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Role Of Vaginal Misoprostol Prior To Levonorgestrel-Releasing IUD Insertion

Obstetrics and Gynaecology

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ABSTRACT

Background: Women who had never delivered vaginally may experience higher failure rates during insertion of Levonorgestrel-releasing insertion intrauterine device.

Aim of the work: To assess the effect of receiving vaginal misoprostol before Levonorgestrel-releasing intrauterine device (Mirena IUD) insertion regarding the easiness of insertion and pain score.

Patients and methods: We studied 113 women who used the Mirena IUD for contraception, divided into three groups, and received vaginal tablets 4 hours before Mirena IUD insertion. Group 1(n37) received vaginal placebo tablets, group 2 (n38) received 200mcg vaginal misoprostol, group 3 (n 38) received 400mcg vaginal misoprostol.

Results: Compared to group 1 (placebo group), Mirena IUD insertion in group 2 and group 3 (misoprostol groups) was significantly easier (P=0.027 and 0.007, respectively) and expressed lower pain score (P=0.031 and 0.035, respectively). Regarding the side effects, nausea and/or vomiting and uterine cramps were found significantly more frequently among women who had misoprostol 400mcg (group 3) compared to women in group 1 (P=0.003 and 0.001, respectively) as well as compared to women in group 2 (P=0.042 and 0.048, respectively).

Conclusion: 200mcg of vaginal misoprostol was equally effective to 400mcg with fewer side effects. Both groups were superior to the placebo group in the easiness of insertion, with women experiencing less pain.

Keywords: *Misoprostol; Levonorgestrel-releasing IUD; Mirena.*

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INTRODUCTION

Intrauterine contraceptive devices (IUDs) are one of the most effective forms of long-acting reversible contraception (LARC), and 14.3 percent of adolescents and women aged 15 to 49 years use them with high patient satisfaction [1]. However, the high cost in some countries and expecting pain at insertion time may cause some limitations to its use. For healthcare professionals, the obstacles to its use include lack of training, fear of causing pain with the procedure, and difficulties that could end in insertion failure [2].

Since its introduction as a contraceptive device, The levonorgestrel intrauterine system (LNG-IUD) (Mirena) 's efficacy, safety, tolerance, and acceptability in young, nulliparous, and parous women have been demonstrated in various trials [3]. When compared to the copper IUD (Cu-IUD), the LNG-IUD is associated with a much lower chance of pregnancy, including ectopic pregnancy [4]. The levonorgestrel intrauterine system (LNG-IUD) is a long-acting hormone-releasing uterine device that has many non-contraceptive benefits [5].

Misoprostol is a prostaglandin E1 analogue that is used to stimulate uterine contractions, cervical dilation, and increased uterine tone. Misoprostol improved cervical ripening and dilation before minimally invasive gynaecological treatments such uterine evacuation and hysteroscopy, which could help in reducing pain and problems associated with these procedures [6]. Misoprostol, on the other hand, has been linked to side effects that include fever, shivering, moderate diarrhoea, nausea, and vomiting [7].

Women who had never delivered vaginally may experience higher failure insertion rates and more common cervical problems. A difficult sounding of the cervical canal or even inability to insert the IUD could be linked to cervical stenosis and a considerable ante- or retroverted position of the uterus [8]. Despite the fact that misoprostol treatment was found to be effective in lowering IUD insertion pain and difficulty in a previous trial [9]. Misoprostol has been proven to be ineffective in assisting IUD insertion and may potentially enhance patient felt discomfort in other investigations [10].

Sublingual misoprostol could be used before IUD placement in previous CS patients [11]. In addition, taking 400 micrograms of misoprostol vaginally 3 hours prior to IUD insertion in women who had previously delivered via elective caesarean section

had a substantial influence on ease of insertion and pain perception during the procedure [12].

PATIENTS AND METHODS

This prospective double-blinded clinical trial study had been carried out on 113 women who chose to have hormonal IUD (Mirena) as a contraceptive method. Cases have been collected over a period of 18 months, from February 2020 till August 2021.

Women included in the study were recruited from the National Research Center and private clinics. All women have been informed about the nature of the study, and proper explanation has been done. Verbal consent has been taken from each participant.

Women with the following criteria had been included in the study: Previous elective cesarean section(s), age: 25-45 years, no history of previous vaginal deliveries, no known allergic reaction sensitivity for progesterone, and women should present within two days of the last day of menstruation, or by the end of puerperium.

Our exclusion criteria were abnormal uterine pathology, undiagnosed uterine bleeding, pregnancy, abnormal cognitive functions that could not correlate with the visual analog scale (VAS), contraindication to IUD insertion, i.e., pelvic inflammatory disease, nulliparity, women with a history of cervical procedure that may cause cervical stenosis, i.e., Loop excision of the transformation zone (LETZ), and malignant tumors that are sensitive to progesterone, i.e., some types of breast cancer

Cases had been divided into 3 groups; group 1: a control group who received placebo vaginal tablets 4 hours prior to IUD insertion, group 2: received vaginal 200mcg misoprostol 4 hours before IUD insertion, and group 3: received vaginal 400mcg misoprostol 4 hours before IUD insertion.

All women had vaginal ultrasound prior to IUD insertion to exclude any uterine or pelvic pathology that contraindicates IUD insertion. Also, to detect uterine size and axis.

Women were given a closed envelope containing the tablet and were asked to insert the tablet vaginally in the posterior fornix (the highest point in her vagina) and come for IUD insertion 4 hours later.

For IUD insertion, women were put in the lithotomy position, and a sterile Cusco speculum was inserted to expose the vaginal walls and cervix. Vagina and cervix have been disinfected using diluted vaginal betadine. Tenaculum was applied to grasp the cervix to apply pulling to straighten the uterine angle. Uterine sounding was done to determine uterine cavity length and angle. Mirena IUD was held using a non-touch technique to maintain sterilization. After insertion, the threads were cut, leaving 2 cm, and vaginal ultrasound was done to confirm the IUD position inside the uterine cavity. The arms of the levonorgestrel-releasing IUD are only echogenic at the proximal and distal ends, with characteristic central posterior acoustic shadowing on transverse images [13]. IUD fundal distance (IUD-FD) and IUD myometrial distance (IUD –MD) were measured from the upper tip of the IUD to the outer and inner surfaces of the myometrium, respectively. Measures were documented for follow-up of the IUD site.

Immediately after the procedure, the assisting nurse asked the patient about the pain felt during the procedure. Patients were asked to rate pain intensity during the procedure from 0 (zero, painless) to 10 (ten, highest pain) on VAS. Also, they have been asked about the side effects of the medication(uterine cramps, nausea, diarrhea, rigors). The gynecologist who inserted the Mirena IUD documented the difficulty of insertion as easy, difficult, or unsuccessful.

Six weeks after insertion, women came for the first appointment to check the IUD in place and report any complications.

Outcomes: Our primary outcomes were to assess the difficulty of Mirena IUD and the pain score during the insertion between the three groups, while secondary outcomes were the side effects of misoprostol according to dose.

Sample size calculation: Based on a previous study, with the mean pain score in the null hypothesis group is 5.7 ± 1.4 while the mean pain score in the alternative hypothesis group is 6.5 ± 0.9, group sample sizes of 36 in each group achieve 81% power with a significance level (alpha) of 0.05. Each group increased by 10% (40 women) to allow for dropout.

Statistical analysis: Statistical analyses were performed using the SPSS software (SPSS, version 25, SPSS, Inc., IL, USA). Numerical variables were presented as means± standard deviation (SD), while categorical variables were presented as numbers and percentages. Statistical significance of differences was tested using the ANOVA test for numerical variables. On the other hand, we used the Chi-square test to compare the categorical data differences. For all statistical tests, p-values were considered statistically significant if less than 0.05.

RESULTS

Our study screened 345 women planning for reversible, long-lasting contraception; however, 225 women were not fulfilling the inclusion criteria or preferred other types of IUD, and only 120 women planned to use Mirena IUD for contraception. Unfortunately, 7 Women refused to take part in the research. Therefore, our study included 113 women, divided into three groups. Group 1 (n=37) included women with vaginal insertion of placebo tablet four hours before inserting the Mirena IUD, while group 2 (n=38) and group 3 (n=38) received vaginal misoprostol tablets, 200 and 400mcg, respectively, four hours before inserting the Mirena IUD. Table 1 showed that there were no significant variations in demographic data across the groups, including age, body mass index (BMI), uterine position, parity, and past spontaneous and/or induced abortions (P>0.05) (Table 1).

Our primary outcomes were to assess the difficulty of Mirena IUD and the pain score during the insertion between the three groups. We noticed that Mirena IUD insertion in group 2 and group 3 (Misoprostol groups) was significantly easier than in group 1 (placebo group) (P=0.027 and 0.007, respectively). On comparing the misoprostol groups, there was no significant difference (P=0.602) (Table 2). Along the same line, we found that pain score during Mirena IUD insertion in group 2 and group 3 (misoprostol groups) is significantly lower than in group 1 (placebo group) (P=0.031 and 0.035, respectively), with no significant difference between the misoprostol groups themselves (P=0.913) (Table 3).

Regarding the side effects, nausea and/or vomiting and uterine cramps were found significantly more frequently among women who had misoprostol 400mcg (group 3) compared to women in group 1 (P=0.003 and 0.001, respectively) as well as compared to women in group 2 (P=0.042 and 0.048, respectively). Diarrhea was presented only in groups 2 and 3, making a significant difference when compared with group 1 (P=0.022 and 0.003, respectively). On the other hand, there were no significant differences between all groups regarding fever or perforation (Table 4).

Only four women among the three groups were dropped out during follow-up. The remaining were re-examined and re-assessed by ultrasound 6 weeks after Mirena IUD insertion. We found no significant differences between all groups regarding IUD displacement, expulsion, or vaginal bleeding (Table 5).

	Group 1 Placebo (n=37)	Group 2 Misoprostol 200mcg (n=38)	Group 3 Misoprostol 400mcg (n=38)	P-Value
Age	31.57 ± 4.29	32.24 ± 4.54	32.50 ± 4.01	0.630
BMI	27.39 ± 4.01	28.75 ± 3.43	27.80 ± 3.85	0.172
Uterine position				
- AVF	28 (75.68%)	26 (68.42%)	25 (65.79%)	
- Midposition	5 (13.51%)	7 (18.42%)	9 (23.68%)	0.833
- RVF	4 (10.81%)	5 (13.16%)	4 (10.53%)	
Parity	1.89 ± 0.94	2.08 ± 0.88	1.95 ± 1.04	0.596
History of previous abortion	5 (13.51%)	4 (10.53%)	6 (15.79%)	0.684

Table 1: Demographic characteristics of women in the three groups

	Group 1 Placebo (n=37)	Group 2 Misoprostol 200mcg (n=38)	Group 3 Misoprostol 400mcg (n=38)	P-Value		
				Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3
Easy	17 (45.95%)	27 (71.05%)	29 (76.32%)	**0.027***	**0.007***	0.602
Difficult	20 (54.05%)	11 (28.95%)	9 (23.68%)			

Table 2: Difficulty of Mirena IUD insertion

	Group 1 Placebo (n=37)	Group 2 Misoprostol 200mcg (n=38)	Group 3 Misoprostol 400mcg (n=38)	P-Value		
				Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3
0 (no pain)	2 (5.41%)	7 (18.42%)	8 (21.05%)			
1-3 (mild)	10 (27.03%)	18 (47.37%)	16 (42.11%)			
4-6 (moderate)	13 (35.14%)	7 (18.42%)	9 (23.68%)	**0.031***	**0.035***	0.913
7-10 (severe)	12 (32.43%)	6 (15.79%)	5 (13.16%)			

Table 3: Pain Score during Mirena IUD insertion

	Group 1 Placebo (n=37)	Group 2 Misoprostol 200mcg (n=38)	Group 3 Misoprostol 400mcg (n=38)	P-Value		
				Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3
Nausea/vomiting	0 (0.00%)	2 (5.26%)	8 (21.05%)	0.157	**0.003***	**0.042***
Uterine cramps	15 (40.54%)	22 (57.89%)	30 (78.95%)	0.133	**0.001***	**0.048***
Diarrhea	0 (0.00%)	5 (13.16%)	8 (21.05%)	**0.022***	**0.003***	0.361
Fever/rigors	0 (0.00%)	2 (5.26%)	1 (2.63%)	0.157	0.321	0.556
Perforation	0 (0.00%)	1 (2.63%)	0 (0.00%)	0.321	N/A	0.314

Table 4: Side effects of misoprostol

	Group 1 Placebo (n=36)	Group 2 Misoprostol 200mcg (n=37)	Group 3 Misoprostol 400mcg (n=36)	P-Value		
				Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3
Displacement	1 (2.78%)	3 (8.11%)	1 (2.78%)	0.317	1	0.317
Expulsion	2 (5.56%)	0 (0.00%)	1 (2.78%)	0.146	0.555	0.307
Bleeding	7 (19.44%)	5 (13.51%)	8 (22.22%)	0.494	0.772	0.331

Table 5: Six weeks follow-up of Mirena IUD

DISCUSSION

With a global cumulative pregnancy rate of 2% after five years, the IUD is one of the most effective types of contraception available today. According to multiple studies, the LNG-IUD is arguably the most effective IUD available, with a global cumulative pregnancy rate of less than 0.5 percent [14].

This long-acting reversible contraception (LARC) is cost-effective with a high continuation and satisfaction rate [15,16]. The main characteristic of LARCs is that it is a single intervention that provides substantial contraceptive effectiveness for a long period of time and that they can be used for an extended time [17].

Age, parity, time of menses, time since last pregnancy, pregnancy delivery mode, breastfeeding status, anticipated pain, and IUD type are all factors that have previously been suggested to influence the ease of IUD insertion or patient suffering [18].

Mirena IUD has a slightly wider sheath than some other IUDs (i.e., NovaT), making the insertion process somehow more painful. According to the manufacturer's description, the outer diameter of the insertion tube is 4.4 mm (Mirena, Bayer HealthCare Pharmaceuticals, Pittsburgh, PA, USA).

Our research studied the possible role of vaginal administration of misoprostol prior to insertion to facilitate the insertion and decrease associated discomfort and pain. Misoprostol has some known adverse side effects, so we compared two doses to reach the smallest effective dosage with the least side effects.

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 [19].

In our study, we used vaginal misoprostol in order to get the most benefit of the drug by direct local effect as well as higher plasma concentration. In the two groups who received the vaginal misoprostol 200mcg and 400mcg, we found that the insertion of Mirena IUD was much easier in most of the cases than the group who did not receive the misoprostol. We found fewer side effects (nausea and/or vomiting and uterine cramps) in group 2, who received 200 mg, compared to the group who received the 400mcg misoprostol group. Pain perception during insertion in both groups was found to be less than in the placebo group.

In accordance with our findings, A research group in AL Azhar university stated that using vaginal misoprostol before IUD insertion in parous women who had previously failed insertion enhanced the rate of successful insertion, especially in women who had previously caesarean delivery [20]. However, in their work, they used the copper IUD. In our study, we compared two doses of misoprostol to compare efficacy to side effects, while in their study, they compared the timing of insertion using the same dose of 200mcg 4 hours and 10 hours prior to insertion.

El-Gawad et al. (2021) concluded that, in women who delivered exclusively via elective caesarean section, misoprostol at a dose of 400mcg taken vaginally 3 hours before to IUD insertion had a substantial influence on the ease of insertion and reduced the incidence of pain during the procedure. [12] After we compared both concentrations 200mcg and 400mcg vaginal misoprostol in our study, we found that 200mcg gives the same results regarding facilitating the Mirena IUD insertion but with fewer side effects. So a single dose of vaginal 200 mg vaginal misoprostol could be enough to facilitate the insertion of IUD.

M. El-Garhy et al. (2020) studied the effect of 600mcg sublingual misoprostol given two hours before Tcu 380 A IUD insertion on 120 women with previous cesarean section and no prior vaginal delivery. Their results suggested that misoprostol before IUD insertion decreased the pain perceived by the patients but increased the incidence of mild side effects as nausea, fever, and abdominal cramps before insertion [11]. The dose they used was higher than ours, and the route was sublingual, not vaginal.

On the contrary, Elgharabawy et al. (2020) and her research group found that the use of sublingual 200mcg misoprostol to facilitate IUD installation in women with a tight cervix had no effect on pain relief or IUD insertion ease; however, the results with misoprostol are better than placebo, but the difference is not statistically significant [21]. This could be attributed to different routes and timing as they used sublingual misoprostol 1 hour prior to insertion.

Also, in a systematic meta-analysis in 2020, Tassi et al. concluded that sublingual misoprostol did not show improvement in the facilitation of insertion. However, the use of misoprostol is usually associated with patient comfort [22]. Some other studies did not demonstrate enhancement in the facilitation of insertion [23,24].

Chaves et al. (2021) found that when compared to nulligravidas and women who had an elective caesarean delivery without any previous labour, women who had a previous vaginal delivery had lower pain levels at the time of levonorgestrel IUD placement [25]. In our study, we found that women with a history of previous elective cesarean-delivery who received vaginal misoprostol experienced a less painful levonorgestrel IUD insertion.

In our study, we focused on the levonorgestrel-releasing hormone IUD as its cost is very high compared to copper IUD, so we tried to offer the best circumstances during insertion in order to decrease the risk of failure adding an extra cost on the women. Also, Mirena IUD is in high demand because it is ideal for women with a hyperestrogenic hormonal environment, menorrhagia due to hormonal imbalances, adenomyosis, or myomas, as well as cases of symptomatic endometriosis or endometrial protection during hormone estrogenic replacement therapy in women with preserved uterus [26].

The main limitation of our study was that pain perception evaluated by the patient was subjective and could be over-expressed.

CONCLUSION

According to our results, vaginal insertion of misoprostol prior to insertion of Mirena IUD could help in easing the insertion process with minimal adverse effects when given in a dose of 200mcg compared to higher doses.

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