

Study of Oral Versus Vaginal Misoprostol in the Management of Early Pregnancy Loss

Ahmed Mahmoud Abdou, Taha Abdelfatah Ahmed,

Mohammed Ahmed Elsayed Abd elhafez*, Mohammed Mostafa Zayton

Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University, Egypt

*Corresponding author: Mohammed Ahmed Elsayed Abd elhafez,

Mobile: (+20) 01092546747, E-Mail: m.abdelhafez6@gmail.com

ABSTRACT

Background: Research conducted by specialists does not show that oral misoprostol is more successful than vaginal misoprostol to manage early pregnancy loss, and vice versa.

Objective: To compare oral versus vaginal misoprostol for managing early pregnancy loss.

Subjects and Methods: A prospective randomized controlled trial that was performed on 102 women attending to Obstetrics and Gynecology Department and diagnosed with missed abortion on ultrasound. They were divided into 2 groups. (Group A: Vaginal Misoprostol): Intravaginally into the posterior fornix, 51 patients were administered 600 µg of misoprostol soaked in normal saline solution, which was repeated three-hourly up to a maximum of two doses. Group B (Oral Misoprostol): Misoprostol 600 g was orally administered to 51 patients with a maximum of two doses, each separated by three hours.

Results: All of incidence of hypotension, mean of satisfaction, and mean of successful rate were statistically significantly higher as compared with the cases in group B. incidence of side effects was statistically significantly higher in the cases of group B as compared with the cases in group A. Mean induction-expulsion interval in the cases of group A (9.5 ± 3.3) was shorter as compared with the cases in group B (10.8 ± 2.2) with non-statistically significant difference ($p=0.078$).

conclusion: Misoprostol use by the vaginal route is more efficacious than oral route. Vaginal route was found to have cervical ripening effect and did not need much monitoring to become the first choice even over surgical for induction of labor.

Keywords: Misoprostol, Early Pregnancy Loss.

INTRODUCTION

Early pregnancy loss is defined as the loss of a pregnancy before 20 weeks of gestation or the birth of a fetus weighing less than 500 grammes, as stated by the World Health Organization. Approximately spontaneous abortion may complicate 15% of all clinically detectable pregnancies ⁽¹⁾. Fetal development stop and ultrasound indications of an empty gestational sac or absence of fetal heart activity indicate a missed abortion in the first trimester of pregnancy. A little over 10% of all pregnancies that can be verified by a medical professional end in a miscarriage or stillbirth ⁽²⁾. A high standard of medical care is essential for the successful induction of an abortion. Several medicinal and surgical options exist for preventing a pregnancy from continuing ⁽³⁾. Miscarriages discovered before 14 weeks of pregnancy were traditionally treated with emergency surgery. However, several risks, such as postoperative infection, accompany surgical procedures. However, effective, safe, and socially acceptable medical care has emerged in recent years ⁽⁴⁾.

Due to its effectiveness, low cost, and long shelf life (2 years at room temperature), the prostaglandin analogue misoprostol is frequently used for pregnancy termination ⁽²⁾. However, the ideal dose and delivery method of misoprostol have not been determined by randomised studies, despite its widespread use in the treatment of miscarriages, especially missed miscarriage. Misoprostol for the treatment of missed miscarriage does not have a universally approved dosing schedule, not even from the World Health Organization ⁽⁵⁾. The oral route has a number of drawbacks, including lower absorption and more gastrointestinal side effects than the vaginal route ⁽⁶⁾.

The impact of misoprostol route on its pharmacokinetic profile was investigated in a recent study. Misoprostol was most well absorbed when administered vaginally. The uterus could be induced into labor with a slow, steady contraction by using vaginally delivered, low-dose drugs. The peak was higher after oral delivery, but the side effects were also more severe than those seen after vaginal management ⁽⁷⁾.

Even several trials have been conducted, professionals still can't decide whether oral or vaginal misoprostol is more beneficial. Researchers have found that vaginal misoprostol is more successful than oral misoprostol at emptying the uterus. Some studies have shown that the vaginal form of misoprostol is more effective than the oral form, whereas others have shown no such difference ⁽⁸⁾.

It was the goal of our study, to compare oral versus vaginal misoprostol for managing early pregnancy loss.

SUBJECTS AND METHODS

Subjects:

One hundred and two women who required care and support at the Department of Obstetrics and Gynecology, Medical School, Zagazig University Hospitals participated in this prospective randomised controlled experiment from October 2021 to April 2022.

Inclusion criteria:

- Fetal demise diagnosed by ultrasound.
- Aged between 18 and 45.
- Gestational age to be equal or less than 13 weeks by LMP.
- Bimanual pelvic exam revealed a closed cervix.

- Hemoglobin level to be equal or higher than 9 gm/dl.
- Women who committed to following the prescribed follow-up protocol.

Exclusion criteria:

- Medical disorder
- Blood clotting abnormalities
- Unstable hemodynamics
- Abnormally heavy uterine bleeding
- Sacs for twin pregnancies
- Molar pregnancy
- Women who are at a greater risk of having their uterus burst
- Severe infection
- Noncompliant women who were advised to comply with a follow-up plan.

Randomization was done using computer program:

- Group A (Vaginal Misoprostol): Misoprostol 600 µg soaking in normal saline solution was inserted intravaginally into the posterior fornix of 51 individuals, with dosing occurring every three hours for a total of two doses.
- Group B (Oral Misoprostol): At a maximum of 2 doses, 600 µg of misoprostol was orally administered to 51 patients at 3-hour intervals with water.
- Characteristics data were collected (age, location, number of children, weeks pregnant, history of spontaneous abortions and caesarean sections). General examination (body mass index, blood pressure, pulse rate, temperature) was done. Participants underwent initial evaluations and ultrasonographic confirmation of a missed abortion before being randomly assigned to Group A (Vaginal Misoprostol) or Group B (Oral Misoprostol).
- Complete evacuation of uterine material was confirmed by clinical examination and ultrasonography in all patients. When ultrasonography and clinical observation showed that complete expulsion still hadn't happened 12 hours after the final dose, surgery was performed.
- Time between induction and expulsion was documented in both groups.
- After a full abortion or surgical evacuation, patients in both groups were observed for 24 hours before being sent home with pain medication and prophylactic antibiotics to take for 5 days.
- About a week after being sent home, patients returned for their first follow-up appointment. Negative outcomes, such as sickness, vomiting, severe cramping pain, dizziness, headache, diarrhea, fever, chills, heavy bleeding, discharge per vaginally, and uterine rupture, were documented and treated as necessary. The total amount of blood lost after an abortion was calculated by weighing soaked things and using the following formula: wet item gramme weight - dry item gramme weight = millilitres of blood within the item. The bleeding was classified as either

quick (5 days), average (5-10 days), or extended (>10 days).

- At 6 weeks, patients were expected to return for an update on their treatment's efficacy, side effects, and overall acceptance. However, if any difficulties emerged or doubts were raised, women were urged to return to the hospital.
- In addition, at the follow-up appointment, the patients' levels of contentment, willingness to accept the treatment, and propensity to suggest it to others were recorded.

Ethical approval:

This experiment was ethically approved by the Faculty of Medicine, Zagazig University's Ethical Committee. After being fully informed, all participants provided written consent. The study was conducted in line with the Helsinki Declaration.

Statistical analysis

To conduct the quantitative study, we used version 20 of the Statistical Package for the Social Sciences (SPSS). The numerical data were presented with their respective means and standard deviations (SD). Qualitative data were presented as frequency and %. The student's t test was used for analysing quantitative data with independent variables. Using Pearson's Chi-Square (X²), we analysed data that was qualitatively different from one another. To be statistically significant, we determined that a P value of 0.05 or lower was necessary.

RESULTS

Table (1) shows that non statistical significant differences were found between both groups regarding maternal age (years), gestational age (weeks), parity, previous abortion, body mass index (BMI) and previous cesarean section (CS) distribution.

Table (1): Demographics of study population

Demographic data	Group A N (51)	Group B N (51)	P
Maternal age (years)			
Mean ± SD.	23.6±2.9	23.2±2.9	0.842
Parity			
Nullipara	12(23.5)	7(13.7)	0.035
Multipara	39(76.5)	44(86.3)	
Abortion			
Yes	10(19.6)	12(23.5)	0.554
No	41(80.4)	39(76.5)	
Prev CS			
Yes	7(16.8)	8(15.7)	0.426
No	44(83.2)	43(84.3)	
BMI (kg/m²)			
Mean ± SD	21.7±2.2	21.8±2	0.893
Gestational age(weeks)			
Mean ± SD.	10.3±2	9.9±2.2	0.659

When comparing the two groups' success rates, there was a statistically significant distinction. In contrast, when comparing I-E Interval, neither group significantly differs from the other (Table 2).

Table (2): Analysis of abortion process among the study sample

Variable	Group A N(51)	Group B N(51)	P
Induction-Expulsion Interval			
Mean ± SD	9.5±3.3	10.8±2.2	0.078
Successful rate			
Successful	47(92)	41(80.4)	<0.001*
Unsuccessful	4(8)	10(19.6)	

* Significant.

There was significant difference between two study population regarding hypotention, nausea and vomiting, and severe crampy pain. On contrast, there was no significant difference regarding diarrhea, fever, headache, and dizziness (Table 3).

Table (3): Complications among study population

Complications	Group A N(51)	Group B N(51)	P
Hypotension			
Yes	6(11.8)	1(2)	0.05*
No	45(88.2)	50(98)	
Nausea and vomiting			
Yes	30(58.8)	36(70.6)	<0.001*
No	21(41.2)	15(29.4)	
Headache			
Yes	11(21.5)	12(23.5)	0.778
No	40(78.5)	39(76.5)	
Severe crampy pain			
Yes	17(33.3)	24(47)	<0.001*
No	34(66.7)	27(53)	
Dizziness			
Yes	10(19.6)	12(23.5)	0.634
No	41(80.4)	39(76.5)	
Diarrhea			
Yes	6(11.8)	6(11.8)	0.981
No	45(88.2)	45(88.2)	
Fever			
Yes	2(4)	3(6)	0.669
No	49(96)	48(94)	

* Significant

Both pre- and postoperative hemoglobin levels were similar between the two groups, and there was also no statistically significant difference in the time it takes for menstruation to resume after an abortion (days) (Table 4).

Table (4): Characteristics among study population

Variable	Group A N(51)	Group B N(51)	P
Hb level (preoperative)			
Mean ± SD	11.3±1.2	11.5±1.3	0.956
Hb level (postoperative)			
Mean ± SD	10.25±1.26	10.35±1.23	0.996
Duration of post abortion bleeding			
Mean ± SD	8.6±3	9.2±2.7	0.831
Resumption of menstruation(days)			
Mean ± SD.	36.7±6.9	36.4±6.8	0.850
Excessive bleeding			
Yes	1(2)	3(6)	0.434
No	50 (98)	48(94)	

There was significant difference between the two study group regarding satisfaction, chosen again, and recommended to other (Table 5).

Table (5): Characteristics among study population

Characteristics	Group A N(51)	Group B N(51)	P
Satisfaction			
Satisfied	49(96)	40(78.4)	0.001*
Unsatisfied	2(4)	11(21.6)	
Chosen again			
Yes	49(96)	38(74.5)	<0.001*
No	2(4)	13(25.5)	
Recommended to other			
Yes	49(96)	38(74.5)	<0.001*
No	2(4)	13(25.5)	

* Significant

DISCUSSION

Missed abortion, also known as silent miscarriage, is a condition where the fetus dies but remains in the uterus, without causing any symptoms of miscarriage. There are several methods of managing missed abortion, depending on the gestational age and the patient's medical history. One common method is expectant management, where the patient is monitored closely for signs of spontaneous expulsion of the fetus. Another method is medical management, which involves the use of medications such as misoprostol to induce uterine contractions and expel the fetus. Surgical management, including dilation and curettage (D and C) or vacuum aspiration, may also be used to remove the retained products of conception. The choice of method depends on the patient's preferences, the size of the gestational sac, and the presence of any complications such as infection or bleeding ⁽¹⁾.

Induction of abortion is a procedure used to terminate a pregnancy in the second trimester or beyond. This is typically done using medication or a combination of medication and surgery. There are various methods of induction of abortion, including the use of prostaglandins, mifepristone, and misoprostol. Each method has its own advantages and disadvantages, and the choice of method

will depend on the gestational age of the fetus, the woman's medical history, and other factors ⁽⁹⁾.

Misoprostol is a medication used for the induction of abortion, also known as medical abortion. It is a synthetic prostaglandin E1 analogue that causes uterine contractions and cervical ripening, leading to the expulsion of the pregnancy. Misoprostol is highly effective and has a success rate of up to 98%, making it a safe and reliable option for women seeking abortion ⁽¹⁰⁾.

The dosage and route of administration vary depending on the gestational age of the pregnancy and the clinical indication. However, misoprostol is not recommended for use in women with previous uterine surgery or a history of uterine rupture. Studies have also shown that the use of misoprostol in abortion is associated with few adverse effects, including nausea, vomiting, diarrhea, and abdominal pain. In conclusion, misoprostol is a safe and effective medication for the induction of abortion, providing women with a safe and less invasive alternative to surgical abortion ⁽¹¹⁾.

The use of misoprostol, a synthetic prostaglandin E1 analogue, has gained popularity in the induction of abortion due to its high efficacy and low cost. Misoprostol can be administered via different routes, including orally, vaginally and intravenously. While oral administration is the most common route, vaginal administration has been proposed as a more effective method ⁽¹²⁾. The oral approach has a number of drawbacks, including lower absorption and more gastrointestinal side effects than the vaginal route ⁽⁶⁾.

Our study was a prospective randomized controlled trials study which was conducted on 102 women (divided into two groups 51cases for each) attending to Obstetrics and Gynecology Department and diagnosed with missed abortion on ultrasound. In our study we found no statistically significant difference between the studied groups regarding body mass index, the mean maternal age, the mean gestational age according to last menstrual period and regarding parity.

Our finding came in agree with **Tanha et al.** ⁽¹³⁾, where two hundred and twenty women with verified missed abortions were included in a randomised control trial with misoprostol 400 mg/6 h administered sublingually or vaginally. Ages averaged 28.49 and 29.04 in the oral and vaginal groups, respectively, while gestational ages ranged from 10.55 to 10.76 weeks. Also, in agree with us **Rabiei et al.** ⁽¹⁴⁾; they found in the vaginal and sublingual subgroups of the misoprostol group, the average gestational age was 10.86 ± 2.83 weeks, and in the total group it was 10.85 ± 2.52 weeks. Also, in agree with us **Farhadifar et al.** ⁽⁸⁾ found ages in the vaginal and oral groups averaged 30.7 and 28.8 years, respectively, while gestational ages ranged from 14.3 to 14.5 weeks. Also, in agree with us **Boutalaq et al.** ⁽¹⁵⁾; The (Mean \pm SD) of maternal age was 28.5 ± 2.86 in group A and 28.5 ± 2.86 in group B. The research was conducted at the High-Risk Unit of Zagazig University and the Whada Derna Teaching Hospital. Moreover, they also found that (Mean \pm SD) of gestational age was 17 ± 3 and 16 ± 3 in

group A and group B respectively, For BMI they found (Mean \pm SD) was 28 ± 3.2 and 28 ± 3.4 in group A and group B respectively.

The main results regarding complications were as follow: In our result, we found that, the incidence of hypotension was statistically significantly higher in the cases of group A (11.8%) as compared with the cases in group B (2%).

The incidence of side effects related to misoprostol as nausea and vomiting was statistically significantly higher in the cases of group B (70.6%) as compared with the cases in group A (58.8%), and the incidence of side effects related to misoprostol as severe crampy pain was statistically significantly higher in the cases of group B (47%) as compared with the cases in group A (33.3%). On contrast, there was no significant difference regarding diarrhea, fever, headache, dizziness, and excessive bleeding. In agreement with us **Tanha et al.** ⁽¹³⁾ as there was significant difference regarding diarrhea and crampy pain but they found no significant difference regarding vomiting. Also, our results were supported by **Chandhiok et al.** ⁽¹⁶⁾ in their prospective clinical trial, there was no significant difference regarding dizziness, vaginal bleeding and diarrhea. **Pang et al.** ⁽¹⁷⁾ had a prospective randomized controlled study that was in agree with us when showing a significant difference between the two groups regarding diarrhea p value (<0.001), but in contrast with us in other side effects like nausea, vomiting and fever.

Boutalaq et al. ⁽¹⁵⁾ found that there was no statistically significant difference between the two groups with respect to side effects of misoprostol, including stomach discomfort, nausea, vomiting, headache, diarrhea, fever, dizziness, and bleeding intensity.

Saeed et al. ⁽¹⁸⁾ found that, overall, 12 (24%) of the vaginal group and 10 (20%) of the oral group experienced problems and side effects. Five (10%) women in the vaginal group experienced excessive bleeding, followed by three (6%) who experienced vomiting, three (6%) who experienced extreme abdominal discomfort, and one (1%) who experienced diarrhea (2 percent). Most people experiencing adverse effects in the oral group experienced gastrointestinal pain, followed by bleeding, fever, and diarrhea (2%). Neither group experienced any uterine ruptures or infections. None of these problems or side effects were significantly different from one another ($p > 0.05$). We found that, the mean of satisfaction in group A (96%) was statistically significantly higher as compared with the cases in group B (78.4%). The mean of cases who would choose again in group A (96%) was statistically significantly higher as compared with the cases in group B (74.5%). The mean of cases who would recommend to other in group A (96%) was statistically significantly higher as compared with the cases in group B (74.5%). The mean induction-expulsion interval in the cases of group A (9.5 ± 3.3) was shorter as compared with the cases in group B (10.8 ± 2.2) with no statistically significant difference ($p = 0.078$). The mean of successful rate in group A (92%) was statistically

significantly higher as compared with the cases in group B (80.4%). On contrast, there was no significant difference regarding duration of post abortion bleeding and resumption of menstruation (days).

In the same line with us, **Farhadifar et al.** ⁽⁸⁾ in their study, oral and vaginal groups had significantly different times between misoprostol administration and the excretion of gestation products (4.09 ± 1.56 h and 3.67 ± 1.40 h, respectively; $P > 0.05$). There was no statistically significant difference between groups in the number of hours that pass between when misoprostol was given and when a miscarriage occurred.

Similar to our results, **Saeed et al.** ⁽¹⁸⁾. They found that (Mean \pm SD) of time interval was 14.65 ± 4.769 in vaginal group and 13.69 ± 4.28 in oral group. There was no significant difference regarding time interval between misoprostol administration and miscarriage in hours between the two groups. But in contrast with us, **Ganguly and colleagues** ⁽¹⁹⁾ evidenced a shorter interval in the sublingual group compared to the oral ($P < 0.0001$) and vaginal ($P < 0.001$) groups. **Tanha et al.** ⁽¹³⁾ found that sublingual regime had a significantly higher proportion of patient satisfaction (93.6% vs. 53.6%) than vaginal administration. Most patients presumably disliked having their vagina inserted by the researchers since it was uncomfortable, and embarrassing.

In contrast to our results, **Kaur et al.** ⁽²⁰⁾ observed a statistically significant ($P < 0.0001$) reduction in abortion time after misoprostol administration in the oral group (2.62 ± 0.64) compared to the vaginal group (3.17 ± 0.17)
Study limitations: The duration of our study seemed to be short to follow up the patients. Increase the dosing systems of the drug is one of our limitations.

CONCLUSION

Misoprostol use by the vaginal route is more efficacious than oral route. Vaginal route was found to have cervical ripening effect and not need much monitoring to become the first choice even over surgical for induction of labor.

Disclosure statement: No author has any financial interest or received any financial benefit from this research.

Conflict of interest: The authors state no conflict of interest.

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