

## Comparison of Efficacy and Side Effects of Different Administration Routes of Misoprostol (Oral, Vaginal, and Sublingual) for Second-Trimester Abortion

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### Abstract

#### Background

The current study was designed to compare the effectiveness and side effects of oral, vaginal, and sublingual misoprostol in termination of second-trimester pregnancy.

**Materials and Methods:** In this clinical trial (2014 to 2015), 85 pregnant women in the second trimester of pregnancy were included in Imam Reza hospital, Kermanshah, Iran. They were randomly divided into three groups as follows: oral misoprostol (n=28), vaginal misoprostol (n=30), and sublingual misoprostol (n=27). Misoprostol was administered orally (oral misoprostol group), vaginally (vaginal misoprostol group), or sublingually (sublingual misoprostol group). The dosage was similar in three groups (400 micrograms every four hours up to a maximum of five doses). The mothers were followed and induction-abortion interval time, number of dosages required, and misoprostol side effects were documented. The data were analyzed by SPSS version 20.0 software.

**Results:** The mean (standard deviation) age of the sample was 28.27 ( $\pm 4.97$ ) years. Mean gestational age was 16.58 weeks and mean gravidity was 1.99. Mean number of administered misoprostol doses was 3.89 and most patients responded to three doses of misoprostol. Mean abortion time was 20.08 hours. No side effects were reported in 60% of the subjects. Others experienced side effects such as nausea (16.5%), fever and chills (12.9%), and vaginal bleeding (9.4%). The abortion duration in 35.3% of the subjects was within 18 hours. The most successful method was oral route (82.1%), followed by vaginal route (80%), and sublingual route (70.4%). The abortion duration was statistically different between the three groups ( $P= 0.001$ ).

**Conclusion:** Finding of the presented study showed that misoprostol is a safe medication to be used for medical abortion in the second trimester of pregnancy. Oral route of administration was superior to vaginal or rectal use of misoprostol.

**Key Words:** Abortion, Misoprostol, Oral, Second trimester, Sublingual, Vaginal.

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## 1- INTRODUCTION

Abortion is defined as expulsion of the fetus prior to the stage of viability, whether spontaneous or induced. According to the reports by the World Health Organization (WHO), annually 50 million abortions are reported (1). Although most cases of abortions occur in the first trimester of pregnancy, a gradual increase of abortion rate in the second trimester of pregnancy is seen. This is attributable to factors such as prenatal screening programs and diagnosis of serious fetal abnormalities including cardiovascular and skeletal anomalies which are usually detected by ultrasound examination (2, 3). The second trimester abortions are of more importance than the first-trimester abortions owing to more risks associated. Different causes can lead to abortion such as fetal demise, mother's life threatening, conditions such as preeclampsia and eclampsia, kidney diseases, uncontrolled diabetes, serious congenital anomalies, intrauterine infections, premature rupture of membranes, malignant diseases, and cardiovascular disorders (4-7).

In order to perform necessary medical abortions, different methods are available like surgical dilatation and medical induction (abortion induction). Surgical dilatation, even in the hands of experienced doctors, can be associated with a high rate of complications and mortality (8, 9). Also, surgical methods need expertise by the surgeon and use of anesthesia. Hence, nowadays medical abortion is considered as an effective alternative method to surgical methods. One of the advantages of medical abortion is that there are various types of abortion medications available including oxytocin and prostaglandins. Although pregnancy termination with medication is longer and is associated with more pain, satisfaction of women with this method is higher (10). Among various abortion medications, prostaglandins such as misoprostol and E1

(PGE1), prostaglandin E2 (PGE2), and prostaglandin F2 $\alpha$  (PGF2 $\alpha$ ), are usually used. Misoprostol, a prostaglandin analogue, is considered as the main method of abortion in the second trimester of pregnancy (11). Misoprostol can be administered via oral or rectal routes, but vaginal administration is associated with less frequent digestive side effects (abdominal pain) and bleeding (12). There is evidence that sublingual misoprostol is effective for medical abortion (13). The results of a randomized clinical trial studying abortion showed that administration of vaginal misoprostol (600 micrograms) and then 400 micrograms every 4 hours was resulted in more rapid abortion (12 hours) compared to concentrated oxytocin with PGE2 (17 hours). The 24-hour efficacy was 95% for vaginal misoprostol and 85% for oxytocin (14). A variety of treatment regimens with misoprostol have been studied and reported in the literature. However, none had advocated a uniform guideline.

It seems that misoprostol dosages higher than 400 micrograms not only increases the effectiveness, but also can be associated with more side effects. On the other hand, lower doses at 200 micrograms have lower efficacy (15). Advantages of misoprostol include low cost, no need to store in special conditions, availability, and ease of use for doctor and patient. Misoprostol has been cited as a good abortion medication for developing countries (16-18). As misoprostol is used more frequently than other methods for abortion and its favorable side effect profile and satisfaction of patients, we decided to select a method that can have fewer side effects and good outcome in a timely manner. Misoprostol can be administered via four routes namely oral, sublingual, rectal, or vaginal routes. Side effects including fever and chills, abdominal cramps, nausea and vomiting and diarrhea occur with different rates in

each of the mentioned administration routes. Most studies have compared two administration routes and head-to-head comparison studies of three routes are scarce. Currently we use vaginal route to administer misoprostol at our center for second-trimester abortions. If it fails, the second dosage of misoprostol is administered vaginally in 24 hours. In addition to side effects, another important clinical consideration is shorter abortion time. As there is limited evidence about abortion medication for second-trimester abortions and the importance of such abortions in clinical practice, we decided to compare three administration routes including oral, vaginal, and sublingual for misoprostol to determine which route has fewer side effects with shorter abortion time.

## 2- MATERIALS AND METHODS

This clinical trial was conducted in the labor department of the obstetrics and gynecology department of our university hospital (Imam Reza hospital affiliated to Kermanshah University of Medical Sciences, Kermanshah, Iran) which lasted 12 months in 2014 and 2015. The study protocol was registered at the Iranian Registry of Clinical Trials website (IRCTID: IRCT2015123014333N47).

The sample was selected among pregnant women within gestational weeks of 13 to 22 who were candidate due to fetal demise or congenital anomalies. The sampling method was consecutive and sampling was done until the required sample size was completed. They were randomly divided into three groups as follows: oral misoprostol (n=28), vaginal misoprostol (n=30), and sublingual misoprostol (n=27). The previous studies reported success rates of oral, vaginal, and sublingual routes as 94.4%, 86.3%, and 74.9%, respectively (19, 20). The difference in success rate between vaginal and oral routes was lower than that of vaginal and

sublingual routes. Considering  $\alpha=5\%$  and power= 80%, the sample size was calculated as 205, 185, and 50 subjects for two-by-two comparisons of the three administration routes. However, due to relatively low number of patients available for the study, difficulty in access misoprostol suppository, and lower rate of consent of patients to participate at the study, the sample size in each group was determined as 30 subjects and a total number of 90 subjects were included. Exclusion criteria consisted of previous history of cesarean section or any uterine scar because of previous procedures such as myomectomy, multiple pregnancy, anemia (defined as hemoglobin level lower than 10 g/dl), systemic and chronic diseases in mother, cardiovascular diseases (such as mitral stenosis), pulmonary diseases (such as bronchial asthma), kidney diseases, known allergy to prostaglandins, coagulopathies, glaucoma, uncontrolled seizure disorders, hemolytic diseases, hepatic diseases, and inflammatory conditions.

When eligible patients were identified, firstly the objectives of the study were explained to them and if agreed informed consent was obtained from them. The subjects were not charged. The gestational age was determined using the first day of the last menstrual period (LMP) with ultrasound confirmation. Before any therapeutic intervention, vital signs (blood pressure, pulse rate, respiratory rate, and temperature) of the mothers were recorded. Initial pelvic examination, gestational age determination, and documentation of vital signs were done by a physician. The information including maternal age, gestational age, gravidity, number of administered misoprostol dosages, abortion induction duration, side effects of misoprostol, the need for blood transfusion, and abortion were recorded in a pre-designed checklist. All gathered data were entered into a computer system.

Selective dose of misoprostol (Searle, High Wycombe) was 400 micrograms which was administered every four hours up to a maximum of five doses. In vaginal subgroup, two misoprostol tablets (400 micrograms) were dissolved in water and placed at the end of posterior fornix. In oral and sublingual groups, misoprostol was given in the same equivalent dose. Vital signs and side effects (abdominal pain, nausea, vomiting, diarrhea, fever, and bleeding) were recorded two times; once at the time of administration (hour 1) and for the second time four hours later.

At the beginning of administration of each misoprostol dose, vaginal examination was performed to assess the progress of treatment. The time interval from the first misoprostol administration and expulsion of products of conception was recorded. After expulsion, the products of conception (i.e., placenta and fetus) were examined. For all patients, curettage was done in the operation room and hemoglobin level was assayed six hours later. If expulsion of products of conception did not occur within 24 hours, this was regarded as abortion failure. In such cases, the further decision was made by the doctor in charge.

The data were analyzed using the SPSS software (ver. 16.0). Descriptive statistics such as mean and standard deviation ( $\pm$ SD) were used to express data. Normal distribution of the variables was controlled by the Kolmogorov-Smirnov (KS) test. In order to compare the side effects between the groups, the Chi-square test was used. In order to compare continuous variables, after use of KS test, the Kruskal-Wallis test and analysis of variance (ANOVA) were used for normally and non-normally distributed variables. The significance level was set at 0.05.

### 3- RESULTS

The included subjects were divided into three groups including vaginal, oral, and

sublingual misoprostol. There were 30 subjects in oral misoprostol group, 27 in sublingual misoprostol group, and 30 in vaginal misoprostol group. Mean ( $\pm$ SD) maternal age was 28.27 ( $\pm$ 4.97) years (range, 19 to 40 years). Oral misoprostol group with a mean age of 26.68 years was the youngest group. No significant difference existed among the groups regarding maternal age ( $P=0.369$ ); **Table.1.** The results showed that gestational age ( $P=0.292$ ) had a mean of 16.58 weeks (range, 13 to 22 weeks). The most common time for successful abortion was in week 16 (19 cases), followed by week 15 (13 cases), and week 18 (12 cases). In two subjects, abortions occurred in week 22 ( $P=0.017$ ). Mean gravidity number was 1.99 ( $P=0.594$ ) and most cases with successful abortion were gravidas 2 (38 cases, 44.7%). Primigravida (27 cases, 31.8%), gravida 3 (16 cases, 18.8%), gravida 4 (2 cases, 2.4%), and gravida 5 (2 cases, 2.4%), were in order other common groups.

In 31 cases (36.5%) abortion occurred with the third dose of misoprostol; twenty-nine cases (34.1%) required 4 doses, 23 cases (26.5%) required 5 doses, and two patients (2.4%) required two doses of misoprostol to achieve successful abortion. Mean number of administered misoprostol doses was 3.89. Abortion occurred within 18 hours following the first dose of misoprostol in 30 patients (45.4%). Induction to abortion interval was within 24 hours in 16 cases (24.2%), within 23 hours in 10 cases (15.2%), and within 20 hours in 6 cases (9.1%). In each time intervals of 3 hours, 12 hours, 14 hours, and 22 hours one patient achieved successful abortion. In 19 cases, induction to abortion interval was more than 24 hours. This was considered treatment failure. Mean induction to abortion interval was 20.08 hours. Of 85 studied cases, 66 patients (77.6%) aborted successfully and 19 cases experienced treatment failure.

Observed successful induced abortions in oral, vaginal, and sublingual groups were 82.1% (23 subjects), 80% (24 subjects), and 70.4% (19 subjects), respectively ( $P=0.57$ ). Oral misoprostol exhibited the best efficacy, followed by vaginal and sublingual misoprostol groups. In general, 77.6% of the sample aborted successfully. Fifty-one cases (60%) did not experience any side effects of misoprostol. Nausea was reported in 16.5% of cases, and fever and chills was recorded in 12.9% of the sample (**Table.2**). Only two patients (7.1%) required blood transfusion. Both

patients received misoprostol orally. Blood transfusion was not required in other groups. The Kruskal-Wallis test results showed that there was no significant difference among the three groups regarding gestational age, gravidity, and administered misoprostol dosage ( $P>0.05$ ). However, a significant difference existed regarding abortion duration ( $P<0.001$ ). Abortion time was significantly longer in vaginal misoprostol group in comparison to oral and sublingual groups; **Table.3**.

**Table-1:** Mean age of patients in oral, vaginal and sublingual routes of misoprostol administration for second-trimester induced abortion

| Misoprostol group | No. (%)    | Mean ( $\pm$ SD)    | Range |
|-------------------|------------|---------------------|-------|
| Vaginal           | 30 (35.3%) | 28.27 ( $\pm$ 5.36) | 20-40 |
| Oral              | 28 (32.9%) | 26.68 ( $\pm$ 4.56) | 19-35 |
| Sublingual        | 27 (31.8%) | 28.67 ( $\pm$ 4.88) | 22-40 |
| Total             | 85 (100%)  | 27.87 ( $\pm$ 4.97) | 19-40 |

**Table-2:** Comparison of misoprostol side effects between the three (oral, vaginal, and sublingual) administration routes

| Side effects     | Vaginal    | Oral       | Sublingual | Total      | P- value |
|------------------|------------|------------|------------|------------|----------|
| No side effect   | 17 (56.7%) | 17 (60.7%) | 17 (63%)   | 51 (60%)   | -        |
| Fever and chills | 4 (13.3%)  | 3 (10.7%)  | 4 (14.8%)  | 11 (12.9%) | 0.900    |
| Abdominal pain   | 0          | 1 (3.6%)   | 0          | 1 (1.2%)   | 0.357    |
| Nausea           | 6 (20%)    | 5 (18.9%)  | 3 (11.1%)  | 14 (16.5%) | 0.646    |
| Vaginal bleeding | 3 (10%)    | 2 (7.1%)   | 3 (11.1%)  | 8 (9.4%)   | 0.873    |
| Total            | 30 (100%)  | 28 (100%)  | 27 (100%)  | 85 (100%)  | -        |

**Table-3:** Comparison of induction-abortion interval, gravidity, gestational age, and misoprostol dose between the three studied groups

| Statistics         | Gestational age | Gravidity | Misoprostol dose administered | Abortion duration |
|--------------------|-----------------|-----------|-------------------------------|-------------------|
| Chi-square value   | 1.995           | 1.043     | 3.824                         | 13.916            |
| Degrees of freedom | 2               | 2         | 2                             | 2                 |
| P- value           | 0.369           | 0.594     | 0.148                         | 0.001             |

#### 4- DISCUSSION

This study was carried out with the purpose of comparing the efficacy and side effects of three administration routes (oral, vaginal, and sublingual) for misoprostol for second-trimester medical abortion. Different studies have evaluated the efficacy of misoprostol for pregnancy termination in the second trimester of

pregnancy. Different misoprostol doses have been studied, as well as various administration routes. The reported efficacy rates and side effects vary among studies. The obtained findings showed that pregnancy termination with oral misoprostol was more successful compared to vaginal and sublingual routes,

however, no significant difference was observed regarding misoprostol side effects between the three groups. No serious side effects were reported in any of the groups. In general, 77.6% aborted successfully and 22.4% of the patients did not achieve successful abortion. No significant difference was seen regarding successful abortion rate and the administration route groups. In contrast to the presented findings, in a previous study (21), rate of complete abortion was higher in sublingual group in comparison to oral ( $P= 0.03$ ), and vaginal route ( $P= 0.56$ ). Induction-abortion interval was also the least with the sublingual route when compared to oral ( $P< 0.001$ ), and vaginal ( $P= 0.0011$ ) routes.

In Hemlata study, successful abortion rate was 94.4% in oral misoprostol group and 86.8% in vaginal misoprostol group. Although reported success rates were higher than our study, oral misoprostol was superior to vaginal misoprostol, a finding compatible with what we observed here (19). Another study reported that buccal and vaginal routes of misoprostol administration have similar efficacy. Hence, buccal route may serve as an alternative to vaginal misoprostol. In second trimester, success rate was 96% in buccal group and 80% in vaginal group (22). Their higher success rate may be due to received oral mifepristone followed by misoprostol. In another study recruiting 140 patients candidate for pregnancy termination in the second trimester, the patients were divided into two groups, namely vaginal misoprostol (49 subjects) and oral misoprostol (65 subjects) (23).

According to the reported findings, successful abortion rate was 85.1% in vaginal misoprostol group and 39.5% in oral misoprostol group. These findings contradict ours. In another study, success rate in vaginal and oral misoprostol groups were respectively 90% and 46.6% (24), which are not compatible with our

findings. Likewise, in another study success rate for pregnancy termination in the first 24-hour time for vaginal misoprostol was 93% which was higher than in oral misoprostol group (19%) (25). It had been suggested that since absorption of misoprostol is better from the vagina (26), this justifies better outcomes with vaginal misoprostol than oral misoprostol in shorter induction-to-abortion time and effectiveness. Although the previously mentioned studies (23, 25, 26) are compatible with this explanation, our findings as well as those reported by another study (19) are not consistent with this explanation and we observed better outcome with oral misoprostol than with vaginal misoprostol.

Here, regarding induction-abortion interval, about half of the patients experienced pregnancy termination within 18 hours (30 cases, 45.5%), and 24.2% (16 subjects) experienced abortion within 24 hours. Mean abortion times in a former study in vaginal and oral routes were, respectively 17.5 and 33 hours (25). In another study, mean induction-abortion time was 18.87 hours. This study examined lower doses of misoprostol compared to what we examined (27). In another study, administration of 600 micrograms of misoprostol in two groups every 6 hours and every 12 hours, in experimental group mean pregnancy termination time was 15 hours and in control group this was 15.8 hours (28).

In Pongsatha and Tongsong study, mean induction-abortion interval was 25.9 hours (29). In another study, the time interval since the first dose of misoprostol to abortion had a mean of 16.05 hours (range, 2 to 36 hours) (30). In another study by Dilbaz et al. (31) which included pregnant women within gestational age of 12 to 20 weeks, the results showed that in 98% of the sample, abortion occurred within the first 24-hour period. With increase in gestational age (more than 16 weeks),

mean induction time prolonged. We observed nausea, fever and chills, and vaginal bleeding as the side effects of misoprostol. None of the patients experienced abdominal pain. In a previous study, fever (47.1%), chills (23.5%), nausea (17.6%), and need for analgesia (29.4%) have been reported as side effects (29). These figures are higher than what we observed. However, in another study, 9% had fever and 7% had nausea which was lower than ours (30). In Herabutya et al. study, administration of misoprostol every 12 hours was as effective as administration every 6 hours and fever was lower in the group for whom misoprostol was administered every 12 hours which was due to lower total dose of administered misoprostol (28).

In a similar study, minor side effects (fever, pain, and diarrhea) were common but major side effects such as need for blood transfusion or re-admission were few. Misoprostol was described as a safe and less invasive method for second-trimester abortions (11). In the study conducted by Dehbashi et al, women in sublingual group experienced more complications including diarrhea (22.2% versus 20.0%), nausea and vomiting (22.2% versus 0.0%), and abdominal pain (3.7% versus 0.0%) (32).

#### 4-1. Limitations of the study

We faced some limitations. Access to misoprostol suppository was difficult during the study period. Due to the sample size, we were not able to assign additional subjects to the fourth route of administration (i.e., rectal route). As a limited number of research studies are available in the literature studying three methods of administration simultaneously, we think this can be considered strength of the presented study that compared three administration routes.

#### 5- CONCLUSION

In general, the results of the current study showed that success rate and side effects did not show significant differences among the three administration (vaginal, sublingual, and oral) routes for misoprostol. However, only abortion time was longer in vaginal route compared to oral and sublingual routes.

**6- CONFLICT OF INTEREST:** None.

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