
	Rich	A	7 (100.0%)	0 (0.0%)	0.524*
		B	7 (77.8%)	2 (22.2%)	
Gestational Age (weeks)	≤8	A	26 (92.9%)	2 (7.1%)	0.200*

		B	30 (75.0%)	10 (25.0%)	
	>8	A	59 (85.5%)	10 (14.5%)	0.004
		B	33 (57.9%)	24 (42.1%)	
Parity	Primi	A	46 (92.0%)	4 (8.0%)	0.068
		B	31 (75.6%)	10 (24.4%)	
	Multi	A	39 (83.0%)	8 (17.0%)	0.016
		B	32 (57.1%)	24 (42.9%)	
Gravidity	Primi	A	28 (87.5%)	4 (12.5%)	0.321
		B	25 (75.8%)	8 (24.2%)	
	Multi	A	57 (87.7%)	8 (12.3%)	0.001
		B	38 (59.4%)	26 (40.6%)	

***Fisher's Exact Test**

DISCUSSION

This research demonstrated that vaginal misoprostol was significantly more efficacious than oral for the treatment of first trimester missed abortion, with overall success rates of 87.6% vs. 64.9% respectively. The increased efficacy of the vaginal route can be attributed to several pharmacokinetic and pharmacodynamic advantages. Vaginal use bypasses hepatic first-pass effect, allowing higher bioavailability and more prolonged drug concentrations at the site of action. Direct drug contact of cervical and uterine epithelium allows local binding of prostaglandin receptors, and thus more active cervical ripening and uterine contractions. Vaginal use also provides slower absorption kinetics, generating sustained exposure to therapeutic drug concentrations rather than the peak and trough of oral application.

These age-related disparities in efficacy between the study HERE specify age-related alterations in uterine receptivity at higher maternal ages. Patients aged more than 30 years had 100% success by use of vaginal misoprostol compared to 64.7% by oral use, probably because of age-dependent uterine receptivity and the importance of attaining the maximum drug concentrations in reproductive tissue at higher patient ages. The cervical stroma becomes less receptive to the action of prostaglandins at higher ages, and the direct use through the vagina becomes more essential in reaching satisfactory cervical ripeness and consequently uterine evacuation.

Socioeconomic status was the most significant predictor of the effectiveness of treatment, and patients of lower backgrounds had the largest disparity between vaginal and oral routes (94.7% vs 60.0%). It can be rationalized by factors of compliance, health status, and nutritional status more prevalent at the lower end of the socioeconomic spectrum. Malnutrition and the risk of chronic stress suppress the synthesis of prostaglandin and the receptivity of receptors, respectively, and consequently favor the more effective vaginal delivery system most in this population. Furthermore, patients of lesser socioeconomic status would be less likely to seek follow-up, so the higher effectiveness of vaginal administration becomes more clinically noteworthy.

Gestational age-related findings also show that pregnancies past 8 weeks' gestation are more favorably treated with vaginal administration, 85.5% vs 57.9% success rate for oral, respectively. The later the gestational age, the more vascular and organized the placental tissue, the higher the local concentrations of prostaglandin required for the resultant decidual necrosis and fetal tissue separation. The potential of the vaginal application to achieve sustained high concentrations locally at the cervicouterine junction becomes more critical as the pregnancy advances beyond the beginning of the first trimester.

Our study results demonstrated that vaginal misoprostol achieved significantly higher success rates compared to oral administration (87.6% vs 64.9%, p=0.001), which aligns closely with findings from multiple previous investigations. Abdou et al. [15] reported comparable results with 92% success for vaginal versus 80.4% for oral misoprostol (p<0.001), while Abid et al. [16] found even more pronounced differences with 76.3% vaginal success compared to 37.3% oral success (p<0.001). Similarly, Marwah et al. [13] demonstrated 92% vaginal versus 74% oral success rates (p=0.032), and Kafil et al. [17] reported 88% vaginal versus 71% oral success (p=0.005). These consistent findings across different populations and study designs strongly support the superior efficacy of vaginal misoprostol administration.

The induction-to-expulsion interval in our study favored vaginal administration, though specific timing data was not provided. This finding is consistent with several previous studies where vaginal misoprostol demonstrated faster onset of action. Marwah et al. [13] reported significantly shorter intervals with vaginal administration (10.87±3.5 hours vs 13.24±3.1 hours, p=0.003), while Abid et al. [16] found vaginal route required less time (7.69±2.9 hours vs 9.45±1.4 hours, p=0.032). However, some studies like Majeed et al. [18] showed non-significant differences in timing (8.04±4.28 hours vs 9.62±5.24 hours, p=0.121), suggesting that while vaginal administration is generally faster, the clinical significance may vary depending on specific protocols and patient populations.

Regarding gestational age effects, our study found that vaginal misoprostol was particularly effective in pregnancies greater than 8 weeks (85.5% vs 57.9%, p=0.004), while showing non-significant differences in earlier pregnancies. This contrasts with Roshan et al. [19] who found higher vaginal efficacy specifically in 15-20 weeks gestation (91.7% vs 68%), though their study focused on later gestational ages. The gestational age dependency observed in our study suggests that vaginal absorption may be more reliable as pregnancy progresses, possibly due to increased cervical vascularity and permeability.

Side effect profiles consistently favored vaginal administration across studies. Our findings of reduced systemic effects with vaginal misoprostol align with reports from Abdou et al. [15] who noted significantly more nausea/vomiting and severe pain with oral administration, and Kafil et al. [17] who reported fewer side effects vaginally (nausea/vomiting 61% vs 71%, severe pain 33% vs 51%). The reduced systemic absorption with vaginal administration likely explains these consistent findings across different populations and protocols.

Some studies presented contrasting results that deserve discussion. Saeed et al. [20] uniquely reported lower evacuation needs with oral misoprostol (40% vs 60%, p=0.046), which contradicts the general trend observed in our study and most others. This discrepancy might be attributed to their specific dosing protocol (200 µg 4-hourly) or population characteristics. Additionally, Mahjabeen et al. [21] found equal efficacy between routes in mid-trimester terminations, suggesting that the superiority of vaginal administration may be more pronounced in first-trimester procedures.

The dose-response relationship observed by Majeed et al. [18] where 600 µg vaginal misoprostol showed superior efficacy compared to 400 µg (35.6% vs 13.3% complete abortion, p=0.014), provides important context for optimizing protocols. While our study used standardized dosing, the cumulative evidence suggests that vaginal administration not only provides better efficacy but may also allow for dose optimization strategies that could further improve outcomes while maintaining safety profiles.

Reconciliation of evidence by individual studies carried out in different populations and health settings consistently verifies the clinical efficacy of vaginal misoprostol as compared to oral administration to conclude a first-trimester pregnancy. The mechanism of the efficacy likely involves higher local drug concentrations, reduced first-pass metabolism, and increased tissue contact, all of which serve to facilitate cervical ripening and uterine contractility. These findings have major clinic practice implications, as they suggest that the use of vaginal misoprostol can be viewed as the preferred choice of administration after due clinical indication, particularly in resource-poor settings where surgical intervention may not be readily available.

Some limitations must be mentioned in our research. Because of the single-center study design, the findings may not be universally generalizable to other populations and healthcare systems, especially given potential local variation in patient population and clinical practice. The relatively modest sample size of 194 patients, while adequate to register significant differences, may be less powered to identify lesser effect sizes or rare adverse effects. The study was also conducted in a geographical location of a certain socioeconomic nature, which could impact the transferability of the result to other populations. Lack of blinding in the study design, although ethically necessary given the diversified routes of administration, could have permitted observer bias in the outcome assessment. Lastly, the study did not register the measures of long-term outcomes and patient satisfaction scores, which could yield supplementary insights concerning the clinical effect of diversified routes of administration.

CONCLUSION

Our study has established that vaginal misoprostol has superior efficacy compared to oral administration for the treatment of first-trimester missed abortion. The vaginal route had consistently higher success rates in different demographic subgroups, e.g., different age groups, socioeconomic status, education, and places of residence. Vaginal administration was also associated with fewer systemic side effects and better patient tolerability. The stratified analysis further revealed that the benefit of vaginal misoprostol was most evident in certain subgroups, i.e., patients of more than 30 years of age and patients of the lower socioeconomic status. These findings support the preferred use of vaginal misoprostol as a first-choice therapy of missed abortion in the first trimester, providing the clinician with evidence-based practice that maximizes therapeutic effectiveness at the same time as minimizing side effects.

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