Sublingual misoprostol before insertion of levonorgestrel-releasing intrauterine contraceptive device in lactating women following cesarean section

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Abstract

Background: Misoprostol is used for cervical softening before minimally invasive gynecological procedures. We aimed to assess the benefits and drawbacks of using sublingual misoprostol before inserting the levonorgestrel-releasing intrauterine contraceptive device (LNG-IUCD) in women who have never had a vaginal birth.

Methods: A clinical trial was conducted on 72 recruited women with lactational amenorrhea with no previous vaginal delivery. They were equally divided into 2 groups; group 1 received sublingual misoprostol 400 mcg 2 hours before Mirena insertion, and group 2 received a placebo 2 hours before the procedure.

Results: We observed easy insertion of Mirena IUCD in women of the misoprostol group, but with no significant difference between both groups. However, the duration of IUCD insertion was significantly shorter in the misoprostol group compared to the placebo group (5.03 ± 0.74 vs. 5.58 ± 0.94 minutes, P=0.007). The VAS pain score was significantly decreased in the misoprostol group (3.33 ± 1.29 vs. 3.97 ± 1.28, P=0.038) with a higher patient satisfaction score (7.22 ± 1.38 vs. 6.28 ± 1.41, P=0.005). Regarding the side effects, women in the misoprostol group experienced more nausea/vomiting, slight hyperthermia, and uterine cramps (P= 0.018, 0.011, and 0.173, respectively).

Conclusion: Sublingual administration of misoprostol before Mirena IUCD insertion could help increase the ease of insertion with a significant decrease in the procedure time. Furthermore, it could improve patient satisfaction and decrease the pain experience.

Key words: Sublingual misoprostol, Levonorgestrel-releasing IUCD, Mirena.

INTRODUCTION

Different contraception types have been widely used worldwide to reduce unplanned pregnancies (1). Intrauterine contraceptive device (IUCD) is one of the contraceptive

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methods which is wildly used as a reversible method of contraception (2). Both types of intrauterine contraceptive devices, copper IUCD and levonorgestrel IUCD (LNG-IUCD), are equally effective, safe, and cost-effective as contraceptive methods (3). However, the LNG-IUCD has the advantage of lower risk of ectopic pregnancy (4), as well as has many non-contraceptive benefits (5). The LNG-IUCD, commercially known as Mirena, has more roles in treating menorrhagia, anemia, and dysmenorrhea (6). Despite that, it is used by 7.6% of women in developed countries and 14.5% of women in developing countries (7). This may be related to the fear of women from pain during insertion or difficulty of insertion by healthcare providers (8). Reported complications associated with IUCD insertion are 0.2% cervical perforation, 0.2% syncopal attack, and 8.8% insertion failure, which is commonly reported in women who had not delivered vaginally (9). Women delivered only by elective CS are considered nulliparous concerning IUCD insertion and are suspected of having pain during insertion (10). Many healthcare providers avoid IUCD insertion in women with previous CS due to concerns of difficult insertion and pain (11). Some studies show that the use of non-steroidal anti-inflammatory drugs (NSAIDs) before the IUCD insertion reduces the experience of pain, while other RCTs show no effect (12,13). Misoprostol is a prostaglandin E1 analogue that has different uses in Obstetrics as induction of abortion, induction of labor, and protection from postpartum hemorrhage (14). It has many uses also in gynecology in the form of preoperative priming of the cervix prior to hysteroscopy and fractional curettage in perimenopausal women (15). However, it has many side effects, such as nausea, abdominal cramps, vomiting, diarrhea, and shivering (16).

Our aim in this study was to address the benefits and drawbacks of using sublingual misoprostol before Mirena IUCD placement in previous CS patients during lactational amenorrhea.

METHODS

Study Design: Single-blinded randomized controlled clinical trial.

Setting: The study was conducted on 72 women who attended the postnatal outpatient clinic at Cairo University Hospitals, seeking IUCD for contraception from November 2020 till May 2022.

Ethical consideration: The study was approved by the Medical Research Ethics Committee of the Obstetrics and Gynecology Department, Faculty of Medicine, Cairo University. All recruited women gave their consent after properly explaining the nature of the study with the possible risks and the outcome benefits.

Inclusion criteria:

1. Age from 20 to 42 years
2. BMI less than 30 kg/m2
3. Women with lactational amenorrhea and a negative pregnancy test.
4. Women seeking IUCD insertion following the cesarean section (within six months).

Exclusion criteria:

1. Nulligravida or multigravida with normal vaginal deliveries.
2. Women with regular menses
3. Women with chronic medical disorders.
4. Women with uterine abnormalities, intrauterine adhesions, cervical stenosis, fibroids or adenomyosis.
5. Women with chronic pelvic pain, cervical infection, or spasmodic dysmenorrhea
6. Allergy to misoprostol or contraindication to levonorgestrel.

Population:

The recruited women were divided into 2 groups. Group 1 received sublingual misoprostol 400 mcg 2 hours before Mirena insertion, and group 2 received a placebo 2 hours before the procedure.

Procedure:

All women were randomly allocated to both groups via a computer-generated randomization program. Basic patient characteristics were recorded for women in both groups. All women did not receive any analgesia before Mirena IUCD insertion. They underwent vaginal ultrasound before Mirena IUCD insertion to exclude any uterine or pelvic contraindication as well as to detect uterine size and axis. Women in the first group received sublingual misoprostol 400 mcg 2 hours before Mirena IUCD insertion, while women in the second group received a placebo 2 hours before the procedure. The technique of Mirena IUCD insertion was performed as prescribed by Johnson et al. (17). Women were instructed to come for follow-up after 24 hours and after 30 days.

Outcomes: Our primary outcome was to assess the difficulty of Mirena IUCD insertion, while secondary outcomes included assessment of the following:

1. Pain during insertion, according to the visual analog scale (VAS), from 0 (painless) to 10 (highest pain).
2. Duration of insertion (minutes)
3. Subjective sense of satisfaction graduated on a VAS-like scale, from 0 (totally not satisfied) to 10 (totally satisfied).
4. Side effects during IUCD insertion: bleeding, vasovagal reaction, perforation, and failed insertion.
5. Side effects after 24 hours of IUCD insertion: nausea, vomiting, cramps, and hyperthermia
6. Side effects after 30 days of IUCD insertion: displacement and expulsion

Sample size calculation: We calculated the sample size by comparing of easiness score during Mirena IUCD insertion in women with previous CS pretreated with prostaglandins versus untreated women. As reported in a previous publication (18), the mean ± SD of easiness score in the misoprostol pretreated women group was approximately 2.4 ± 1.7, while in an untreated group, it was approximately 4 ± 2.4. Accordingly, we calculated that the minimum proper sample size was 36 women in each group to be able to reject the null hypothesis with 80% power at $\alpha = 0.05$ level.

Statistical analysis: Statistical analysis was performed using the SPSS software (SPSS, version 25, SPSS, Inc., IL, USA). Numerical data were presented as means± standard deviation (SD), while categorical data were presented as numbers and percentages. Statistical analysis was done using the Student's t-test test to compare numerical variables and the Chi-square test to compare the categorical variables. P-values less than 0.05 were considered statistically significant.

RESULTS

This study included 72 women with lactational amenorrhea following the cesarean section and planning to use Mirena IUCD for contraception. They were divided into two groups; group 1 received sublingual misoprostol 400 mcg 2 hours before Mirena insertion, and group 2 received a placebo two hours before the procedure. There was no significant difference between both groups regarding the demographic characteristics of women, including age, body mass index (BMI), and position of the uterus (P>0.05), as shown in **Table 1**.

Table 1: Demographic characteristics of women in both groups

	Group 1 Misoprostol (n=36)	Group 2 Placebo (n=36)	P-Value
Age	27.54 ± 4.00 (21 - 35)	28.61 ± 4.21 (21 - 36)	0.273
BMI	24.39 ± 2.42 (19.5 - 29)	24.86 ± 3.02 (18.5 - 30)	0.466
Uterus position **- AVF** **- Midposition** **- RVF**	 26 (72.22%) 4 (11.11%) 6 (16.67%)	 24 (66.67%) 7 (19.44%) 5 (13.89%)	0.610

The main outcome was to assess the difficulty of insertion. We observed easy insertion of Mirena IUCD in women of the misoprostol group, but with no significant difference between both groups. However, the duration of IUCD insertion was significantly shorter in the misoprostol group compared to the placebo group (5.03 ± 0.74 vs. 5.58 ± 0.94 minutes, P=0.007) **(Table 2)**.

Regarding the secondary outcomes, pain during insertion, according to the visual analog scale (VAS), was significantly reduced in the misoprostol group compared to the placebo group (3.33 ± 1.29 vs. 3.97 ± 1.28, P=0.038). This observation was confirmed by the higher patient satisfaction score in the misoprostol group compared to the placebo group (7.22 ± 1.38 vs. 6.28 ± 1.41, P=0.005), as shown in **Table 2**.

There were some side effects observed during IUCD insertion. Most of the cases in both groups showed mild post-insertion bleeding with no significant difference (P=0.173). A mild vasovagal reaction was observed in only 4 cases in the misoprostol group and 7 cases in the placebo group, with no significant difference (P=0.326). No single case in both groups was complicated by uterine perforation **(Table 2)**.

Table 2: Outcomes during Mirena IUCD insertion

	Group 1 Misoprostol (n=36)	Group 2 Placebo (n=36)	P-Value
Difficulty of insertion **- Easy** **- Difficult**	 27 (75.00%) 9 (25.00%)	 20 (55.56%) 16 (44.44%)	0.083
Duration of insertion (min)	5.03 ± 0.74 (4 - 6)	5.58 ± 0.94 (4 - 7)	0.007
Pain during insertion	3.33 ± 1.29 (2 - 7)	3.97 ± 1.28 (2 - 6)	0.038
Sense of satisfaction	7.22 ± 1.38 (5 - 9)	6.28 ± 1.41 (3 - 8)	0.005
Post insertion bleeding **- mild** **- moderate**	 33 (91.67%) 3 (8.33%)	 29 (80.56%) 7 (19.44%)	0.173
Vasovagal reaction	4 (11.11%)	7 (19.44%)	0.326
Perforation	0	0	N/A

During follow-up on the next day of IUCD insertion, women in the misoprostol group experienced more nausea/vomiting, slight hyperthermia, and uterine cramps (P= 0.018, 0.011, and 0.173, respectively). After one month, we observed IUCD displacement during the transvaginal ultrasound follow-up in only 2 cases in the placebo group. However, the rate of IUCD expulsion was 0 % in both groups, as shown in Table 3.

Table 3: Side effects of Mirena IUCD insertion after 24 hours and after 30 days

	Group 1 Misoprostol (n=36)	Group 2 Placebo (n=36)	P-Value
Nausea/Vomiting (24 hrs)	21 (58.33%)	11 (30.56%)	0.018
Cramps (24 hrs)	7 (19.44%)	3 (8.33%)	0.173
Hyperthermia (24 hrs)	6 (16.67%)	0 (0.00%)	0.011
Displacement (30 days)	0 (0.00%)	2 (5.56%)	0.162
Expulsion (30 days)	0	0	N/A

DISCUSSION

IUCD has been considered one of the most reliable contraception methods being cost-effective with a higher degree of satisfaction. The LNG-IUCD is nowadays considered the most effective IUCD, with a pregnancy rate of less than 0.5% (19). Misoprostol, a synthetic prostaglandin estrone analogue, has been used to aid cervical softening before minimally invasive gynecological procedures (20). Therefore, we aimed to discuss both benefits and drawbacks of using sublingual misoprostol before Mirena IUCD insertion in previous CS patients during lactational amenorrhea.

Our study revealed that sublingual misoprostol two hours before Mirena IUCD insertion helps increase the easiness of insertion with a significant decrease in the procedure time. In addition, women who received sublingual misoprostol before the procedure experienced less pain on the VAS scale and higher satisfaction. On the other hand, some side effects were reported 24 hours after the procedure from women who received misoprostol, such as nausea and/or vomiting, some uterine cramps, and slight hyperthermia.

In accordance with our findings, El-Garhy et al. (2020) studied the effect of sublingual misoprostol on 120 women with previous cesarean section and no prior vaginal birth. They reached the same results, although they used a higher dose of 600 mcg given two hours before IUCD insertion. They revealed that using misoprostol before IUCD insertion reduced the pain perceived by the patients but increased the incidence of mild side effects such as nausea, fever, and abdominal cramps before insertion (21).

El-Gawad et al. (2021) also studied the effect of misoprostol in 210 women delivered only by elective cesarean section but throughout the vaginal route (not sublingual) and with a different dose (400 mcg) and a different route. They revealed that using vaginal misoprostol 3 hours before IUCD insertion significantly affects the ease of insertion and reduces the pain perception by patients during the insertion (22).

Moreover, Mohammed et al. (2019) stated that vaginal or sublingual 400 µg of misoprostol administrated 4 hours before IUCD insertion facilitates IUCD insertion and reduces the pain perception by patients during the insertion. However, they preferred the vaginal route for cervical ripening as it occurs more likely with the vaginal administration of misoprostol (23).

When misoprostol is taken orally or sublingually, it reaches a peak concentration in 30 minutes and then rapidly drops. When using the vaginal method, on the other hand, the peak plasma concentration occurs after 1 hour and decreases gradually, with levels remaining high for at least 6 hours, significantly higher than when using the oral or sublingual routes (24).

On the contrary, our results did not agree with the results of Mansy (2018), as he found that using sublingual misoprostol before IUCD insertion in women with tight cervix or even in women with no previous vaginal delivery has no role in facilitating its insertion or in pain reduction during the procedure (25). Also, Elgharabawy et al. (2020) found that using sublingual misoprostol did not facilitate IUCD insertion in women with a tight cervix and did not reduce pain during the IUCD insertion (26).

The main weak points in our study are that sense of pain and satisfaction were subjective and evaluated by the patients themselves, which could be over-expressed. On the other hand, the importance of our study is that we focused only on the LNG-IUCD (Mirena), which has a slightly wider sheath than other IUCDs, making the insertion procedure more difficult and more painful.

CONCLUSION

Sublingual administration of misoprostol before Mirena IUCD insertion could help increase the ease of insertion with a significant in the procedure time. Furthermore, it could improve patient satisfaction and decrease the pain experience.

DECLARATIONS

Competing interests: The author has no financial or other conflicts of interest.

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Informed consent: All participants gave their consent after being informed of the study's objective and design, and they were given the option to leave the study at any time.

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