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EFFICACY AND SAFETY OF SUBLINGUAL AND BUCCAL ROUTE MISOPROSTOL FOR FIRST AND SECOND TRIMESTER MISCARRIAGES USING THE INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS (FIGO) 2017 PROTOCOL

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ABSTRACT

Background: Miscarriage affects about 10% of pregnancies and causes significant physical and emotional distress. Medical management with misoprostol is a safe and effective alternative to surgery, especially in low-resource settings where mifepristone may not be available. Traditionally, misoprostol is given vaginally, but this can be uncomfortable for women. FIGO's 2017 guidelines introduced sublingual and buccal routes as effective and more acceptable alternatives. Evaluating these routes helps improve patient care and treatment outcomes. **Objectives**: To evaluate the safety and efficacy of sublingual and buccal route administration of misoprostol according to the latest 2017 International Federation of Gynecology and Obstetricians (FIGO) protocol in the management of first and second-trimester miscarriages. **Methodology:** This study was carried out at Ziauddin University Hospital, Karachi, Pakistan, between January and December 2022. A total of 110 patients presenting with first or second trimester miscarriage, or requiring termination of pregnancy before 24 weeks, were treated with misoprostol administered exclusively via the sublingual or buccal route, following the latest FIGO 2017 protocol. Treatment success was defined as complete expulsion within 12 hours of completing the medication course, confirmed by pelvic ultrasound during inpatient monitoring. **Results:** A

total of 84 (76.4%) patients received misoprostol for first-trimester miscarriage, whereas 26 (23.6%) were treated during the second trimester. In the first trimester group, the primary indications for medical termination were missed miscarriage in 74 cases (67.5%) and anembryonic pregnancy in 10 cases (9.1%). Among second-trimester patients, 16 (14.5%) had missed miscarriages, and 10 (9.1%) were diagnosed with lethal fetal anomalies. Treatment success, defined as complete uterine evacuation confirmed by pelvic ultrasound, was achieved in 98% of cases without any significant adverse effects. **Conclusion:** Misoprostol, when administered through non-vaginal routes, is safe, effective, and more acceptable to patients for the management of miscarriages.

KEYWORDS: Misoprostol, miscarriage, medical termination of pregnancy, sublingual administration, buccal administration.

INTORDUCTION

Spontaneous pregnancy loss is the most common complication of pregnancy; it occurs before 24 weeks of gestation in around 20% of pregnancies and 12–15% of clinically recognized pregnancies.[1] While the rates for post-implantation and biochemical pregnancy loss seem to be about 30%.[2] Most miscarriages happen in the early stages, before 12 weeks of gestation. Pregnancy loss in the second trimester accounts for under 4% of total pregnancy losses, with fewer than 5% of miscarriages happening after fetal heart activity is detected.[2]

Miscarriage affects pregnancies and is frequently linked to significant distress for women, their partners, and families, and is often linked to considerable psychological distress for both partners and their marital status as well.[1]

Bleeding happened in one-fifth of identified pregnancies before the 20th week, and more than half of these ended in miscarriage.[3]

According to the World Health Organization, an estimated 47,000 women die each year from unsafe abortion practices, with the vast majority of these deaths occurring in developing countries where access to safe abortion care remains limited.[4]

Historically, surgical curettage was considered the primary method for treating miscarriage. The implementation of medical and expectant management for miscarriage has expanded choices for both women and clinicians in handling this prevalent condition. Surgery is the preferred option for severe bleeding when vital signs are unstable or if the woman has a

suspected infection or gestational trophoblastic disease. In stable patients, surgical intervention can be conducted as an outpatient procedure.[5]

Medical management of pregnancy termination offers a safe, effective, and accessible alternative to surgical procedures, giving patients more choices in their care. Research shows that using mifepristone followed by misoprostol is generally more effective than using misoprostol alone.[6,4] However, misoprostol-alone regimens may be the treatment of choice in settings in which mifepristone is not available or is too costly, as in our country. Misoprostol alone is the gold standard treatment, and the conventional vaginal route was preferred, but it can be painful and disturbing for women who are already in distress due to the trauma of miscarriage.

In June 2017, FIGO released an updated chart informed by recent scientific evidence and developed through consultation with maternal health experts. The FIGO Recommended Regimens for Misoprostol-only 2017 chart (Fig. 1) stems from comprehensive collaboration among a global team of experts. In certain situations, it may be the sole medication accessible, which is the reason FIGO thinks this "misoprostol-only" chart is necessary.[6]

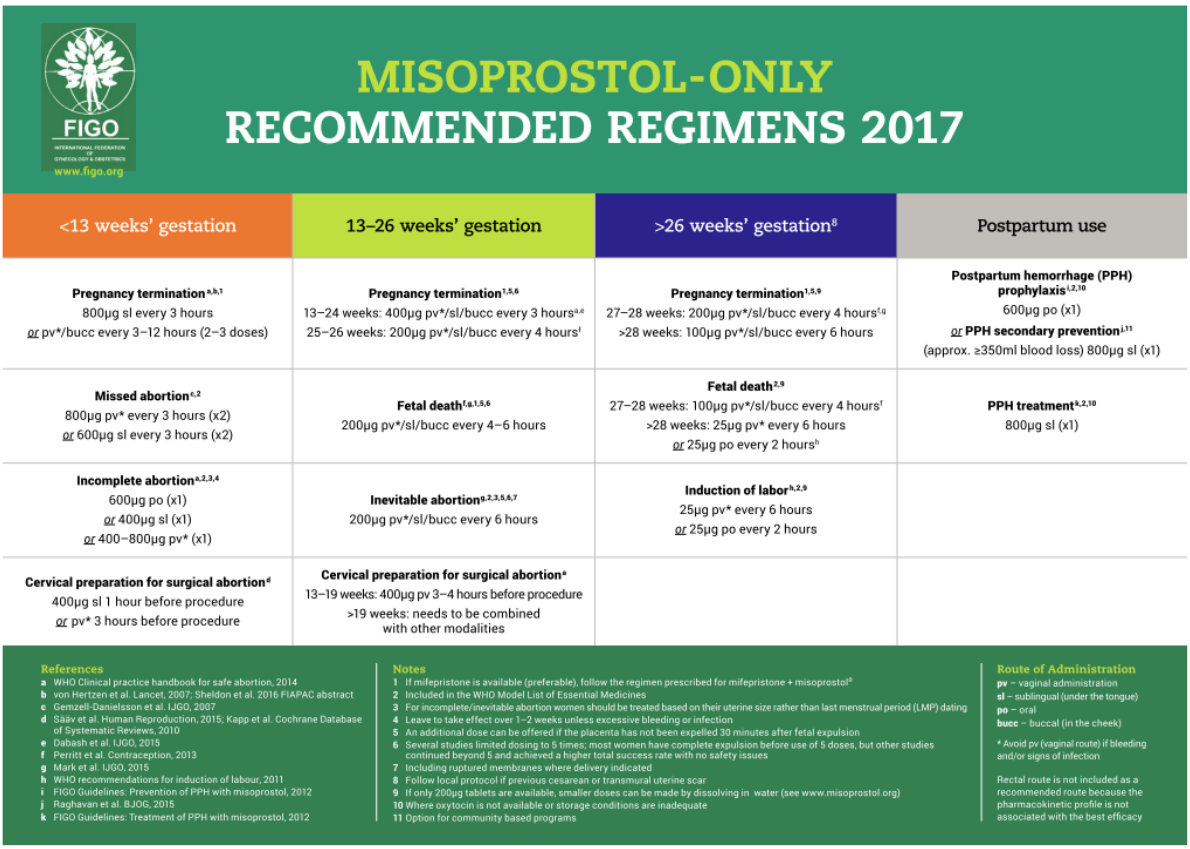


FIGURE 1 The FIGO misoprostol-only recommended regimens 2017 chart.

Given recently published evidence, they have added alternative routes for taking misoprostol; in most cases, this has meant the addition of the buccal route, in which the tablets are placed in the cheek for 30 minutes, after which any remnants are swallowed. This route has a similar pharmacokinetic profile to the vaginal route.

We conducted this study to evaluate the efficacy of misoprostol in the termination of pregnancy by introducing the dosage protocol as laid down by FIGO in 2017, and the route of administration was sublingual/oral only, thus avoiding the vaginal route so that patient acceptability and mental status are not disturbed by repeated vaginal examinations.

METHODLOGY

This study was carried out at Ziauddin University Hospital, Karachi, from January to December 2022, with ethical approval from the hospital board. It included women with singleton pregnancies experiencing first or second-trimester miscarriage. All participants gave informed consent and were admitted for evaluation, including medical history, physical exam, ultrasound, and necessary lab tests.

Pregnancy termination was done using misoprostol, following the 2017 FIGO guidelines. Women with scarred uteri received half the standard dose. A total of 110 patients received misoprostol sublingually or buccally, based on current recommendations. They were monitored in the hospital until the process was complete. Misoprostol was considered effective if the miscarriage was complete within 12 hours of finishing the dose, confirmed by a pelvic scan.

Table 1: Patient Distribution, Parity, and Indications by Trimester.

Trimester	No. of Patients	% of Total (110)	Parity	Count	% within Trimester	Indications	Count	% within Trimester
First Trimester	84	76.30%	Primi	54	64.20%	Missed	74	88%
			Multi	30	35.70%	Anembryonic	10	12%
Second Trimester	26	23.60%	Primi	11	42.30%	Missed	16	61.50%
			Multi	17	65.30%	Lethal Fetal Anomalies	10	38.

Table 2: Distribution of Reported Side Effects Among Patients.

Side Effect	Number of Patients	Percentage (%)
Shivering	22	20%
Fever	11	10%
Loose Motions	12	10.90%
Heavy Vaginal Bleeding	0	0%

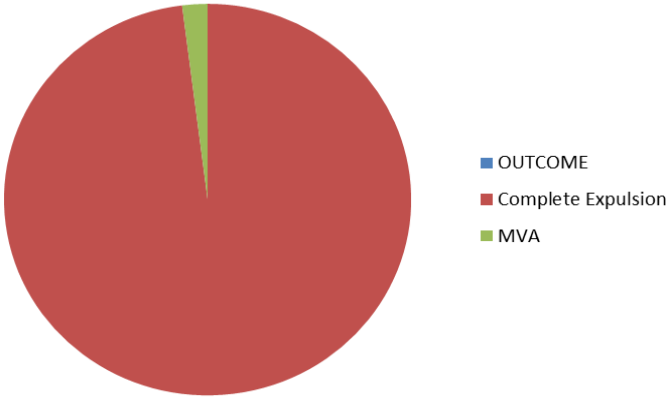


Figure 1: Patient Outcome Distribution.

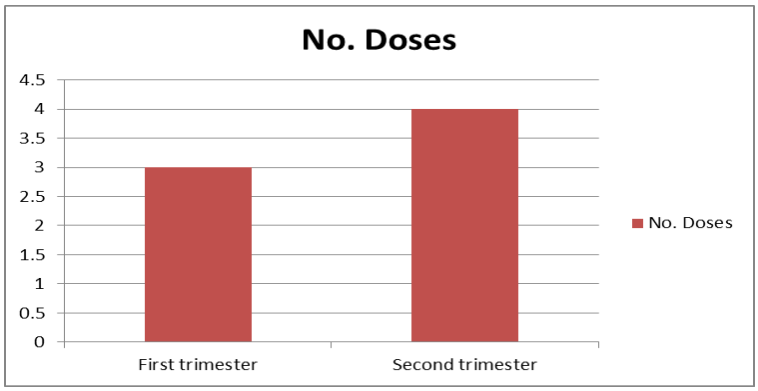
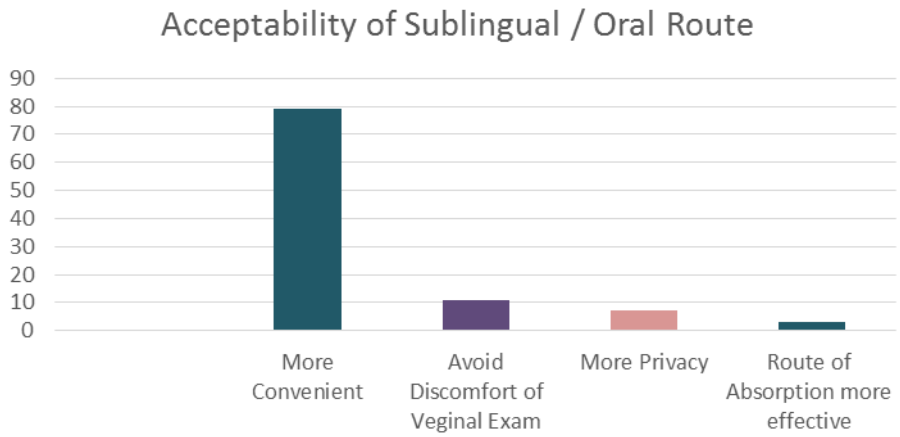


Figure 2: Number of Sublingual Oral Doses Given per Trimester.



RESULTS

Patient Distribution, Parity, and Indications by Trimester were reported in 110 patients; 76.3% were in the first trimester and 23.6% in the second trimester. Among first-trimester patients, 64.2% were primigravida and 35.7% multigravida. The main indication in this group was missed abortion, accounting for 88% of cases, followed by anembryonic pregnancy at 12%. In the second trimester group, multigravida patients were more prevalent at 65.3%, with

primigravida making up 42.3%. Missed abortion was the leading indication in 61.5% of second-trimester cases, while lethal fetal anomalies represented 38.5%.

Distribution of reported Side Effects among patients**,** the most common side effect reported was shivering, affecting 20% of patients. Fever was noted in 10% of cases, and loose motions in 10.9%. Notably, there were no reported cases of heavy vaginal bleeding among the patients.

The outcome of the treatment showed a high rate of complete expulsion, occurring in 98% of patients. Manual vacuum aspiration (MVA) was required in only 2% of cases. The dosing regimen of sublingual oral medication varied according to the trimester of pregnancy. Patients in the first trimester were given a total of 3 doses, while those in the second trimester received an increased dosage of 4 doses. This difference likely reflects the clinical considerations related to gestational age and treatment efficacy, with a higher number of doses required during the second trimester to achieve the desired therapeutic outcome. The acceptability of the sublingual/oral route was found to be unanimously high among all participants. As illustrated in Figure 3, 100% of patients (110 out of 110) reported that they found this route acceptable. No patients expressed dissatisfaction or refusal, indicating that the sublingual/oral method was universally well-tolerated and preferred in the study population.

DISCUSSION

Miscarriage is a frequent occurrence among women of reproductive age, occurring at a rate of 10–20%. Bleeding during early pregnancy is the leading cause for women to visit the gynecology emergency department. The implementation of medical and expectant approaches to miscarriage has expanded choices for both women and healthcare providers in addressing this prevalent issue. Surgery is the preferred approach for severe bleeding when vital signs are unstable or if there is a suspected infection or gestational trophoblastic disease. In stable patients, surgical treatment can be carried out as an outpatient procedure.[5] Nonetheless, the patient's preferences should be considered when managing a miscarriage, if appropriate.

Different kinds of medical therapies may serve as appropriate substitutes for either expectant or surgical management. Over the last twenty years, medical techniques have gained popularity, with most early research focused on pregnancy termination.[6]

The primary pharmacological agents consist of prostaglandins (misoprostol, gemeprost) utilized either independently or alongside the anti-progestogen mifepristone. Mifepristone (RU486), a progesterone blocker, was identified in 1980 by scientists at Roussel-Uclaf in France.[7] The competitive inhibition of natural progesterone, this C19 steroid, enhances the responsiveness of the myometrium to Prostaglandins, increasing by fivefold, achieving peak impact on uterine contractions and cervical softening within 36–48 hours after therapy.[8]

The analogue of prostaglandin E1, gemeprost, received approval for early medical abortion in 1991 at a vaginal dose of 1 mg.[9] A substantial amount of evidence demonstrates that misoprostol, another prostaglandin E1 analogue, exhibits comparable efficacy and safety across all gestations[10,11], despite lacking official approval for this use.[12] Tablets of misoprostol at 200 micrograms are designed for addressing peptic ulcers. Misoprostol has been thoroughly investigated in reproductive health and is highly recommended for managing missed and incomplete miscarriages, inducing abortion, preparing the cervix before uterine procedures, and both preventing and treating postpartum hemorrhage**.**

A comprehensive array of services must be contracted, encompassing options for both medical and surgical care procedures for all pregnancies up to the legal threshold, as an element of a care pathway.[13]

Routes for administering misoprostol consist of oral, vaginal, sublingual, buccal, or rectal. Pharmacokinetic studies examining oral versus vaginal administration indicate that vaginal misoprostol exhibits slower absorption, reduced peak plasma concentrations, and slower clearance, akin to an extended-release formulation.[14,15] There is no notable clinical difference between vaginal misoprostol that is given dry and vaginal misoprostol dampened with water, saline, or acetic acid.[14,16–18]

The sublingual method of administration shares similarities with vaginal administration but enables quicker absorption (higher Tmax) and greater peak concentrations (Cmax) compared to both vaginal and oral routes.[17] This results in increased rates of gastrointestinal side effects. However, the sublingual method induces uterine contractions at a pace similar to vaginal administration and shows less variability in absorption.

The buccal route is an alternative method of administration that has been less commonly researched in clinical trials. The medication is positioned between the teeth and the cheek and

is absorbed through the buccal mucosa. The Tmax following buccal administration is identical to that of vaginal administration; however, the serum drug concentrations achieved are significantly lower, reaching only half of those from the vaginal route.

The sublingual administration of misoprostol is four times more effective than buccal use. The sublingual route, in contrast, experienced a greater occurrence of gastrointestinal side effects compared to the buccal route due to a higher peak plasma concentration.

Our study demonstrates that misoprostol administered via sublingual or buccal routes, following the FIGO 2017 protocol, is an effective and well-accepted option for managing first and second-trimester miscarriages. We observed a 98% success rate for complete uterine evacuation, with minimal need for surgical intervention, aligning with outcomes reported in similar low-resource settings using medical management alone.

The complete expulsion rate closely mirrors previous reports of high efficacy with sublingual misoprostol in early pregnancy loss, including rates of over 92% in first-trimester miscarriages. Although evidence supports the superiority of combined mifepristone and misoprostol regimens, misoprostol alone remains a viable alternative when mifepristone is unavailable, as is common in resource-limited settings.[19,20]

The side effect profile observed—predominantly shivering (20%), with fever (10%) and loose motions (10.9%)—was consistent with previous findings that sublingual or buccal administration produces higher systemic absorption and more frequent systemic symptoms compared to vaginal or oral routes.[21] Importantly, we found no instances of heavy vaginal bleeding, supporting the safety of non-vaginal routes.

Patient acceptability was excellent, with 100% of participants reporting satisfaction with the sublingual/oral route. This underscores the potential psychological benefits of avoiding vaginal administration in women already experiencing distress due to miscarriage.

The dosing regimen (3 doses in the first trimester, 4 in the second) likely reflects the increased need for uterine response in later gestation, in alignment with FIGO guidelines recommending tailored dosing across gestational ages.[6]

Limitations include the observational design and single-center setting, which may limit generalizability. Nonetheless, our findings are consistent with other FIGO-based protocols

and pharmacokinetic data showing that sublingual and buccal routes offer high bioavailability and comparable efficacy to vaginal delivery.[22]

Overall, sublingual/buccal misoprostol provides a safe, feasible, efficient, and patient-centered alternative for miscarriage management, particularly crucial in contexts where mifepristone is inaccessible and prolonged patient comfort is desired.

CONCLUSION

Misoprostol, used according to the FIGO protocol, is a safe, feasible, and acceptable option for managing first and second-trimester miscarriages. It showed high rates of complete expulsion with minimal need for surgical intervention. Side effects were mild and well-tolerated. The sublingual/oral route was universally accepted by patients. It has received support from the FIGO Working Group on the Prevention of Unsafe Abortion and the FIGO Safe Motherhood and Newborn Health Committee, and is sanctioned by the FIGO Officers. There is an expectation that it will be as broadly shared and utilized as the earlier version.

While these suggested dosages have been established based on existing evidence and expert judgment, new information is continuously coming to light, necessitating a reassessment and update of these recommendations moving forward.

Misoprostol should remain emphasized as a crucial medication and be incorporated into international documents, national protocols, and lists of essential medicines. Additionally, we need to strive for the accessibility of high-quality misoprostol along with the creation of policies and initiatives that facilitate its availability and utilization.

This misoprostol chart is intended for use by all healthcare providers mentioned in the WHO publication, and through its implementation, we will move closer to delivering optimal care for the women we aim to support.

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Data curation, Methodology,

Author's full name 3,4,5: Professor Habiba Sharaf Ali, Dr Shagufta Gulzar, & Professor Haleema Yasmin, Formal Analysis.

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DATA AVAILABILITY STATEMENT

The data is available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST

"The authors declare no conflicts of interest."

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