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## OBSTETRICS

# Effectiveness of Vaginal Misoprostol Application for Cervical Priming in First-Trimester Pregnancy Termination: A Randomized Clinical Trial

Suchati Chiawchanchaiaratana MD,
Pavit Sutchritpongsa MD,
Dittakarn Boriboonhirunsarn MD., M.P.H., Ph.D.

*Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand*

**ABSTRACT**

**Objective** To evaluate the effectiveness of vaginal Misoprostol application for cervical priming in first-trimester pregnancy termination, and its side effects.

**Design** Randomized clinical trial.

**Setting** Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University.

**Subjects** A total of 40 pregnant women of less than 13 weeks' gestation who were indicated for termination of pregnancy and agreed to participate.

**Methods** All pregnant women were randomized into two groups. Women in the treatment group received vaginal application of Misoprostol 400 μg, while those in control group received nothing before uterine curettage. Cervical dilatation was assessed at baseline and 4 hours later. Termination of pregnancy by either dilatation and curettage or sharp curettage alone was then performed according to the condition of the cervix.

**Main outcome measures** Cervical os diameter at baseline and 4 hours apart.

**Results** After 4 hours of vaginal Misoprostol administration, the mean cervical os diameter in the treatment group was significantly greater than that of control group ($8.0 \pm 1.7$ mm and $4.4 \pm 2.0$ mm respectively, $p < 0.001$). Proportion of women who achieved cervical os dilatation of at least 8 mm was also significantly higher in treatment group than control group (85% and 5% respectively, $p < 0.001$). Operative time was significantly shorter in the treatment group while blood loss was comparable between the 2 groups. Only 2 women in the treatment group experienced minor side effects.

**Conclusion** A single-dose vaginal suppository of Misoprostol 400 μg without any solvent added for 4 hours was highly effective for cervical priming before first-trimester pregnancy termination, without significant side effects or any serious complications. The regimen appeared to be useful in decreasing the need for mechanical cervical dilatation and may also prevent possible complications from such procedure.

**Key words:** misoprostol, termination of pregnancy, first-trimester gestation

For first-trimester termination of pregnancy, the method traditionally performed in Siriraj Hospital is dilatation and sharp curettage (D&C). Cervical dilatation by mechanical means has been reported to result in histological proven ruptured of cervical connective tissue.[1] Cervical lacerations from the procedure has been reported in 0.01 - 1.6% of abortions.[2-4] The major concern is the derangement of cervical functions, such as cervical incompetence, in subsequent pregnancy, which known to be the cause of many adverse pregnancy outcomes such as spontaneous 2nd trimester abortion, preterm premature ruptured of membranes and preterm labor. However, it uncommonly occurs when proper techniques were employed by experienced physicians.

Search for a safe, effective, quick and hygienic method for termination of pregnancy is a continuing effort worldwide. Prostaglandins are among the medications that are in active research in this field. There are many subtypes of prostaglandins that are synthesized for the use in gynecologic and obstetric practices, which are reported to be relatively safe and effective for second trimester termination of pregnancy,[5-9] induction of labor,[10] and for treatment of postpartum uterine atony.[11]

But almost all of these substances are very expensive, required cool environment (4°C) for storage and transportation and have significant side effects. These make them less appropriate for clinical use in developing countries, including Thailand.

Misoprostol (Cytotec®, Searle Ltd., Chicago, IL) is a prostaglandin E1 analogue (15-deoxy-16-hydroxy-16-methyl PGE1) originally synthesized for oral use for treatment and prevention of gastric ulcer induced by nonsteroidal anti-inflammatory agents. Its low price, better stability at room temperature, and few side effects makes Misoprostol attractive for clinical use. Recently the pharmacokinetics of Misoprostol administered by vaginal suppositories has been reported.[12] When compared with oral administration, vaginal suppositories result in more sustained plasma concentrations, and therefore may be more effective for clinical purposes.[13]

Reported data have shown that vaginally administered misoprostol have the similar effects on the cervix as Gemeprost®, which is another prostaglandin E1 analogue (16, 16-dimethyl-trans-ΔPGE1 methyl ester) that has been approved for cervical priming.[14]

Effective use of vaginal Misoprostol for cervical priming in termination of pregnancy in first trimester has been reported and the optimal dose appeared to be 400 μg.[15] The evacuation interval 3-4 hours after vaginal Misoprostol for pre-abortion cervical priming was considered appropriate.[16] This method for cervical priming can reduce the necessity of other mechanical means for cervical dilatation and its possible complications.

The main purpose of this study is to evaluate the effectiveness of vaginal Misoprostol application for pre-termination cervical priming in first-trimester abortion, as well as its side effects in Thai women.

## Materials and Methods

The women included in this study were healthy pregnant women of less than 13 weeks' gestation who were indicated for termination of pregnancy and agreed to participate. Gestational age was confirmed either by menstrual history, physical and/or pelvic examination, ultrasonography or in combinations. Those who were contraindicated for prostaglandins use, had previous cervical surgery, and whose cervical os were already dilated for 8 mm or more were excluded.

A total 40 women were recruited. The informed consents were obtained from all women, and then they were randomly assigned to either receiving 400 μg (200μg, 2 tablets) of Misoprostol administered vaginally (Treatment group), or receiving nothing (Control group) before termination of pregnancy. Obstetric record was reviewed and data were recorded, including baseline characteristics, diagnosis, and indication for pregnancy termination.

Initial pelvic examination for cervical os assessment was performed in all women. Cervical os diameter was determined using Hegar dilators,

started with the largest one (12 mm), followed by smaller ones in descending order (11, 10, 9, 8 mm, etc.). Cervical os diameter was recorded to be equal to the largest Hegar dilator that can pass external and internal cervical os without any resistance. Misoprostol was then administered vaginally at posterior fornix to women in treatment group without adding any solvent, while nothing was administered in control group.

Follow up examination was performed 4 hours later and cervical os diameter was determined and recorded in similar manner. In addition, the presence of product of conception in vagina or at external cervical os was also recorded. Dilatation and curettage or sharp curettage alone was then performed as indicated, depending on cervical conditions. Mechanical dilatation was needed if the cervical os diameter was less than 8 mm to permit the passage of the instrument for sharp curettage. If the cervical os diameter dilated for 8 mm or more, sharp curettage was performed without further mechanical dilatation.

Operative time, blood loss, as well as other complications during and after the procedure were recorded. Side effects such as abdominal pain, nausea, vomiting, fever or chills, and diarrhea were assessed by verbal interviewing and physical examinations as necessary.

The randomization process and administration of Misoprostol were done by a research assistant, blinded to the investigator. The investigator was the only person who assessed all the outcomes and performed all necessary surgical procedures without knowledge of which group the women were assigned to.

Descriptive statistics, including mean, standard deviation, number, and percentage, were used to describe characteristics and outcomes of all participants. Comparison of baseline characteristics and other outcomes between groups were made using Student t-test, Chi square test, and Fisher Exact test as appropriate. The difference was considered significant statistically when p value $< 0.05$.

This study was approved by the Ethical Committee on Research Involving Human Subject, Faculty of Medicine Siriraj Hospital, Mahidol University.

## Results

A total of 40 women were enrolled, 20 in treatment group and 20 in control group. Baseline characteristics of these women were shown in Table 1.

**Table 1.** Baseline characteristics of pregnant women

| Characteristics | Treatment Group (n = 20) | Control Group (n = 20) | P value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Age (year) | 31.3 ± 6.2 | 29.8 ± 7.2 | 0.501* |
| Weight (kg) | 57.1 ± 9.1 | 53.2 ± 9.0 | 0.185* |
| Height (cm) | 157.4 ± 4.2 | 155.7 ± 4.8 | 0.258* |
| BMI (kg/m$^2$) | 23.0 ± 3.7 | 22.0 ± 4.0 | 0.385* |
| | N (%) | N (%) | |
| Primigravida | 9 (45) | 8(40) | 0.749** |
| Women with prior vaginal delivery | 6 (30) | 5 (25) | 0.723** |
| Women with prior abortion | 6 (30) | 7 (35) | 0.736** |

* Student t-test ** Chi square test

Women's age, weight, height, and body mass index (BMI) were comparable between the 2 groups. Additionally, gravidity, proportion of women previously delivered vaginally and ever had abortion were not significantly difference.

**Table 2.** Clinical characteristics of pregnant women

| Clinical Characteristics | Treatment Group (n = 20) | Control Group (n = 20) | P value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| GA (weeks) | 9.6 ± 1.9 | 9.4 ± 1.9 | 0.870* |
| | N (%) | N (%) | |
| Chief Complaints | | | |
| Vaginal bleeding | 9 (45.0) | 12 (60.0) | 0.342** |
| Vaginal bleeding with abdominal pain | 3 (15.0) | 4 (20.0) | 1.000*** |
| Incidental findings by U/S | 8 (40.0) | 4 (20.0) | 0.167** |
| Diagnosis | | | |
| Blighted ovum | 14 (70.0) | 11 (55.0) | 0.327** |
| Dead fetus in utero | 6 (30.0) | 9 (45.0) | |

* Student t-test ** Chi square test *** Fisher Exact test

Table 2. showed clinical characteristics of both groups. Gestational age at admission was not significantly different between groups. Chief complaints, diagnoses or indications for pregnancy termination were also comparable.

**Table 3.** Cervical dilatation and operative findings

| Variables | Treatment Group (n = 20) | Control Group (n = 20) | P value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Cervical os diameter at baseline (mm) | 2.0 + 2.0 | 2.6 + 2.3 | 0.251* |
| Cervical os diameter at curettage (mm) | 8.0 + 1.7 | 4.4 + 2.0 | < 0.001* |
| Blood loss (ml) | 18.5 + 7.4 | 17.3 + 12.0 | 0.719* |
| Operative time (min) | 11.7 + 8.4 | 19.3 + 7.2 | 0.004* |
| | N (%) | N (%) | |
| Cervical dilation ≥ 8 mm at curettage | 17 (85.0) | 1 (5.0) | < 0.001** |
| Conceptus in vagina at curettage | 7 (35.0) | 1 (5.0) | 0.043*** |

* Student t-test ** Chi square test *** Fisher Exact test

Comparison of cervical dilatation and other operative findings were shown in Table 3. Initial pelvic examination demonstrated that the mean cervical os diameter in the treatment group and the control group were 2.0 mm and 2.6 mm respectively, which were not significantly different.

After 4 hours interval the mean cervical os diameter in the treatment group was significantly

greater than that of control group ($p < 0.001$). The dilatation was 8.0 mm in the treatment group while it was only 4.4 mm in the control group. When cervical os dilatation of 8 mm or more was considered successful cervical dilatation, we found that 85% of women in the treatment group compared with only 5% of women in the control group achieved this endpoint ($p < 0.001$).

Spontaneous expulsion of the conceptus in the vagina or at external cervical os at the time of curettage was found significantly higher in the treatment group compared to control group (35% and 5%, respectively, $p = 0.043$).

The mean time required to complete the uterine evacuation in the treatment group was also significantly lower than that of control group (11.7 minutes and 19.3 minutes, respectively, $p = 0.004$). Blood loss in two groups was not significantly difference.

**Table 4.** Side effects experienced by the women in the study

| Side effects | Treatment Group (n = 20) | Control Group (n = 20) | P value |
|---|---|---|---|
| | N (%) | N (%) | |
| Abdominal pain | 2 (10) | 0 (0) | 0.487* |
| Fever ($\geq 38^{\circ}$ C) | 1 (5) | 0 (0) | 1.000* |

* Fisher Exact test

With regard to possible side effects, only 2 women in the treatment group reported adverse events during the study. Both women experienced abdominal pain, and one of them also had fever. All these side effects were successfully relieved with single dose of acetaminophen (500 mg) 2 tablets per oral. Other side effects such as nausea, vomiting or diarrhea were not found in our study. No acute complications occurred during uterine evacuation procedures, and none of the women required blood product transfusion.

## Discussion

The results showed that a single-dose vaginal suppository of Misoprostol 400 μg, without any solvent added, at posterior fornix for 4 hours was highly effective for cervical priming before termination of first trimester gestation. There was approximately 6 mm increment in cervical os diameter while average increment in control group was only 1.8 mm. Cervical os diameter was 8 mm or more in 85% of cases, in which no further mechanical dilatation was needed. This appeared to be more effective than other regimens with lower dosage (200 μg) and longer interval (5-6 hours) of vaginal suppository that were previously reported to be effective in 72.5 - 74% of cases.[17, 18] The results also demonstrated that substance added (e r®) to create acidic milieu, believed by some investigators[18] to increase solubility and hence the absorption of Misoprostol may be unnecessary for its effectiveness in this purpose.

The achievement of adequate cervical dilatation (8 mm or more) could avoid cervical injuries that can be caused by mechanical dilatation. Other potential benefits of the medical cervical priming are the reduction in the failure rate of the uterine evacuation, and the decrease in the risk of uterine perforation which can be caused by the stiffness of the unprimed cervix that makes the uterine cavity be less accessible by instrumentation.

Although there are significant numbers of women in the treatment group that aborted spontaneously (35% compared with only 5% of women in the control group), we do not recommend using this regimen for this purpose for at least three reasons. First, as the figure shown, the effectiveness of this regimen at 4 hours interval in such purpose was quite low (35%). Second, if the women were left to wait

longer for spontaneous abortion, this would lead her to experience unnecessary discomfort and blood loss. Finally, the most important reason, we found in our study that all women who experienced spontaneous abortions the type of abortions were always incomplete abortions.

The operative time among the treatment group was significantly shorter than that of the control group ($11.7 \pm 8.4$ min., and $19.3 \pm 7.2$ min. respectively). This can be explained by the readiness of the cervix for instrumentation for uterine curettage, hence the ease to proceed the operation.

Blood loss of the women in our study was comparable between the 2 groups, which was similar to earlier report.[16] The bleeding encountered was minimal and clinically irrelevant that neither women in our study nor those in earlier studies required any blood transfusion.[15,16]

Only minorities of the women in this study experienced significant side effects such as abdominal pain and fever, which were not different statistically from control group. However, this insignificant result may be due to inadequate power of this study to detect such differences, or it may be the true nature of Misoprostol itself that actually produces only few side effects. Further study on this aspect may be warranted. Anyway, these adverse events appeared to be only temporal phenomena, and can easily be managed with simple medication (e.g. acetaminophen).

Because of its effectiveness as an abortifacient,[19] and birth defects has been reported to be associated with its use during early pregnancy,[20-23] so that the unregulated use of Misoprostol can be dangerous. In countries which allow trading Misoprostol as an over-the-counter medicine, there have been reported about the adverse consequences resulted from the abuse of this medication by women without appropriate medical supervision. However, if this agent is used selectively under medical profession it seems to produce more benefit than risk to the population, and because of its low price it may be suitable for use in Thailand from cost-effective point of view.

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