

# Efficacy of Misoprostol for Medical Treatment of Missed Miscarriage in Clinical Practice: A Single Saudi Center Experience

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**Purpose:** This study aims to evaluate the success rate of misoprostol in managing missed miscarriages, identify factors affecting outcomes (such as gestational age and bleeding), and measure the rate of surgical intervention required after misoprostol use in Saudi Arabia due to the lack of data on this region.

**Patients and Methods:** A retrospective cohort study was conducted at King Khalid University Hospital, Riyadh, Saudi Arabia, from 2019 to 2023. Women aged 18–45 years with a diagnosis of missed miscarriage and uterine size less than 12 weeks were included. Misoprostol was the primary treatment, while those who received primary surgical management were excluded. Data were collected from electronic medical records, including demographics, gestational age, misoprostol dosage, blood loss, and surgical indications. The primary outcome was successful medical management, defined as complete uterine evacuation without surgery. Complications such as heavy bleeding, hemoglobin drop, and transfusion were documented. Statistical analysis involved descriptive statistics and Fischer's exact test, with significance set at  $p < 0.05$ .

**Results:** A total 317 women met inclusion criteria. The success rate of misoprostol was 78.5%, with 58.3% achieving complete evacuation confirmed via ultrasound. Most patients had an empty uterus with a mean endometrial thickness of 11.1 mm. Retained products of conception (RPOC) were seen in 14.8% of cases. Complications were rare: 3.2% required transfusion and 21.5% needed surgical evacuation. Previous cesarean sections and misoprostol dose were significantly associated with higher complication rates and longer hospital stays ( $p < 0.05$ ).

**Conclusion:** Misoprostol is an effective, non-invasive treatment for missed miscarriage, with a high success rate and low complication risk. These findings support its use as a practical first-line treatment, potentially reducing the need for surgical intervention and associated healthcare burdens.

**Keywords:** first-trimester pregnancy loss, medical intervention of missed miscarriage, ultrasound, endometrial thickness, Miscarriage management, failed medical treatment

## Introduction

Missed miscarriage refers to an empty gestational sac or undetected death of the fetus or embryo inside the uterus without the expulsion of the products of conception.<sup>1</sup> This occurs in 15–20% of confirmed pregnancies in the first and second trimesters.<sup>2–5</sup> A missed miscarriage during the first trimester is characterized by an intact gestational sac on ultrasound, absence of fetal heart activity with a closed cervix on clinical examination and a history of little to no bleeding.<sup>2</sup> Immunogenic factors have also been implicated in pregnancy loss, with studies showing that altered expression of human leukocyte antigen G (HLA-G) and its gene polymorphisms, such as the rs1063320 variant, may influence maternal-fetal immune tolerance and contribute to recurrent spontaneous abortion.<sup>6</sup> In addition to genetic factors such as HLA-G variants, inflammatory pathways also contribute to pregnancy loss, with studies showing that cytokine dysregulation, particularly elevated serum IL-27 levels and its rs153109 polymorphism in women with recurrent abortion

associated with *Toxoplasma gondii* infection, may influence maternal immune responses implicated in miscarriage.<sup>7</sup> The management of missed miscarriages can be either expectantly by spontaneous expulsion, through medical management using Misoprostol alone or along with other medications such as Mifepristone or through surgical evacuation. Surgical evacuation by dilatation and curettage (D&C) is the standard treatment of missed miscarriages with a 95% success rate. However, it comes with the risk of complications, the need for hospitalization, and high costs.<sup>8,9</sup> Among the possible complications are infection, bleeding, uterine perforation, and decreased fertility caused by intrauterine adhesions (Asherman's syndrome), which may represent an obstacle to women with missed miscarriages who desire to become mothers.<sup>8,9</sup> Regarding to medical treatment, Misoprostol, a prostaglandin E1 analog, is widely used for managing early pregnancy failure, with success rates of 77–92% reported across various administration routes. Factors like high hCG levels, multiparity, and delayed treatment may impact outcomes, often increasing the need for surgical intervention.<sup>2,8</sup> As missed miscarriage is a common condition in the Kingdom of Saudi Arabia and the entire world, limited research is available regarding the medical management of missed miscarriage in Saudi Arabia.<sup>10</sup> Additionally, there is a lack of data examining the effectiveness of medical management using Misoprostol and the factors affecting treatment by misoprostol, this study aims to fill these gaps in the literature, in addition to measuring the rate of surgical intervention needed after misoprostol administration.

## Material and Methods

### Study Design

This retrospective cohort study was conducted among all women who sought care at King Khalid University Hospital in Riyadh, Saudi Arabia between 2019 and 2023.

### Study Setting

The study took place within the Obstetrics and Gynecology Department of King Khalid University Hospital in Riyadh, Saudi Arabia.

### Study Population

The study comprised females diagnosed with missed miscarriage, whose information was recorded in the hospital's electronic system. Inclusion criteria encompassed women diagnosed with missed miscarriage, with a uterine size of less than 12 weeks of gestation by ultrasound and clinical judgment, aged between 18 and 45 years, and planned for Misoprostol. Exclusion criteria included primary surgical management.

### Data Collection

Comprehensive data collection involved retrieving and reviewing the medical records of eligible patients. Data variables included demographic information (age, parity), presenting complaints, BMI, gestational age, details of Misoprostol administration (dosage, route), blood loss volume, indications for surgical intervention (lack of effect of medical treatment, heavy bleeding, prolonged bleeding, patient request, and unknown reasons), and occurrence of complications (severe bleeding, hemoglobin drop, need for transfusion).

### Outcomes

The primary outcome was the success of treatment, defined as complete uterine evacuation without surgical intervention, and the occurrence of complications (severe bleeding, drop in hemoglobin, need for blood transfusion).

### Statistical Analyses

Simple descriptive statistics of the sociodemographic characteristics and other categorical variables in the form of frequencies and percentages were calculated and tabulated. For, continuous variables means/standard deviations and medians/Interquartile ranges were reported as measures of central tendency and dispersion respectively. Additionally, the data was visualized where possible for easier interpretation. To find out the factors associated with post-intervention

complications, Fischer's exact test was applied and interpreted for categorical variables. Significance was established at a p-value of 0.05 or less indicating a 95% confidence interval. All statistical calculations were performed using IBM SPSS version 27.0.1.

## Ethical Approval

The study received approval from the Institutional Review Board (or Ethics Committee) of King Saud University (No. E-23-7793) on 05/07/2023. The IRB waived the requirement for informed consent as the study involved retrospective review of anonymized medical records without direct patient contact. All procedure were conducted in accordance with the ethical standards of institutional and national research committees and with Helsinki Declaration. All data were handled confidentially for scientific purposes.

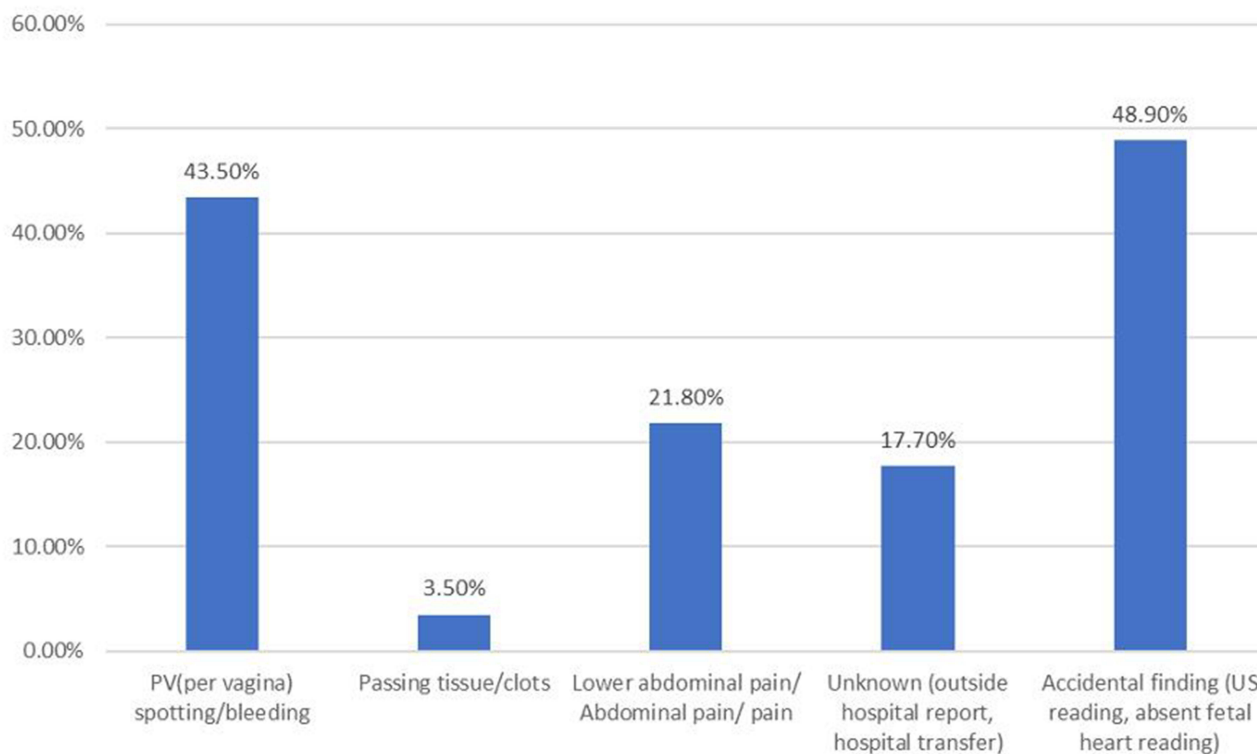
## Results

This study included 317 women diagnosed with missed miscarriage before 12 weeks gestation. The mean age was 34.1 years. With (22.7%) aged 26–31, (33.8%) aged 32–37, and (33.8%) aged 38 or older. The obstetric history of the participants was recorded with gravidity varying across the sample, with the highest frequency observed for gravida 5 or more (42.0%) followed by gravida 4 (19.6%) and gravida 3 (17.0%). Parity distribution indicated that a substantial portion of participants had parity 2 (22.7%) or 3 (22.7%). Regarding miscarriages, the majority of participants had experienced none (53.6%). Gestational age (GA) at presentation revealed that most participants presented at GA of 7 weeks 1 day to 11 weeks 6 days (54.3%). The participants' medical and surgical histories were examined with a significant proportion of participants (58.0%) were medically free, while (42.0%) reported having a medical condition. Among the reported diseases, diabetes mellitus (DM) was the most prevalent (10.1%), followed by hypothyroidism (7.6%) and asthma (7.6%). Past surgical history revealed that (43.8%) of participants had no history of surgery, while (56.2%) had undergone at least one surgical procedure. Cesarean section (C-section) was the most common surgical intervention, with (34.1%) of participants having undergone the procedure. Among those who had C-sections, the majority had undergone one (15.8%), followed by two (8.8%) or three (5.0%) C-sections. Other surgical interventions included dilation and curettage (11.7%).

Participants commonly presented with per vaginal (PV) spotting or bleeding, reported by (43.5%) of participants. This was followed by accidental findings, such as abnormal ultrasound readings or absent fetal heart readings, which constituted (48.9%) of cases. Lower abdominal pain was reported by (21.8%) of participants. A smaller proportion reported passing tissue or clots (3.5%), Unknown complaints, possibly from outside reports, accounted for (17.7%), and (2.5%) mentioned other symptoms like brownish discharge (Figure 1).

The first administration of Misoprostol showed a proportion received two doses (55.5%), followed by a single dose (18.0%). Sublingual (45.4%) was the most common route followed by vaginal (31.9%) and oral (8.5%). The most frequent dose was 600 mcg (36.0%), followed by 800 mcg (29.0%) and 400 mcg (14.2%). Further breakdown by route and dose revealed various administration patterns. In the sublingual route, 2 doses of 600 mcg were most commonly administered (23.3%), while in the vaginal route, 2 doses of 800 mcg were predominant (16.7%). Among oral administrations, a single dose of 600 mcg was the most frequent (2.5%). A complete breakdown of the route, number of doses, and dosages is presented in Table 1. Additional doses were needed in (41.6%) of participants, with most receiving one (18.3%) or two (12.9%) extra doses. Sublingual (20.8%) was again the preferred route, followed by vaginal (16.7%) and oral (9.5%) (Table 1).

Surgical intervention was undertaken in (21.5%) of cases. Among the surgical interventions performed, dilation and curettage (D&C) were conducted in (14.5%) of cases, while suction evacuation and dilation and curettage (Suction, D&C) were performed in (6.3%) of cases. The primary reasons for surgical intervention included failed medical management in (9.1%), retained products of conception (RPOC) in (2.2%), or incomplete miscarriage in (4.1%), accounting for 15.5% of cases total. Patient choice accounted for 3.2% of interventions, while complications such as bleeding or hematoma were observed in (3.5%) of cases. Misoprostol contraindications necessitated surgical intervention in (0.6%) of cases.



**Figure 1** Reasons for presentation among patients with missed miscarriage.

Postoperative complications were relatively low, with bleeding exceeding 500 mL observed in (3.8%) of cases. Similarly, a drop in hemoglobin greater than 2 g within three weeks was noted in (20.5%) of cases, while it was not repeated in (58.7%) of cases. Blood transfusions were required in only (3.2%) of cases. A minority of participants (6.9%) reported multiple visits to the emergency room post-intervention. Hospital stays varied, with (50.5%) of participants discharged within one day, (35.3%) staying for 2–3 days, and (14.2%) requiring a hospital stay of four or more days.

Post-miscarriage ultrasound was conducted at various intervals post-discharge among participants, with the highest proportion occurring between 10–18 days after discharge (17.0%). A considerable percentage of participants had no ultrasound performed (44.8%).

Among those who underwent ultrasound, the majority (58.3%) exhibited an empty uterus, indicating successful evacuation. The mean endometrial thickness was 11.1 mm, with a standard deviation of 5.8 mm among those with available data. Retained products of conception (RPOC) were observed in (14.8%) of cases. Endometrial thickness measurements revealed that 49.1% had thicknesses less than 10 mm, (36.6%) fell within the range of 10–15 mm, and (14.3%) had thicknesses exceeding 15 mm (Table 2).

The timing of post-discharge and post-miscarriage ultrasound examinations was associated with variations in endometrial thickness among participants. Among those examined between 2–9 days after discharge, the median endometrial thickness was 11.5 mm, with (7.4%) exhibiting thicknesses less than 10 mm. In contrast, for participants examined 10–18 days after discharge, the median thickness was 10.0 mm, with (15.4%) displaying thicknesses less than 10 mm. Similarly, for those examined 18–30 days after discharge, the median thickness was 8.5 mm, with (11.4%) showing thicknesses less than 10 mm. The trend continued for participants examined 31 or more days after discharge, with a median thickness of 7.0 mm and (13.1%) exhibiting thicknesses less than 10 mm. Notably, for examinations conducted before discharge, the median thickness was 13.0 mm, with only (1.7%) showing thicknesses less than 10 mm. These findings suggest a progressive decrease in endometrial thickness over time post-discharge, highlighting the importance of timing in assessing post-miscarriage uterine changes (Table 3).

**Table 1** Breakdown of Doses of Misoprostol

Route	Dose	Number of Doses	N	%
<i>Sublingual Dose</i>				
Sublingual	200 mcg	1	1	0.3%
		2	5	1.6%
		3 or more	6	1.8%
	300 mcg	2	11	3.5%
		3 or more	2	0.6%
	400 mcg	1	11	3.5%
		2	10	3.2%
		3 or more	8	3.1%
	600 mcg	1	11	3.5%
		2	74	23.3%
		3 or more	3	0.9%
	800 mcg	1	1	0.3%
2		7	2.2%	
3 or more		3	0.9%	
<i>Vaginal Dose</i>				
Vaginal	200 mcg	2	5	1.6%
		3 or more	1	0.3%
	300 mcg	3 or more	1	0.3%
	400 mcg	1	5	1.6%
		2	8	2.5%
		3 or more	7	2.1%
	600 mcg	1	2	0.6%
		2	7	2.2%
		3 or more	2	0.6%
	800 mcg	1	11	3.5%
		2	53	16.7%
		3 or more	11	3.4%
<i>Oral Dose</i>				
Orally	200 mcg	–	0	0
	300 mcg	2	2	0.6%

(Continued)

**Table 1** (Continued).

Route	Dose	Number of Doses	N	%
	400 mcg	1	3	0.9%
		2	1	0.3%
		3 or more	1	0.3%
	600 mcg	1	8	2.5%
		2	6	1.9%
		3 or more	2	0.6%
	800 mcg	1	2	0.6%
		2	2	0.6%
	<i>Additional Doses</i>			
Number of Doses	No Additional Dose		185	58.4%
	1		58	18.3%
	2		41	12.9%
	3 or more		33	10.2%
Route of Additional Dose	Sublingual		66	20.8%
	Vaginally		53	16.7%
	Orally		30	9.5%

**Table 2** Ultrasound Time and Findings

		N	%	Mean	Standard Deviation
Ultrasound after how many weeks	2–9 days after discharge	31	9.8%		
	10–18 days after discharge	54	17.0%		
	18–30 days after discharge	33	10.4%		
	31 or more days after discharge	31	9.8%		
	Before Discharge	26	8.2%		
	Not done	142	44.8%		
Empty Uterus (n=175)		102	58.3%		
Endometrial Thickness (n=154)				11.1	5.8
RPOC (n=175)		47	14.8%		
Endometrial Thickness (n=154)	<10mm	86	49.1%		
	10–15mm	64	36.6%		
	More than 15mm	25	14.3%		

**Table 3** Ultrasound Time and Association with Endometrial Thickness

		Endometrial Thickness (mm)			Endometrial Thickness					
		Median	Percentile 25	Percentile 75	<10mm		10–15mm		More Than 15mm	
					N	%	N	%	N	%
Ultrasound	2–9 days after discharge	11.5	8.0	13.0	13	7.4%	15	8.6%	3	1.7%
	10–18 days after discharge	10.0	8.0	14.0	27	15.4%	18	10.3%	9	5.1%
	18–30 days after discharge	8.5	6.0	13.5	20	11.4%	9	5.1%	4	2.3%
	31 or more days after discharge	7.0	5.0	10.0	23	13.1%	6	3.4%	2	1.1%
	Before Discharge	13.0	12.0	17.0	3	1.7%	16	9.1%	7	4.0%

Complications faced by the patients were investigated in relation to the patient's age, GA, dose of Misoprostol received, and past medical history. In patients who suffered from post-miscarriage bleeding exceeding 500 mL, age distribution did not significantly impact bleeding occurrences ( $p=0.566$ ). Likewise, gestational age and dose of Misoprostol did not show significant associations ( $p=0.221$  and  $p=0.750$ , respectively). However, past surgical history, specifically, the number of previous C-sections exhibited significance with those with 5 C-sections demonstrating the highest prevalence of bleeding (50%) ( $p=0.025^*$ ). In patients who suffered from a drop in hemoglobin greater than 2 g, age, and gestational age did not significantly correlate with this drop ( $p=0.506$  and  $p=0.675$ , respectively). Notably, the dose of Misoprostol demonstrated marginal significance ( $p=0.092$ ). Additionally, past surgical history demonstrated no significance (all  $p$  values  $>0.05$ ). In patients who undertook blood transfusions. While age and gestational age did not show significant associations, the past surgical history ( $p=0.047$ ) and history of suction evacuation were significant ( $p=0.032^*$ ). Of the participants with a previous history of surgical intervention, (5.1%) had to receive blood transfusion compared to (0.7%) of those with no past surgical intervention history. For patients who had multiple ER visits post-intervention. Of all the factors, only age distribution revealed significance ( $p=0.037^*$ ) with the highest prevalence of multiple ER visits observed in the females of the 26–31 years age group (11.1%). Finally, for factors associated with prolonged hospital stay. The dose of Misoprostol ( $p=0.002^*$ ) and past surgical history ( $p=0.035$ ), notably a higher number of previous C-sections ( $p<0.001^*$ ), were significantly associated with prolonged hospitalization.

## Discussion

Our study reports similar success rates for Misoprostol in managing missed miscarriages consistent with previous literature. Studies, such as those by Kobryn et al (2019) and Ali et al (2022), reported success rates of 83.6% and 76.7%, respectively, aligning with the 77–92% range seen in various other studies.<sup>2,6,11–15</sup> In our study, 55.5% received two doses, with the sublingual route being the most common 45.4%, at a dose of 600 $\mu$ g 36%. Previous research highlights the efficacy of vaginal Misoprostol at doses between 200–800 $\mu$ g, with success rates of 80–83%.<sup>2</sup> As it is demonstrated, there are inconsistencies in the recommended regimens.<sup>16–18</sup> It is noteworthy that regimen modifications were done over the past decade, which included dose reduction, different routes of administration, as well as home use of Misoprostol.<sup>19</sup> The World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics (FIGO) 2017 recommendations concerning missed abortions were followed by administering Misoprostol 800 $\mu$ g by the vaginal route every three hours or Misoprostol 600 $\mu$ g sublingually every three hours.<sup>20,21</sup> A similar approach to medical management was described in other studies.<sup>11,22</sup> It is worth mentioning that a recent systematic review and meta-analysis by Wu et al (2017) found that sublingual Misoprostol given at 600 $\mu$ g was the most effective mode of treatment for missed miscarriages.<sup>8</sup> Additionally, the expectant management has unpredictable success rates ranging between 25–76% and can cause emotional distress to the mother while waiting for spontaneous expulsion, which is uncertain to succeed.<sup>23</sup> Women experiencing such an event, especially if recurrent, were found to have elevated anxiety, depression, and grief for up to one year after the event. Along with social and financial burdens.<sup>24–26</sup> This emphasizes the importance of identifying the

most effective management method to decrease physical and psychological complications. After receiving the initial recommended doses our findings showed almost 58.4% did not require additional doses of Misoprostol, signifying its effectiveness. The sublingual route remained significant for additional dosing at 20.8%, aligning with findings from a review by Wu et al (2017), which emphasized the superiority of the sublingual and vaginal routes in terms of efficacy.<sup>8</sup> Surgical evacuation was undertaken in 21.5% of participants, primarily caused by failed medical management and retained products of conception (RPOC). This result is comparable to previous studies in which surgical evacuation was performed in 9–22% of participants.<sup>2,8,15</sup> Postoperative complications were proportionately low, with bleeding exceeding 500 mL observed in 3.8% of cases. This coincides with previous studies which reported low complication rates.<sup>13</sup> The noted decrease in hemoglobin greater than 2g and the minimal requirement for blood transfusions of 3.2% signify a positive safety profile, comparable to previous findings.<sup>2,14,23</sup> The majority of participants 50.5% were discharged within one-day post-intervention, indicating a quick recovery. Agreeing with Kulier et al (2001), where D&C was preferred in late first-trimester miscarriages with minimal, even rare, complications reported.<sup>27,28</sup> These findings suggest favorable postoperative outcomes, with most participants experiencing minimal complications and short hospital stays following surgical intervention for miscarriage management. Ultrasound examinations played a pivotal role in both diagnosis and treatment evaluation. After completing a misoprostol regimen, ultrasound confirmed whether the gestational sac has passed.<sup>29</sup> However, follow-up criteria lack consensus, with transvaginal sonography (TVS) typically performed 1–2 weeks post-treatment, or later if bleeding persists.<sup>30–32</sup> Ultrasound follow-up involved assessing the contents of the uterine cavity and measuring the endometrial thickness.<sup>33</sup> According to the guidelines from the Royal College of Obstetricians and Gynecologists, a complete miscarriage is defined by a clearly visible endometrial line with a maximum thickness of less than 15 mm, along with the absence of vaginal bleeding.<sup>23</sup> In our study, most assessments occurred 10–18 days post-discharge 17.0%, with a significant proportion 44.8% of participants did not undergo ultrasound, highlighting variability in follow-up practices. Among those who did, 58.3% showed an empty uterus, indicative of successful evacuation. In our study, only 14.3% of all women who had an ultrasound done had an endometrial thickness of greater than 15 mm after misoprostol treatment. There was a notable decrease in endometrial thickness over time post-discharge, highlighting the importance of timing in assessing post-abortion uterine changes. This observation suggests that the 15 mm threshold may be overly stringent. Another study found women with thicknesses up to 30 mm often experienced spontaneous expulsion.<sup>34</sup> Rorbye et al (2003), determined that clinical symptoms, like heavy or prolonged bleeding, were more reliable indicators of failure than sonographic findings.<sup>30</sup> Fiala et al (2003), noted that ultrasound results during follow-up could be challenging to interpret. They found that delaying surgical intervention until after the patient's next menstrual cycle, especially in those with a thick endometrium at the initial follow-up, reduced the need for surgical procedures.<sup>31</sup> These researchers suggested that relying on sonographic follow-up might result in unnecessary surgeries. Retained products of conception (RPOC) were observed in 14.8% of cases. In most cases no intervention is usually done in asymptomatic patients with sonographic findings of retained products of conception (RPOC).<sup>35</sup> In our study, only 2.2% of women with RPOC had to undergo surgical intervention after taking misoprostol. This study has several limitations. Its retrospective design relies on the accuracy of medical records and may be subject to incomplete the documentation. Nearly half of participants (44.8%) did not undergo ultrasound follow-up, and the timing of follow-up assessment varied, which may affect the precision and comparability of outcome measurements. Additionally, the outcome with expectant or primary surgical management. This study was conducted at a single center, which may limit the generalizability of the findings. Additionally, some variables that may influence misoprostol treatment outcomes, such as patient socioeconomic factors or provider-related differences, were not assessed. A larger multicenter prospective study is recommended to validate these findings.

## Conclusion

Our study supports the effectiveness of misoprostol as a non-invasive treatment option for missed miscarriages as it is considered a safe and highly successful option, and its side effects were very minor. Furthermore, no major differences in effectiveness between different routes of administration.

## Disclosure

The authors report no conflicts of interest in this work.

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