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Different Routes for Misoprostol Usage Before Intra Uterine Contraceptive Device Insertion in Women with Previous Cesarean Section

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ABSTRACT

Background: Intrauterine device (IUD) is one of the most efficient contraceptive techniques, despite its low use rate due to the user's fear of discomfort and the provider's insertion issues. Misoprostol is a drug that softens and facilitates dilatation of the cervix.

Objectives: The aim of the current work was to evaluate the usage of different routes of misoprostol before insertion of IUD in women with previous caesarean delivery.

Patients and methods: This prospective randomized comparative study included a total of 249 women eligible for IUD insertion, attending at Outpatient Clinics, Departments of obstetrics and gynecology of both the Menoufia university and Quesna Central Hospitals. The included women were randomly divided into three equal groups, and 4 hours before IUD insertion, each woman received 400 ug misoprostol, vaginally (Group A), rectally (group B), and sublingually (group C). Full history taking, clinical examination, and ultrasound (US) examination were done.

Results: In the 1st attempt, group A showed a significant higher success rate (n=80, 96.4%) than group B (n=78, 94%) and group C (n=66, 79.5%), ($p<0.001$). While in the 2nd attempt, the success rate did not show any significant difference among the studied groups ($p=0.904$). Pain during insertion was significantly higher frequent among group C (n=20, 24.1%) than group A (n=5, 6%) and group B (n=7, 8.4%), ($p<0.001$**)**. Regarding 6 weeks follow-up after intrauterine device insertion did not show any significant different among the studied groups ($p>0.05$), except, first menstruation after insertion was significantly differed among the studied groups ($p=0.04$).

Conclusion: It could be concluded that misoprostol is best administered vaginally rather than sublingually or rectally since it has a higher chance of causing cervical ripening. Repeated attempts in the next cycle may be beneficial when a previous insertion attempt has failed.

Keywords: Caesarean section, Insertion complications, intrauterine device, Misoprostol routes, Success rate, Uterine axis.

INTRODUCTION

There are more and more effective contraceptive options available nowadays. Even though they all have negative effects, they all present a lesser risk than pregnancy [1].

50% of pregnancies in the USA are unplanned, and 50% of them result in abortions [2]. This may indicate a gap in the market for quality contraceptive consultation [3].

Various forms of contraception are categorized based on their efficacy. The top tier meets the requirements for ease of use, extended duration of action, low need for follow-up clinic visits, and low user motivation or intervention and provides the greatest degree of efficacy (measured as two pregnancies per 100 women/year). These procedures include male and female sterilization, subdermal contraceptive implants, and intrauterine devices [1]. Even though the failure rate for intrauterine contraception is extremely low (0.2–0.6 per 100 women per year), it is only used by 7.6% and 14.5% of contraceptive users in industrialized and developing nations, respectively [4].

About 17% of Asian women who used contraception in 2015 used an intrauterine device (IUD), and more than 20% of women in 12 Asian nations [5].

The low prevalence of IUD use is brought on by the user's anxiety over discomfort and the provider's difficulties with insertion. In 41% of women and 86% of women, insertion was associated with anxiety [6]. Insertion failure happens in as many as 14% and 20% of porous and nonporous women, respectively. Insertion-related pain is linked to the insertion of the scope, tenaculum traction on the cervix, uterine sonography, transit of the insertion tube through the cervix, and implantation of the device inside the uterine cavity [7].

Misoprostol is a synthetic and affordable estrone counterpart of prostaglandin. It may be supplied orally or vaginally the night before minimally invasive gynecological procedures such as hysteroscopy, and if necessary, again in the morning. It may cause adverse consequences including stomach pain, chills, uterine hemorrhage, diarrhea, nausea, and vomiting [1].

Misoprostol usage prior to IUD placement has had mixed outcomes in the research. While some users have experienced a more comfortable insertion with no change in discomfort, others have seen no improvement at all. Benefits in terms of both insertion difficulty and discomfort were noted in one trial [7].

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The aim of this study was to evaluate the usage of different routes of misoprostol before insertion of an IUD in women with previous cesarean delivery.

PATIENTS AND METHODS

This prospective randomized comparative study included a total of 249 women eligible for IUD insertion, attending at Outpatient Clinics, Departments of obstetrics and gynecology of both the Menoufia university and Quesna Central Hospitals. This study was conducted between January 2021 to January 2022.

Inclusion criteria: Women eligible for IUD insertion, aged between18 and 45 years, not suspected to be pregnant, had previous caesarean and their menstrual cycles are regular.

Exclusion criteria: Women who had delivered vaginally, nulliparous, women with previous cervical operations, or who had contraindications for either misoprostol or IUD use.

All women had full history taking about age, parity, number of C.S, cervical operations and bleeding disorders then clinical examination including signs of anemia or bleeding disorders All women had US examination before insertion using DP 20 from Mindray to determine the uterine axis.

The included women were randomly divided into three equal groups, and 4 hours before IUD insertion, each woman received 400 ug misoprostol, vaginally **(Group A)**, rectally **(group B)**, and sublingually **(group C)**. Full history taking, clinical examination, and ultrasound (US) examination were done.

All participants were instructed to return after 4hrs for the insertion of IUD. After they returned to the clinic, they were asked about experiencing side effects of misoprostol before insertion of the IUD. After the insertion of IUD, all participants were instructed to return after six weeks for follow up for experiencing menstrual flow changes, abnormal vaginal discharge, and examination by US to confirm correctly placed IUD. Participants who had failed IUD insertion in the first attempt were also instructed to return on the 3rd day of the next menstrual cycle to perform a second attempt in the same pattern as the first attempt.

The sample size assumed that the anticipated pain percentage response in the vaginal administration group is % and in the sublingual administration group is 25 % [8]. To reach 80% ability to recognize this difference with a 5% significance level, 83 participants per group are expected to be necessary. Assign an equivalent number to the rectal administration group. With a withdrawal/non-evaluable subject rate of 10%, 92 participants each group will be recruited, resulting in a total sample size need of 276 subjects. A computer performed the randomization process. The pills of misoprostol were placed in an opaque envelope with a serial number. This statistician retained the key for the assigned group based on serial numbers until the completion of the trial.

Ethical Consideration:

This study was ethically approved by Menoufia Faculty of Medicine Ethical Committee (Registration number: 9/2020 OBSG11). Written informed consent of all the participants was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis

SPSS version 25 was used for the statistical analysis by IBM Inc., Chicago, Illinois, USA. The Shapiro-Wilks normality test and histograms were used to analyze the distribution of quantitative data and determine whether parametric or nonparametric statistical testing should be applied. The post hoc (Tukey) test was used to independently analyze each pair of groups after the ANOVA test to compare the parametric variables of the three groups. Measurement variables were expressed in terms of mean and standard deviation (SD). The Chi-square test was used to determine the frequency and percentage of categorical variables, which were then statistically represented. It was deemed statistically significant with a P value of 0.05.

RESULTS

There was no significant variation between the studied three groups regarding age (p=0.397), parity (n=0.11), number of cesarean (p=0.231) or uterine axis (p=0.707), **(Table 1)**.

Table (1): Demographic data and uterine axis among the studied groups.

		Vaginal group (A) (N=83)	Rectal group (B) (N=83)	Sublingual group (C) (N=83)	F test	P value
Age/year	Mean ±SD	27.3± 5.6	28.2± 4.9	27.2± 5.1	0.928	0.397
Parity	Mean ±SD	2.1± 0.8	1.9± 0.7	2.1± 0.6	2.228	0.110
Number of CS	Mean ±SD	1.9± 0.7	1.9± 0.6	1.8± 0.5	1.341	0.231
		N (%)	**N (%)**	**N (%)**	**X^2**	**P value**
Uterine axis	AVF	80(96.4%)	79(95.2%)	81(97.6%)	0.6917	0.707
	RVF	3(3.6%)	4(4.8%)	2(2.4%)		

CS: caesarean section, AVF: Anteverted anteflexed uterus, RVF: Retroverted flexed uterus, SD: Standard deviation, F: ANOVA F test, χ^2: Chi square test

In the 1st attempt, group A showed a significant higher success rate (n=80, 96.4%) than group B (n=78, 94%) and group C (n=66, 79.5%), with p<0.001. While in the 2nd attempt, success rate did not show any significant different among the studied groups (p=0.904). Regarding causes of failure was significantly differed among the studied groups (p<0.001), **(Table 2)**.

Table (2): Success rate of intrauterine device insertion from first or second attempt in the studied groups.

			Vaginal group (A)	Rectal group (B)	Sublingual group (C)	X^2	P value
			(N=83)	**(N=83)**	**(N=83)**		
First attempt	Success	No.	80	78	66	8.51	p<0.001*
		%	96.4%	94%	79.5%		
	Failed	No.	3	5	17		
		%	3.6%	6.0%	20.5%		
Second attempt	Success	No.	2	3	12	0.246	0.904
		%	66.7%	60%	70.6%		
	Failed	No.	1	2	5		
		%	33.3%	40%	29.4%		
Causes of failure	In accessible cervix	No.	1	2	2	7.67	p<0.001*
		%	100.0%	100.0%	40%		
	Cervical Stenosis	No.	0	0	3		
		%	0.0%	0.0%	60%		

X^2: Chi-square test, *Significant

Regarding Insertion complications, there was no significant difference among the studied groups regarding Perforation (p=0.250), heavy bleeding (p=0.573), difficulty of insertion (p=0.546) and vasovagal like reaction (p=0.326). While, Pain during insertion was significantly higher frequent among group C (n=20, 24.1%) than group A (n=5, 6%) and group B (n=7, 8.4%) with p<0.001 **(Table 3)**.

Table (3): Insertion complications among the studied groups.

			Vaginal group (A) (N=83)	Rectal group (B) (N=83)	Sublingual group (C) (N=83)	X^2	P value
Perforation	No	No.	82	81	83	0.870	0.250
		%	98.8%	97.6%	100%		
	Yes	No.	1	2	0		
		%	1.2%	2.4%	0.0%		
Heavy bleeding	No	No.	83	82	83	0.640	0.573
		%	100%	98.8%	100%		
	Yes	No.	0	1	0		
		%	.0%	1.2%	.0%		
Difficulty of insertion	No	No.	81	79	81	0.672	0.546
		%	97.6%	95.2%	97.6%		
	Yes	No.	2	4	2		
		%	2.4%	4.8%	2.4%		
Vasovagal like reaction	No	No.	78	76	79	0.811	0.326
		%	94%	91.6%	95.2%		
	Yes	No.	5	7	4		
		%	6%	8.4%	4.8%		
Pain during insertion	No	No.	78	76	63	5.28	$p<0.001^*$
		%	94%	91.6%	75.9%		
	Yes	No.	5	7	20		
		%	6%	8.4%	24.1%		

X^2: Chi-square test, *Significant

Regarding 6 weeks follow-up after intrauterine device insertion did not show any significant different among the studied groups (p>0.05), except, first menstruation after insertion was significantly differed among the studied groups (p=0.04). Menorrhagia was significantly higher among group C (n=8, 9.6%) than group A (n=7, 8.4%) and group B (n=5, 6%), **(Table 4**).

Table (4): 6 weeks follow-up after intrauterine device insertion among the studied groups.

			Vaginal group(A) (N=83)	Rectal Group (B) (N=83)	Sublingual group (C) (N=83)	X^2	P value
US examination	IUD in situ	No.	80	79	79	0.230	0.909
		%	96.4%	95.2%	95.2%		
	Downward displacement	No.	3	4	4		
		%	3.6%	4.8%	4.8%		
Visual analog scale	No	No.	79	77	75	1.05	0.884
		%	95.2%	92.8%	90.4%		
	Abnormal discharge	No.	4	6	8		
		%	4.8%	7.2%	9.6%		
First menstruation after insertion	Normal	No.	76	78	75	3.27	0.040^*
		%	91.6%	94%	90.4%		
	Menorrhagia	No.	7	5	8		
		%	8.4%	6%	9.6%		

US: Ultrasound, IUD: intrauterine device, X^2: Chi-square test, *Significant

DISCUSSION

In the current study, the success rate in the vaginal group for the first trial was 80 (96.4%), whereas the success rate for the second attempt was 2(66.7%). In the same line, **Bahamondes *et al.*** [9] found that misoprostol was beneficial for the insertion of IUCs, 4% of IUC insertions were unsuccessful on the first try. Similar to this, cervical stenosis caused an 8-woman case series where IUC implantation failed on the first try. The authors reported that all insertions were effective after administering 400 ug of misoprostol vaginally 24 hours before the second insertion.

In contrast, **Mohammed *et al.*** [8] conducted a randomized clinical study to find out if misoprostol taken sublingually or vaginally makes it easier for women who have had CSs in the past to place an IUD. The trial included 200 women who were eligible to have a TCu-380A IUD implanted [10].

The other half received 400 ug of misoprostol pills sublingually, whereas the other half received 400 ug of misoprostol tablets vaginally. They discovered no statistically significant differences between the two groups in terms of both the reasons for failure as well as the success rate from the first and second tries (which occurred during the subsequent cycle). Both the **Bahamondes *et al.*** [9] trial and the **Li *et al.*** [11] participants in a case study with a history of unsuccessful IUD insertion showed a significant improvement in permitting IUD implantation.

According to **Bahamondes *et al.*** [9], randomizing subjects before the first attempt of IUD insertion could lead to the mistaken conclusion that misoprostol is not beneficial in a population that might benefit from misoprostol because the rate of failed IUD insertion on the first attempt is typically quite low.

In the sublingual group of our study, the percentage of success in first attempt were 66 (79.5%) and in the second attempt were 12 (70.6%). **Mohammed *et al.*** [8] found in their study that the use of misoprostol at a dose of 400 µg sublingual before IUD insertion was associated with successful insertion on the first attempt 97% in sublingual group. This contradicted **Ibrahim and Ahmed** [12] who examined if sublingual misoprostol taken one hour before to IUD implantation decreases unsuccessful insertions, insertion-related problems, and discomfort in parous women who solely had elective CS. One hour before to IUD implantation, women who had never given birth other than by elective CS and wanted an IUD were randomly allocated to take either 100 mg of diclofenac alone (control group) or 400 g of misoprostol sublingually (misoprostol group). Misoprostol was added, however the amount of failed insertions indicated that it did not significantly improve outcomes. Also, this was confirmed by **Dijkhuizen *et al.*** [13] in their study.

In our study, there were no significant differences in insertion difficulties or vasovagal-like reactivity between the tested groups. Similar results were found by **Mohammed *et al.*** [8] who found that there is no statistically significant difference between both groups (regarding perforation, heavy bleeding, difficulty of insertion, and vasovagal-like reaction). According to **Shawky *et al.*** [14], there was a statistically significant difference in the difficulty of insertion between the two groups. IUD implantation was simpler in the misoprostol group compared to the placebo group.

In our study, perforation and heavy bleeding did not show any significant differences among the studied groups. **Maged *et al.*** [5] showed that the misoprostol group had a decreased, non-significant incidence of problems such perforation and vaginal bleeding.

In our study, pain during insertion was significantly increased in the sublingual group (24.1%) than vaginal group (6%) and rectal group (8.4%). **Mohammed *et al.*** [8] discovered a statistically significant difference between the two groups in terms of discomfort during IUD insertion. This is consistent with the findings of **Scavuzzi *et al.*** [15] who discovered that women who had previously used misoprostol at a dosage of 400 ug reported less discomfort, less subjective difficulty, and a lower chance of cervical dilatation of 4 mm after IUD insertion, however more cramping was observed. However, several studies failed to identify a decrease in discomfort during the process and showed no improvement in the success rate of insertion [16].

This research revealed that there were statistically significant differences in Visual analogue scale scores across the groups examined. **Mohammed *et al.*** [8] analysis of the visual analogue scale between the two groups revealed a statistically significant difference. These findings were consistent with the research conducted by **Scavuzzi *et al.*** [15] and **Ward *et al.*** [17]. According to **Saav *et al.*** [18] median of VAS score was higher among misoprostol group than control group (7.0 vs. 6.5), however there was no statistically significant difference between the studied groups. These findings contradicted the research conducted by **Dijkhuizen *et al.*** [13]. Another study by **Shawky *et al.*** [14] IUD implantation discomfort In terms of pain level, there were statistically significant differences between the two groups, with the misoprostol group having the lowest pain score (5.73±1.34) and the placebo group having the highest (6.49±0.93).

Before inserting an IUD, **Helmy *et al.*** [19] assessed the effectiveness of various vaginal misoprostol dosages in women with nulliparous cervixes. They discovered that a 200-g dosage of misoprostol made IUD insertion simpler and significantly reduced VAS pain levels. Similar to this, giving women who had previously had a caesarean section 600 mg of misoprostol sublingually two hours before IUD implantation significantly decreased discomfort and facilitated insertion[20].

The present investigation revealed that there was no statistically significant difference between the groups

regarding the onset of the first menstrual period after implantation. This result concurred with **Mohammed *et al.*** [8] concluded that there was no statistically significant difference between the two groups in terms of menstrual alterations following IUD installation (first menstruation).

CONCLUSION

It could be concluded that misoprostol is best administered vaginally rather than sublingually or rectally since it has a higher chance of causing cervical ripening. Repeated attempts of misoprostol in the next cycle may be beneficial when a previous insertion attempt has failed. More studies are needed including control groups to demonstrate whether the use of misoprostol in either of these routes (vaginal, rectal, and sublingual) is more beneficial than no use.

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