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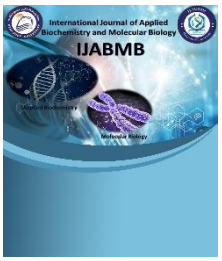


# Comparative study between misoprostol alone versus misoprostol with isosorbide mononitrate in case of second trimester termination of pregnancy in patients with previous caesarean section

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**Running Title: Misoprostol alone or combined in termination of pregnancy**

## Abstract:

**Background:** Misoprostol is a medication that is frequently used to end second trimester abortions. Isosorbide mononitrate (ISMN), a nitric oxide donor, has been used to induce labor and ripen the cervix.

**Objective:** Our goal was to assess the effects of misoprostol alone vs misoprostol with ISMN on cervical ripening and abortion induction during the second trimester of pregnancy.

**Patients and Methods:** This was a randomized clinical trial performed on 100 second trimesters missed abortion pregnant females. Patients were randomly allocated to either group A (n=50) received combined ISMN 40 mg with Misoprostol 100 mcg or group B (n=50) received only vaginal Misoprostol 100mcg. Ultrasound was performed to identify the gestational age, ensure that there was no cardiac pulsation of the fetus, site of the placenta and if there was placental hematoma or separation, any fetal anomalies and the state of previous scare (intact scar).

**Results:** The 2nd trimester termination of pregnancy using ISMN plus misoprostol takes a significantly shorter time than misoprostol alone. In misoprostol group 6 women (12%) that was significantly less than ISMN + Misoprostol group where 15 (30.0%) aborted after the first dose. There was a non-significant difference after 2nd dose, further 18/44 (40.9%) women aborted in misoprostol group and 16/35 (45.7%) women in ISMN with misoprostol group.

**Conclusion:** The use of ISMN in addition with misoprostol in medical induction of second trimester abortion may be more effective than misoprostol alone and was associated with less side effects as vomiting and colic except headache was more with isosorbide mononitrate.

**Keywords**: Misoprostol – Isosorbide mononitrate – Abortion – Second trimester.

## Introduction:

Therapeutic abortion, also known as medical or surgical pregnancy termination, refers to the deliberate ending of a pregnancy before the fetus becomes viable or before the 20th week of gestation, and when the fetal weight is less than 500 g. Globally, it is estimated that around 40 million abortions are performed annually, regardless of their legal status, resulting in an approximate abortion rate of 3.5% (1).

Abortion during the second trimester, typically after 12 weeks of gestation, is less common but still takes place in both developed and developing nations. Interestingly, in certain contexts, a significant portion of abortion-related complications in the second trimester arises from inadequate training or preparation, despite these procedures constituting a minor fraction of total abortion instances (2).

Pregnancy terminations in the second trimester are on the rise because of advancements in the early detection of fetal abnormalities and disorders that pose a threat to the mother's life. Furthermore, the number of women who need second-trimester pregnancy termination with uterine scarring is rising due to an increase in cesarean sections rate and other uterine procedures (3).

There are three main procedures for ending a pregnancy in the second trimester: mechanical, surgical, and medicinal. Since the medical approach is less invasive and more natural than the other two, it is the most recommended one (4).

Surgical abortion was replaced by medical techniques once prostaglandins were discovered in the early 1970s. Over the past 20 years, their utilization has changed, and a variety of medications have been employed for medical first trimester abortions. Numerous investigations have examined the use of mifepristone, methotrexate, and other prostaglandins at varying dosages, delivery methods, and time intervals (5).

Misoprostol, a synthetic analog of prostaglandin E1, serves multiple medical purposes including the prevention of stomach ulcers, management of spontaneous abortions, and induction of abortions. Particularly in the second trimester of pregnancy, it has emerged as a safe and effective medical option for terminating pregnancy. Its mechanism involves acting as a uterotonic agent, facilitating smooth muscle contractions in the uterus and cervical dilatation (6).

In recent years misoprostol, and donors of nitric oxide (NO) have both been used to soften the cervix and start labor. Contrary to prostaglandins, NO donors boost rather than reduce uterine blood flow and promote rather than inhibit uterine myometrial contractions. Because of this, NO donors like IMN appear to be the best cervical ripening agent before labor induction (7).

This study aimed is to assess the effectiveness of utilizing misoprostol alone versus a combination of misoprostol and isosorbide-5-mononitrate in cervical ripening and inducing abortion among patients with scarred uterus experiencing second-trimester missed abortion.

## Patients and Methods:

This study was a randomized clinical trial carried out at the Obstetrics and Gynecology department of Beni-Suef University Hospital on 100 Second trimesters (13-26 weeks) missed abortion pregnant women were admitted for medical induction of abortion.

We included females aged 18-35 years with singleton pregnancy and their BMI ranged between 25 and 29.9 in the second trimester of pregnancy between 16-24 weeks according to date of amenorrhea or early (booking) ultrasonography scan. Females with prior uterine incisions with only previous one lower uterine caesarian section were also included in the study.

The included females should have normal uterus and cervix on clinical examination, cervix is not dilated, no vaginal bleeding. Missed abortion confirmed by ultrasound.

Exclusion criteria included cases with over distended uterus (multiple gestation, polyhydramnios) who were at high risk of uterine rupture, females with more than one lower segment caesarean section, previous classical or T-shaped uterine incision, or extensive trans fundal uterine surgery (e.g., myomectomy). We also excluded cases with history of blood transfusion during the preceding lower segment cesarean section, cases with bleeding tendency (Inherited bleeding disorder, Chronic liver disease, Valve replacement), cases with pre-existing medical disorder (Bronchial asthma, Decompensated heart disease), evidence indicates that spontaneous abortion may precede attempts to induce abortion, alongside factors such as uterine contraction or bleeding, septic abortion, prior cervical surgery or manipulation, uterine anomalies, presence of an intrauterine device (IUD), history of uterine rupture, allergic reactions or adverse effects to transvaginally administered medications like isosorbide-5-mononitrate or misoprostol, and patient unwillingness to participate in the trial.

Based on the inclusion and exclusion criteria, patients were randomly allocated to either group A (n=50) received combined Isosorbide-5-mononitrate 40mg (Effox 20mg) vaginal with Misoprostol 100 mcg (1/2 tablet Cytotec) at first then one tablet of misoprostol every 6 hours to a maximum of four doses or until reaching cervical ripening, isosorbide 5 mononitrate was repeated as 2nd dose if there was no response after 12 hours of 1st dose (was taken with 3rd dose of misoprostol) or group B (n=50) received only vaginal Misoprostol 100mcg (1/2 tablet of Cytotec 200mcg) at first then one tablet of misoprostol every 6 hours to a maximum of four doses or until reaching cervical ripening. (The doses of Misoprostol were following the New FIGO Guidelines for Misoprostol use 2017).

All patients were subjected to full history taking including personal history, obstetric history (Gravidity and parity, first day of last menstrual period, gestational age, previous CS, previous abortion and history of cervical cerclage), medical and surgical history, allergy to any drugs, presence of organic disease or medical disease affecting coagulation profile (Coagulopathy, Steroids treatment, Anticoagulant drugs), previous laparotomies and their types, previous pregnancy complications and pelvic pain.

Thorough clinical examination was performed including general examination (Height (in cm) and weight (in kg) measurements, BMI calculation and blood pressure measurement), abdominal examination (Fundal level, Fundal grip) and obstetric examinations (PV Examination to ensure that the cervix is closed and no vaginal bleeding, previous scars analysis).

Laboratory investigations included coagulation profile, preoperative and postoperative CBC to assess the amount of blood loss, Kidney and liver functions.

All women had Trans-abdominal or Trans Vaginal Ultra-sonography during the Routine examination to confirm the inclusion criteria of the study (Gestational age and confirmation of the intrauterine fetal death). Ultrasound performed by an expert to identify the gestational age, ensure that there was no cardiac pulsation of the fetus, site of the placenta and if there was placental hematoma or separation, if there were any fetal anomalies and the state of previous scare (intact scar). Post abortive ultrasound was performed to identify if the uterus was empty and complete abortion was done or there were any remnants of pregnancy.

Study outcomes: Primary outcomes: Efficacy, specifically measured through the "induction abortion interval," which refers to the duration between the initiation of induction and the complete expulsion of the abortus.

Additionally, the study evaluates the doses of misoprostol required for complete expulsion when prostaglandins are used alone versus when prostaglandins are used in combination with a nitric oxide donor.

Secondary outcomes: Use of this combination will decrease the side effects that occur with misoprostol alone such as bleeding, colic, abdominal pain, severe hypotension, nausea and vomiting and uterine rupture.

Statistical analysis of the collected data: Data were statistically described in terms of mean ± standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi-square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. Two-sided p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

## Results:

The study was conducted among (100) women, randomly selected and randomly allocated to study groups, Group A (50 women) received combined Isosorbide-5-mononitrate with Misoprostol and Group B (50 women) received only vaginal Misoprostol.

Baseline data of the studied patients (Tables 1 & 2).

**Table (1): Comparison between both studied groups regarding demographic and obstetric characteristics.**

| | | Studied Groups | | P-value |
|---|---|---|---|---|
| | | ISMN + Misoprostol group N= 50 | Misoprostol group N= 50 | |
| **Age (years)** | **Mean ±SD** | 28.68 ±5.30 | 28.92 ±5.24 | 0.820 |
| | **Min – Max** | 19 - 39 | 19 – 39 | |
| **Parity** | **Primigravida** | 17 (34.0%) | 19 (38.0%) | 0.851 |
| | **P1** | 25 (50.0%) | 21 (42.0%) | |
| | **P2** | 5 (10.0%) | 7 (14.0%) | |
| | **P3** | 3 (6.0%) | 3 (6.0%) | |
| **Previous abortions** | **None** | 43 (86.0%) | 43 (86.0%) | 0.809 |
| | **One** | 5 (10.0%) | 6 (12.0%) | |
| | **Two** | 2 (4.0%) | 1 (2.0%) | |
| **GA** | **Mean ±SD** | 10.13 ±1.37 | 10.06 ±1.36 | 0.798 |
| | **Min – Max** | 7 – 12 | 7.5 – 11 | |

**Table (2): Comparison between both studied groups regarding medical history.**

| | Studied Groups | | P -value |
|---|---|---|---|
| | ISMN + Misoprostol group N= 50 | Misoprostol group N= 50 | |
| **Free** | 39 (78.0%) | 40 (80.0%) | 0.798 |
| **HTN** | 7 (14.0%) | 6 (12.0%) | 0.500 |
| **DM** | 3 (6.0%) | 3 (6.0%) | 0.661 |
| **Rheumatic fever** | 0 (0.0%) | 1 (2.0%) | 0.500 |
| **SLE** | 1 (2.0%) | 0 (0.0%) | 0.500 |

Female age was ranged from 19 to 39 years old, and gestational age (GA) was ranged from 16 to 24 weeks without a statistically significant differences between both groups. Parity and previous abortions all were comparable between both groups without a statistically significant difference.

Most of the studied women were free from any chronic disease and medical conditions, HTN was the most prevalent medical condition among studied women followed by DM without a statistically significant differences between both groups.

Comparison between both groups regarding abortion circumstances (Tables 3, 4 & 5)

**Table (3): Comparison of Mean induction to expulsion time in both groups.**

| | | Studied Groups | | P-value |
|---|---|---|---|---|
| | | **ISMN + Misoprostol group N= 50** | **Misoprostol group N= 50** | |
| **Induction to expulsion time (minutes)** | **Mean ±SD** | 232.46 ±56.24 | 301.72 ±78.89 | <0.001* |
| | **Min – Max** | 140 – 350 | 205 – 450 | |

**Table (4): Comparison between the studied groups regarding spontaneous expulsion rate after 1st dose.**

| | | Studied Groups | | p-value |
|---|---|---|---|---|
| | | **ISMN + Misoprostol group N= 50** | **Misoprostol group N= 50** | |
| **1st dose** | **Failure** | 35 (70.0%) | 44 (88.0%) | 0.024* |
| | **Success** | 15 (30.0%) | 6 (12.0%) | |

**Table (5): Comparison between the studied groups regarding spontaneous expulsion rate after 2nd dose.**

| | | Studied Groups | | p-value |
|---|---|---|---|---|
| | | ISMN + Misoprostol group N= 38 | Misoprostol group N= 42 | |
| 2nd dose | Failure | 19 (54.3%) | 26 (59.1%) | 0.445 |
| | Success | 16 (45.7%) | 18 (40.9%) | |

Comparison of the mean induction to expulsion time in both groups showed that there was a highly statistically significance difference among both groups with p value ($P<0.01$) indicating that the medical induction of abortion in second trimester using isosorbide mononitrate plus misoprostol takes much shorter time than misoprostol alone.

There was a statistically significance difference regarding number of received doses and spontaneous expulsion among both groups. In misoprostol group 6 women (12) that was significantly less than ISMN + Misoprostol group where 15 (30.0%) aborted after the first dose. There was non-statistically significant difference between both groups after 2nd dose, further 18/44 (40.9%) women aborted in misoprostol group and 16/35 (45.7%) women aborted from ISMN with misoprostol group.

Comparison between both groups regarding complications (Tables 6, 7 & 8)

**Table (6): Comparison of main complications among both groups.**

| | | Studied Groups | | P-value |
|---|---|---|---|---|
| | | ISMN + Misoprostol group N= 50 | Misoprostol group N= 50 | |
| Complications | Uterine infection | 3 (6.0%) | 2 (4.0%) | 0.500 |
| | Cervical Injury | 2 (4.0%) | 1 (2.0%) | 0.500 |

**Table (7): Comparison of drug adverse effect among both groups**.

| | Studied Groups | | P-value |
|---|---|---|---|
| | **ISMN + Misoprostol group N= 50** | **Misoprostol group N= 50** | |
| **Vomiting** | 3 (6.0%) | 10 (20.0%) | 0.027* |
| **Headache** | 8 (16.0%) | 2 (4.0%) | 0.092 |
| **Diarrhea** | 2 (4.0%) | 1 (2.0%) | 0.500 |
| **Colic** | 3 (6.0%) | 11 (22.0%) | 0.020* |

**Table (8): Comparison of Mean intraoperative blood loss in both groups.**

| | | Studied Groups | | P-value |
|---|---|---|---|---|
| | | **ISMN + Misoprostol group N= 50** | **Misoprostol group N= 50** | |
| **Mean intraoperative blood loss (ml)** | **Mean ±SD** | 86.30 ±29.21 | 86.73 ±29.60 | 0.942 |
| | **Min- max** | 50 – 200 | 40 – 210 | |

There was no statistically significant difference among both groups regarding main complications such as uterine infection and cervical injury.

There was a statistically significant difference among both groups regarding drug adverse effects (vomiting and colic). Vomiting was significantly higher among misoprostol group (20%) compared to ISMN with misoprostol group (6%), also, colic was significantly higher among misoprostol group (22%) compared to ISMN with misoprostol group (6%). Only headache occurred at a higher proportion among ISMN with misoprostol group (16%) compared to misoprostol group (4%), however this difference was with non-statistically significance (p-value= 0.092).

There was non-statistically significant difference among both groups regarding intraoperative blood loss with P-Value 0.942.

## Discussion:

Miscarriage, the commonest complication of pregnancy, affects approximately 15%–20% of clinically diagnosed pregnancies. It is characterized by the retention of pregnancy products in the uterus for an extended period following fetal demise (8).

Medical intervention is often necessary for two primary types of miscarriage: missed miscarriage and incomplete miscarriage (9).

Medical management is chosen as the primary treatment option in 20-30% of women. The most used drug is a prostaglandin analogue misoprostol which can be given in single or divided doses. Misoprostol is an important drug in obstetrical and gynecologic practice because of its utero-tonic and cervical ripening action so it has been used extensively for the surgical evacuation of the uterus (10).

Research findings indicate that the application of misoprostol prior to a procedure reduces the amount of force needed for mechanical cervical dilation (11).

An issue encountered in the treatment with misoprostol is that around one-third of women exhibit incomplete evacuation during follow-up ultrasound scans, even in the absence of significant symptoms (12).

Some studies have investigated combining two medicines to boost treatment effectiveness; nitric oxide donors are among the other pharmaceuticals that have been used in conjunction with misoprostol for medical induction of abortion. (13).

Nitric oxide is a free radical gas, has a short half-life of 4 seconds. It is present in the body for around 6–10 seconds before combining with water and oxygen to produce nitrates. Through the reorganization of cervical collagen and ground material, which

softens the cervix, vaginal administration of nitric oxide donors such as isosorbide mononitrate efficiently promotes cervical ripening (14).

The present study aimed to compare the effect of isosorbide mononitrate when combined with misoprostol and misoprostol when used alone in medical induction of the second trimester missed abortion, expecting that both drugs, when used together, may be more effective and associated with less side effects.

In the study two groups of one hundred patients with missed second trimester pregnancy were enlisted for the research. In the first group (the Nitrate group), isosorbide -5-mononitrate and misoprostol were administered to 50 individuals. Just misoprostol was given to 50 patients in the second group (the misoprostol group). The occurrence of total abortion during the first 24 hours was the main goal of the investigation.

Furthermore, our findings revealed a notable disparity in the mean induction to expulsion time between the misoprostol group and the misoprostol plus ISMN group, with the latter exhibiting a considerably shorter duration ($P < 0.01$). This suggests that combining isosorbide mononitrate with misoprostol for medical induction of abortion in the second trimester results in a more expedited process compared to using misoprostol alone.

In the nitrate group, it was observed that the number of doses required for successful abortion was significantly lower compared to the misoprostol group (P value > 0.01).

A statistically significant difference was observed in the time required for the induction of abortion between the groups treated with isosorbide-mononitrate in combination with misoprostol and those treated with misoprostol alone, with a notably shorter duration noted in the nitrate group.

In our study, we found a significantly higher rate of successful abortion in the group treated with isosorbide-mononitrate plus misoprostol compared to the group treated with misoprostol alone.

This result is similar to study by Makhlouf et al. who stated that the complete abortion rate was 100% in nitric oxide (glyceryl trinitrate) induced group after introducing a complementary procedure. The complementary method was oxytocin drip which is not used in our study (15).

Our findings align with those of Makhlouf et al., who reported a 100% complete abortion rate in their study using nitric oxide (glyceryl trinitrate) induction, supplemented with oxytocin drip. However, it's important to note that our study did not incorporate the use of oxytocin drip (15).

This contrasts with the findings of Hidar et al., who conducted a study where they observed no difference in abortion rates between cases primed with isosorbide mononitrate 40 mg administered vaginally 12 hours before induction with vaginal misoprostol, compared to cases without this priming. Additionally, they conducted a trial comparing misoprostol and isosorbide dinitrate for termination of second trimester pregnancy, with both groups receiving oxytocin drip infusion at 30 mU/min. They found that the abortion interval rate at 48 hours did not significantly differ between the two groups, with rates of 90% and 93% respectively (16).

In our study we found that there was a statistically significance difference regarding number of received doses and spontaneous expulsion among both groups. In misoprostol group 6 women (12) that was significantly less than ISMN + Misoprostol group where 15 (30.0%) aborted after the first dose. On the other hand, there was non-statistically significant difference between both groups after 2nd dose, further 18/44

(40.9%) women aborted in misoprostol group and also 16/35 (45.7%) women aborted from ISMN with misoprostol group.

Our findings are consistent with those reported by Eppel et al., who found that the combination of vaginally administered isosorbide mononitrate (IMN) with misoprostol reduced the number of doses required for successful abortion compared to prostaglandin alone. (17).

In contrast, Baroutis et al. conducted a study comparing the efficacy of isosorbide mononitrate (IMN) and misoprostol versus misoprostol alone. They reported that in the misoprostol-alone group, a mean of 8.15 tablets (200 mcg) were used (SD=4.211), compared to 6.6 tablets (SD=2.197) in the misoprostol plus isosorbide mononitrate group. However, this difference was not statistically significant (P value= 0.05). The authors speculated that the lack of significance may be attributed to the number of repeated doses of IMN administered (20 mg every 4 hours) (13).

In our study, we found that induction abortion interval is shorter in nitrate group.

This was like what Baroutis et al. stated, that it took a mean of 20.4 hrs. (95% confidence interval (CI) = 16.6324.17) for patients in the misoprostol group to complete abortion compared to 12.4hrs (95% CI = 10.3314.47) for those administrated IMN plus misoprostol. This difference was significant statistically (P value=0.001) (13).

In the present study, there was no statistically significant difference regarding intraoperative blood loss among both groups (P-value > 0.05) which was like the study done by Ledingham et al. who showed that the mean of intraoperative blood loss in the misoprostol group was less than the combination group of misoprostol plus ISMN. The difference between both groups regarding intraoperative blood loss was not statistically significant (P-value > 0.05) (18).

In the current study we found that there was a statistically significant difference among both groups regarding drug adverse effects (vomiting and colic). Vomiting was significantly higher among misoprostol group (20%) compared to ISMN with misoprostol group (6%), also, colic was significantly higher among misoprostol group (22%) compared to ISMN with misoprostol group (6%). Only headache occurred at a higher proportion among ISMN with misoprostol group (16%) compared to misoprostol group (4%), however this difference was with non-statistically significance (p-value= 0.092).

This finding was like the study conducted by Arteaga et al. who compare the efficacy and safety of 400 ug/1.5 mL misoprostol gel solution with endocervical 80 mg/1.5 mL isosorbide dinitrate gel solution administered for medical induction on a total of 60 women with the first trimester missed abortion. This study reported that headache was the most frequent side effect associated with isosorbide mononitrate administration, which occurred in 18 out of 30 patients, compared with only 5 out of 30 women in the misoprostol group. Women treated with misoprostol reported mainly pelvic pain. The difference regarding headache among both groups was highly statistically significant ($P < 0.001$) (19).

In our study, there was no statistically significant difference in the occurrence of side effects between the two groups, except for headache (P value=0.001).

Nearly all studies investigating NO donors for cervical ripening have reported the occurrence of headaches among their participants, with varying severity. This headache is often attributed to the vasodilatory effects of NO (20).

## Conclusions:

The present study concluded that the use of isosorbide mononitrate (ISMN) in addition with misoprostol in medical induction of second trimesteric abortion may be more effective than misoprostol alone and was associated with less side effects as vomiting and colic except headache was more with isosorbide mononitrate.

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