

# CERVICAL PRIMING WITH SUBLINGUAL MISOPROSTOL PRIOR TO INSERTION OF AN INTRAUTERINE DEVICE IN WOMEN WITH NO PREVIOUS VAGINAL DELIVERY A RANDOMIZED CONTROLLED TRIAL

By

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## ABSTRACT

**Background:** The use of misoprostol at a dose of 600 µg administered sublingual 2 hrs prior to IUD insertion increased the ease of insertion and reduced the incidence of failed insertion and pain during the procedure, although the frequency of cramps increased following misoprostol use.

**Objective:** To evaluate the efficacy of sublingual misoprostol 2 hours prior to intrauterine device (IUD) insertion in women with previous cesarean section.

**Patients and Methods:** This randomized, double-blind clinical trial was conducted on women of reproductive age were submitted to IUD insertion between Jan 2019 and July 2019. A total of 120 women were randomly allocated to two equal groups: Group I received 600 µg of misoprostol sublingual 2h prior to IUD insertion, Group II received placebo.

**Results:** Significant differences were found between the groups for all the immediate end points studied, with less difficulty in inserting the IUD with misoprostol group. A positive balance was detected between the benefits and risks of the use of misoprostol. However, it was not feasible to conclude that its use was imperative prior to IUD insertion in previous CS, and IUD insertion should not be canceled when the medication was unavailable.

**Conclusion:** In view of its effect in promoting cervical dilatation, misoprostol may be used prior to IUD insertion in previous CS.

**Key words:** Sublingual 600 microgram misopristol prior to IUD insertion.

## INTRODUCTION

Each year, more than 100 million of women make decisions about beginning contraception after child birth. Proper family planning programs and adequate methods of contraception are important tools to avoid many problems in our world (Zakiyah et al., 2019).

Intrauterine device insertion is an outpatient procedure that should be performed by trained healthcare professionals, It's an effective and increasingly popular form of reversible contraception (Mosher & Jones, 2010 and Trussell et al., 2011). The increase in popularity has been attributed to their

efficacy, ease of reversibility, and patient satisfaction, with minimal effort required for long-term use (*Peipert et al., 2011*).

Beside to vasectomy, they are the most cost-effective method of long-term contraception available in the United States (*Trussell, 2010*).

The IUDs currently available include the copper T380A IUD (Paraguard) and 2 levonorgestrel-releasing intrauterine systems (Mirena and Skyla). Insertion failures and cervical problems seem to occur more often among women who have never delivered vaginally (*Daniels et al., 2015*).

Cervical stenosis and a significantly ante- or retroverted position of the uterus, have been described as factors associated with a difficult sounding of the cervical canal or even failure to insert the IUD (*Preutthipan and Herabutya, 2010*).

Moreover, *Preutthipan and Herabutya (2010)* have shown the benefit of misoprostol as a cervical ripening agent in women with previous cesarean section.

The aim of this work was to evaluate the efficacy of sublingual misoprostol 2 hours prior to intrauterine device (IUD) insertion in women with previous cesarean section.

## PATIENTS AND METHODS

This is a randomized controlled double blind study that was conducted at Obstetrics and Gynecology Department, El-Hawamdiya General Hospital during the period from Jan 2019 to July 2019.

The study included all women aged from 25 to 40 years with previous cesarean section and with no previous vaginal delivery attending outpatient

clinic for IUD insertion during postpartum period (after puerperium).

While patients with contraindications for misoprostol use (pregnancy and prostaglandin allergy), contraindications for IUD use (gynecologic malignancy, pelvic inflammatory disease and unexplained vaginal bleeding), previous vaginal delivery and medical disorders as bleeding tendency were excluded from the study.

Participants were allowed to breastfeed provided that they left an interval of 4 hours between time of administration of misoprostol and breastfeeding.

**Groups of study:** 120 candidates for Cu T 380A IUD insertion were enrolled in the study. They were divided into two groups: Group 1: Sixty women received 600 micrograms of misoprostol sublingual two hours before IUD insertion. Group 2: Sixty women received the placebo sublingual.

Placebo was the same in size, color and shape to misoprostol.

The placebo and misoprostol were put in 120 numbered closed envelopes according to the table of random numbers and an envelope was allocated to each patient accordingly.

Informed consent was taken from all women before participation in the study.

### Study procedures:

**All patients were subjected to the following:**

#### Complete history taking:

Full history taking, obstetric history, menstrual history, medical history and

data were collected in a special form for each patient.

**Proper counseling:**

Proper counseling of each patient about different types of IUDs, the advantage and side effects of each type, explanation of the menstrual pattern changes, assuring the patient that these changes are very common and that it will disappear after a period of time after insertion. Informed consent was taken from all patients.

**Examination:**

General, Abdominal and Pelvic examination. 600 ug misoprostol (3 tablets Misotac®) (Sigma Pharmaceutical Industries, Egypt) or Placebo were administered sublingual two hours before insertion of the IUD by gynecologist.

Insertion of IUD: (TCu-380A®, Pregna International Ltd, India).

**Post insertion instructions:**

Palpation of strings should be performed monthly by the patient.

**Statistical analysis:**

Data were entered checked and analyzed using Epi-Info version 6 and SPSS for Windows version 8 (SPSS Inc., Chigaco, USA). Data were summarized using: The arithmetic mean, the Standard Deviation (SD), number and percentage. Mann Whitney-U test, Student t test and X2 (chi-squared) (test of significance). The results were considered significant when the probability of error is less than 5% (p < 0.05).

**RESULTS**

There were no statistically significant differences between both groups as regard age. There was no significant difference between misoprostol group and control group as regard number of previous cesarean sections (CS). The proportion of failed insertion (0%) in misoprostol group was statistically significantly lower than

placebo group 2/60, 3.3% p-value 0.02 (this two cases are previous 3 CSs. There was statistically significant difference between both groups regarding difficulty of insertion. The insertion of IUD in misoprostol group was easier than in placebo group; (Table 1).

**Table (1): Comparison between the two study groups as regards age, number of CS of studied groups, failed insertion and difficulty of insertion**

Parameters	Misoprostol group (n = 60)	Control group (n = 60)	p-value
Age (years), Median (Range)	30 (25 – 40)	29 (27 – 38)	> 0.05‡
Number of previous CS			
1 CS	29 (48.3%)	28 (46.7%)	> 0.05*
2 CS or more	31 (51.7%)	32 (53.3%)	
Failed insertion	0 (0.0%)	2 (3.3%)	> 0.05*
Difficulty of insertion			
Total, Median (Range)	4 (1 – 7)	5 (2 – 9)	<0.05‡
1CS, Mean ± SD	3.2 ± 0.6	4.6 ± 0.7	<0.001•
2CS or more, Mean ± SD	5.94 ± 1.3	6.7 ± 1.8	<0.001•

‡: Mann-Whitney test; \*: Chi-square test; •: Independent t-test

### Side effects following sublingual administration of misoprostol or placebo before insertion of IUD:

There were statistically significant differences between both groups as regard abdominal cramp, nausea and fever occurring more in misoprostol group before insertion of IUD. There were no statistically significant differences between both groups as regard headache

and diarrhea. There was statistically significant differences between both groups regarding pain score with pain scoreless ( $5.7 \pm 1.4$ ) in misoprostol group, than placebo group ( $6.5 \pm 0.9$ ), p-value is 0.001; There were no statistically significant differences between both groups regarding other complications as syncope, perforation and heavy bleeding, **Table (2)**.

**Table (2): Comparison between the two study groups as regards side effects following sublingual administration of misoprostol or placebo before insertion of IUD and mean of pain score**

Parameters	Misoprostol group (n = 60)	Placebo group (n = 60)	p-value
<b>Side effects</b>			
Abdominal cramp	26 (43.3%)	19 (31.6%)	> 0.05*
Headache	8 (13.3%)	4 (6.6%)	> 0.05*
Nausea	5 (8.3%)	1 (1.7%)	> 0.05*
Diarrhea	3 (5.0%)	1 (1.7%)	> 0.05*
Fever	3 (5.0%)	0 (0.0%)	< 0.05*
<b>Mean of pain score</b>	5.7 ± 1.4	6.5 ± 0.9	<0.001•
<b>Complications related to IUD insertion</b>			
Syncope	2 (3.3%)	1 (1.7%)	> 0.05*
Perforation	0 (0.0%)	1 (1.7%)	> 0.05*
Heavy bleeding	1 (1.7%)	2 (3.3%)	> 0.05*

\*: Chi-square test; •: Independent t-test

## DISCUSSION

Misoprostol, a prostaglandin E1 analogue marketed as a gastrointestinal mucosal protective agent, is safe, effective and inexpensive for use in cervical ripening and labor induction (*Speroff and Darney, 2010*).

Misoprostol is an effective agent that can be used to increase cervical effacement and dilation and to stimulate uterine contractions. Though it has wide distribution in the United States and many countries, it is not licensed for labor induction and not approved by the FDA for use as a cervical ripening or labor

induction agent, making its continued use controversial. Its FDA approved labeling is for use with gastric ulcer disease for its non-steroidal anti-inflammatory properties, dinoprostone is a long-standing pre induction cervical ripening agent, so it is the only preparation approved by (FDA) for this purpose (*Naghshineh et al., 2015*).

Vaginally-applied misoprostol is an effective cervical ripening agent in term pregnancies and had been validated in multiple trials. Optimal dose, regimen and route of administration are not clearly established. In terms of cost, misoprostol is a very attractive product (*Speroff and Darney, 2010*).

Misoprostol was suggested a cervical ripening agent in gynecological uses as prior to hysteroscopy and recently prior to IUD insertion.

*Preutthipan and Herabutya (2010)*, showed that misoprostol, resulted in effective cervical priming before hysteroscopy in non-pregnant woman. They reported greater cervical dilation, decreased cervical resistance, and less need for mechanical dilatation before hysteroscopy or curettage with oral or vaginal misoprostol.

Misoprostol has also been shown to induce cervical dilatation in non-pregnant women when used prior to a hysteroscopy by another older study (*Saha et al., 2015*).

Our study showed that pretreatment with misoprostol reduced the number of failed insertions and complications during IUD insertion. Moreover, pain during insertion was improved by misoprostol. Difficulty of insertion was estimated in regard to the resistance of the cervix.

A facilitating effect of misoprostol on IUD insertion was found, with significantly less resistance of the internal cervical os, and technically less difficult insertions compared with the untreated controls. This indicated that the insertions were overall easier and more uncomplicated in cases of misoprostol group.

There were two insertions failed due to very narrow cervix in the control group. None of the insertions failed in the misoprostol group.

Side-effects (of which abdominal cramping was the most predominant) occurred in 43.3% of participants using misoprostol and in 31.6% using placebo.

The overall number of side-effects of misoprostol gathered in our study was in line with those from another study (*Naghshineh et al., 2015*).

This study showed a positive effect of administration of misoprostol. This study results agree with results of *Scavuzzi et al. (2013)* and *Bahamondes (2015)*.

*Zapata et al (2016)*, concluded that misoprostol facilitate insertion of IUD in woman with narrow cervical canal. They investigated the use of sublingual misoprostol one hour prior to insertion of a copper-IUD among nulliparous women. Their low number of failed insertions corresponded with our figure. IUD insertion in nulliparous women who used sublingual 200 µg misoprostol and 100 mg diclofenac was significantly easier than in women who used 100 mg diclofenac alone (one hour prior to IUD insertion). The study showed that misoprostol can be used to facilitate the insertion of an IUD in nulliparous women with a narrow cervix. However, the majority of insertions were uncomplicated and the difficulties few in both groups. Shivering was more common in the misoprostol group. The authors suggested that, this could be reduced by using the vaginal route of misoprostol administration.

*Scavuzzi et al. (2013)* found less difficulty in inserting IUD in misoprostol group.

*Bahamondes et al. (2015)* found that pretreatment with intravaginal 100 mcg of misoprostol after IUD insertion failure in patients 4-10 hours before 2nd attempt was significantly better than placebo.

*Dijkhuizen et al. (2011)* conducted a RCT aiming to investigate whether pretreatment with misoprostol facilitates the insertion of an IUD in nulli- and multiparous women and failed to show difference for use of misoprostol prior to IUD insertion about insertion failure incidence misoprostol and placebo groups. However, that study was conducted on heterogeneous group of patients both multiparous and nulliparous. This may indicate that misoprostol may be beneficial only in subset of patients like our patients with previous cesarean section or patients with previous failed insertion of IUD.

*Swenson et al. (2012)* estimated the effects of self-administered misoprostol compared with placebo is 108 patients before intrauterine device (IUD) insertion in women. They failed to show difference in easiness of insertion of IUD with prior use of misoprostol. However this study was not blinded for doctors or patients. More over self-administration misoprostol vaginally may not be effective. These small tablets are better administrated as deep as possible by gynecologist.

*Ibrahim and Sayed Ahmed (2013)* investigated sublingual 400mcg misoprostol administered one hour before intrauterine Device (IUD) insertion reduces failed insertions, insertion-related complications and pain in parous women delivered only by elective caesarean section (CS) and found that sublingual administration of misoprostol doesn't facilitate the procedure. But the misoprostol was given in this study 1 hour only before procedure which may not be effective to soften the cervix.

*Espey et al. (2014)* found that misoprostol does not decrease pain or improve the ease of insertion. But this study was performed only on nulliparous women using only 400 mcg misoprostol.

## CONCLUSION

Our results showed that 600 ug sublingual misoprostol given two hours before Tcu 380 A IUD insertion in patients with previous cesarean section (with no prior vaginal delivery) facilitated the insertion of IUD and decreased the failure rate of insertion (primary outcome measure). Our results also suggested that misoprostol before IUD insertion decreased the pain perceived by the patients, but increased incidence of mild side effect as nausea, fever and abdominal cramps before insertion (secondary outcome measures).

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## إنضاج عنق الرحم باستخدام أقراص الميزوبرستول تحت اللسان قبل تركيب اللولب للسيدات اللاتي لم يسبق لهن ولادة طبيعية

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**خلفية البحث:** يساعد استخدام الميزوبروستول بجرعة 600 ميكروجرام تحت اللسان قبل ساعتين من إدخال اللولب من سهولة التركيب وتقليل حدوث فشل تركيب اللولب والألم أثناء الإجراء، وذلك على الرغم من أن وتيرة الانقباضات زادت بعد استخدام الميزوبروستول.

**الهدف من البحث:** تقييم فعالية الميزوبروستول تحت اللسان قبل ساعتين من إدخال اللولب الرحمي لدى النساء الخاضعات لعمليات قيصرية سابقة.

**المريضات وطرق البحث:** أجريت هذه الدراسة الإكلينيكية العشوائية مزدوجة التعمية على السيدات في سن الإنجاب وتم خضوعهن لتركيب اللولب في الفترة ما بين يناير 2019 ويوليو 2019. وقد تم اختيار 120 سيدة وتم تقسيمهن بشكل عشوائي إلى مجموعتين متساويتين: مجموعة (1) تلقين 600 ميكروجرام من الميزوبروستول تحت اللسان قبل ساعتين من إدخال اللولب ومجموعة (2) تلقين العلاج الوهمي.

**نتائج البحث:** تم العثور على اختلافات كبيرة بين المجموعات لجميع نقاط النهاية المباشرة التي تمت دراستها، مع صعوبة أقل في إدخال اللولب في مجموعة الميزوبروستول. وقد تم اكتشاف توازن إيجابي بين فوائد ومخاطر استخدام الميزوبروستول. ومع ذلك، فليس من الممكن إستنتاج أن إستخدامه أمر حتمي قبل إدخال اللولب للسيدات السابق خضوعهن للولادة القيصرية؛ ولا يجب إلغاء إدخال اللولب عند عدم توافر الدواء.

**الاستنتاج:** يمكن إستخدام الميزوبروستول قبل إدخال اللولب لدى السيدات السابق خضوعهن لولادة قيصرية سابقة.