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Vaginal misoprostol versus dinoprostone before copper IUD application in women with anticipated difficult loop application

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Abstract
Background: Intrauterine device (IUD) are safe, reliable and highly effective forms of long-acting reversible contraception. (1) The major advantage of LARC compared with other reversible contraceptive methods is that they do not require ongoing effort on the part of the patient for long-term and effective use. In addition, after the device is removed, the return of fertility is rapid
Aim and Objectives: The aim of this study was to compare the effect of Vaginal Misoprostol versus vaginal Dinoprostone to facilitate loop application in women with anticipated difficult loop application.
Subjects and Methods: About 270 of women were assessed to select of 100 women were randomized to two groups using simple randomization and classified into:
Group A: (Misoprostol group): Include 50 patients who received one tablet (200mcg misoprostol in posterior fornix of vagina 3 to 4 hour before IUD insertion.
Group B: (Dinoprostone group): Include 50 patients who received one tablet (3mg dinoprostone in posterior fornix of vagina 3 to 4 hour before IUD insertion.
Result: Side effect between two study drugs there is more side effects in group A (Misoprostol) than group B (Dinoprostone)but there is no significant difference between two group p value in all side effect is >0.05. Significance difference between two studied group regarding to satisfaction level p value s.002 where p value >0.05
Conclusion: Both Dinoprostone and Misoprostol were effective in decreasing pain and easing insertion of Copper IUD in women with anticipated difficult insertion. However, more satisfaction lesser, adverse effects in dinoprostone group, we recommend misoprostol as is less cost than dinoprostone and stable at room temperature. This study further supports the clinical using of dinoprostone in an additional-obstetric indication.

Keywords: Vaginal misoprostol, dinoprostone, IUD, loop application

Introduction
Intrauterine device (IUD) are safe, reliable and highly effective forms of long-acting reversible contraception [1]. The major advantage of LARC compared with other reversible contraceptive methods is that they do not require ongoing effort on the part of the patient for long-term and effective use. In addition, after the device is removed, the return of fertility is rapid [2] Studies of IUD use implemented and monitored by Family Health International in 80 centers located in 33 countries found the incidence of IUD insertion failures to be between 2.3 and 8.3 per 1000 insertions [3].
According to the latest practice recommendations for contraceptive use by the Centers for Disease Control and Prevention, the potential barriers to IUD use include anticipated insertion pain and health care providers' concerns about difficult insertion [4]. It is therefore important to identify effective approaches to ease IUD insertion in order to overcome obstacles hindering IUD use [5].
Cervical ripening is made possible by the use of medication through different routes [6-8] the most commonly used agent is misoprostol, a synthetic prostaglandin E1 (PGE1) analogue that is frequently administered in off-label use in obstetrics and gynecology for medical abortion, labor induction, endometrial biopsy, dilatation and curettage, intrauterine device insertion, myomectomy, postpartum hemorrhage, and cervical ripening [9].

Misoprostol is a synthetic methyl analogous of PGE1. Its advantages are thermo stability and reduced costs compared with natural prostaglandins [10-11]. It acts on the extracellular matrix of the cervix dis-solving collagen and increasing hyaluronic acid and cervical water by increasing vascular permeability, thus facilitating the passage of neutrophils to tissue stroma. Interleukin-8produced in the cervix attracts and activates neutrophils, which are an important source of collagenase, facilitating cervical softening [12].

Studies demonstrate the use of misoprostol in many formulations: tablets or gel, in doses of 400, 200, or 100 mcg, given by oral route, rectal, or vaginal route [13]. The absorption of misoprostol occurs rapidly after oral administration, reaching peak plasma concentrations in 30to 60 minutes, soon converting into its free acid form. After vaginal administration, plasma concentration increases, achieving peaks in 60 minutes. Concentration then slowly declines, reaching 60% of the maximum level 240 minutes after administration. These levels remain stable for 4 hours [14].

The main side effects of misoprostol are abdominal cramps, diarrhea, vomiting, and genital bleeding [16].

The aim of this study was to compare the effect of Vaginal Misoprostol versus vaginal Dinoprostone to facilitate loop application in women with anticipated difficult loop application.

Patients and Methods

This is comparative prospective Randomized clinical trial study.

The study participants were consisted of 100 women attending the clinic At Tanta University Hospital and Elsanta central Hospital and the study was conducted directly after approval.

Duration: From February 2020 till February 2021

Eligibity: Patients were selected according to inclusion and exclusion Criteria:

Inclusion criteria

- All women will be 20 to 40 years old.
- Women with previous difficult IUD insertion
- Women with previous cervical operations.
- Women with previous cesarean section.

Exclusion criteria

- Women with amenorrhea.
- Women who have heavy menstrual bleeding.
- Women with Recent pelvic infection such as lower genital tract infection.
- Those known to have hypersensitivity or contraindication to prostaglandins such as hypertension, bronchial asthma, cardiac disease, renal failure, or uncontrolled diabetes mellitus.

Those who received analgesics prior to IUD insertion.

Examination

General examination (Body mass index, vital signs).

Pelvic examination (Uterus position anteverted, erect position retroverted).

IUD insertion protocol

Pre insertion study

Pelvic ultrasound to evaluate uterus and adnexa.

Antibiotics prophylaxis were administrated.

Insertion of copper device CU T 380 A IUD

Urinary bladder evacuation.

Bimanual examination to determine the size, shape, and position of the uterus was done.

A warm, moistened vaginal self-retaining speculum was inserted.

The cervix was cleaned with an antiseptic solution (Betadine)

The sterile insertion instruments were opened without touching the inside of the packet and placed within easy reach.

The tenaculum grasped cervix

Gentle traction with the tenaculum to straighten the cervical canal was applied.

The sound gently inserted to measure until the fundus of the uterus.

Once the sound was inserted and removed, the depth of the uterine cavity was noted.

The IUD (CU T 380 A) was loaded and inserted into the uterine cavity.

The tenaculum was gently removed, tamponade any bleeding from the tenaculum site until resolving. The strings of the IUD were trimmed to 3-4 cm in length.

The outcome measures

The primary outcome of this study measured the success rate of IUD insertion of both groups.

The secondary outcome

Side effect of study drugs pain related to IUD insertion which was measured by visual analogue scale,

The ease of IUD insertion, patients' satisfaction level,

The need for additional analgesics.

Scoring

Statistical analysis

SPSS statistics for windows (Statistical Package for the Social Sciences) version 26 (IBM, Armonk, NY, USA) was used for statistical analysis of the collected data. Shapiro-Wilk test was used to check the normality of the data distribution. All tests were conducted with 95% confidence interval. P (probability) value < 0.05 was considered statistically significant. Quantitative variables were expressed as mean and standard deviation while categorical variables were expressed as frequency and percentage. One-way ANOVA with Bonferroni post hoc analysis and Kruskal Wallis with Dunn's post hoc analysis tests were used for inter-group comparison of parametric and non-parametric continuous data respectively. Categorical Group differences with Fisher exact and Chi square tests were used for inter-group comparison of nominal data. Bivariate Correlations were assessed using Pearson's or Spearman's correlation coefficient depending on the nature of data. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV).

Results

The total number of patients selected for the study are 100 women seeking to compare the effect of Misoprostol versus Dinoprostone to facilitate loop application in women with anticipated difficult loop application.

Table 1: Sociodemographic characteristics among the studied groups.

		Group A Misoprostol (n=50)	Group B Dinoprostone (n=50)	t	P
Age (years) Mean ± SD		23.57 ± 3.94	24.28 ± 3.15	.995	.322
BMI (kg/m^2) Mean ± SD		27.64 ± 3.86	28.31 ± 4.67	.782	.436
Gravidity Mean ± SD		2.86 ± 1.15	2.97 ± 1.26	.524	.721
Residence	Urban	19 (38%)	22 (44%)	χ^2 .372	.542
	Rural	31 (62%)	28 (56%)		
Education	High	26 (52%)	32 (64%)	χ^2 1.48	.225
	Low	24 (48%)	18 (36%)		

This table shows that there was no significant difference between the group A (Misoprostol) and group B (Dinoprostone) regarding to age of woman, BMI, Gravidity, Residence and Education.

Where p value in all data is > 0.05

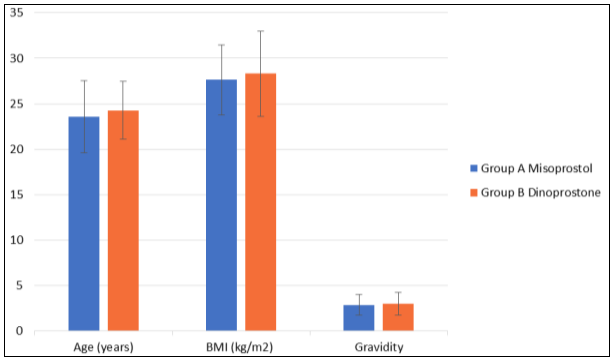

Fig 1: BMI, Gravidity, Residence and Education

Table 2: Compare the effect of uterus position (Anteverted, erect position and retroverted) on IUD insertion.

	Group A Misoprostol (n=50)	Group B Dinoprostone (n=50)	t/χ^2	P
Uterus position				
Anteverted	41 (82%)	39 (78%)	1.14	.565
Erect position	3 (6%)	6 (12%)		
Retroverted	6 (12%)	5 (10%)		

There is no significant difference regarding to Uterus position on IUD insertion p value is. 565 where p value is>0.05.

Table 3: pain score during sound insertion in both studied group.

	Misoprostol N = 50	Dinoprostone N = 50	X^2	P value
Sound Insertion score				
Mean ± SD	2.18 ± 1.37	2.48 ± 1.64	-	.337

This table show no significance difference between two studied group during sound insertion p value is.337. Where p value >0.05

Table 4: pain score during IUD insertion in both studied group

	Misoprostol N = 50	Dinoprestone N = 50	X^2	P value
IUD Insertion score				
Mean ± SD	2.52 ± 1.83	3.14 ± 2.54	-	.184

This table show no significance difference between two studied group during IUD insertion p value is.184 where p value >0.05)

Table 5: Pain score 15 minute after insertion in both studied group

	Misoprostol N = 50	Dinoprostone N = 50	X^2	P value
15 Min after insertion score				
Mean ± SD	2.07 ± 1.65	2.13 ± 2.27	-	.649

This table show no significance difference between two studied group during 15 minute after insertion p value is.649 where p value >0.05

Table 6: Ease of insertion score in both studied group

	Misoprostol N = 50	Dinoprostone N = 50	X^2	P value
Ease of Insertion score				
Mean ± SD	2.5 2±1.64	1.97 ±1.71	-	0.075
Ease of Insertion (Scale)				
Easy	30(60)	29(58)	1.05	0.5929
Moderate	10(20)	9(18)		
Difficult	6(12)	5(10)		

This table show no significance difference between two studied group regarding to ease of insertion score p value is.075 where p value >0.05

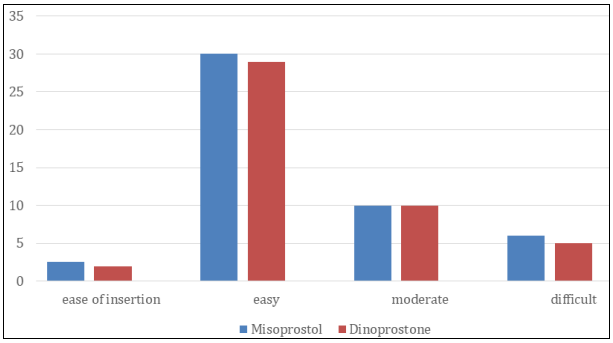

Fig 2: Ease of Insertion

Table 7: Comparative study of Satisfaction Level between two studied groups

	Group A Misoprostol N = 50	Group B Dinoprostone N = 50	X^2	P value
Satisfaction Level score				
Mean ± SD	7.12 ± 2.51	8.54 ± 1.78	-	.002*

This table show significance difference between two studied group regarding to satisfaction level p value s.002 where p value >0.05

Table 8: Need for additional analgesics.

	Group A Misoprostol (n=50)	Group B Dinoprostone (n=50)	T	p
Need for additional analgesics	4 (8%)	2 (4%)	.709	.399

This table show no significance difference between two studied group p value was.399 where p value >0.05

Table 9: Side effects distribution between the two studied groups.

	Group A Misoprostol (n=50)		Group B Dinoprostone (n=50)		χ^2	P
	N	%	N	%		
Nausea	6	12%	4	8%	.444	.505
Vomiting	5	10%	3	6%	.544	.461
Diarrhea	3	6%	1	2%	1.04	.309
Fever	4	8%	2	4%	.709	.399
Shivering	3	6%	1	2%	1.04	.309
Abdominal cramps	13	26%	7	14%	2.25	.134

Table (9): Show side effect between two study drugs there is more side effects in group A (Misoprostol) than group B (Dinoprostone)but there is no significant difference between two group p value in all side effect is >0.05

Table 10: incidence of success and failure rate between the two studied groups.

	Group A Misoprostol (n=50)	Group B Dinoprostone (n=50)	χ^2	p
Failed	4 (8%)	7 (14%)	.919	.338
Success	46 (92%)	43 (86%)		

This table show no significance difference between two studied group regarding to incidence of success an failed IUD insertion p value was.338 where p value >0.05

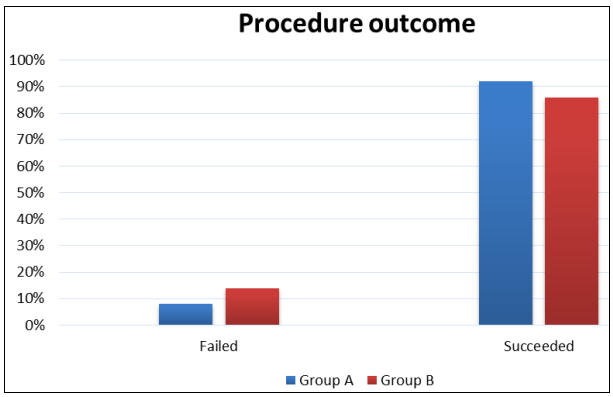

Fig 3: Primary Procedure outcome between the two studied groups

Discussion

The use of IUDs is highly endorsed by the American College of Obstetricians and Gynecologists and American Academy of Pediatrics to avoid unplanned pregnancies among sexually active female and young women (Committee on Adolescence, 2014; American College of Obstetricians and Gynecologists, 2017) [17]. Time period since delivery. In addition, anatomical, cultural or psychological elements can contribute to a more painful experience (Gemzell-Danielsson *et al*., 2015) [18].

Aiming to reduce IUD insertion pain and difficulties, previous studies had investigated different pharmacologic and non-pharmacologic analgesic options Ibuprofen in high doses (800 mg), intramuscular ketorolac, & oral naproxen 550 mg but their results were not conclusive and occasionally contradictory. Even failed to reduce pain during IUD insertion (Lopez *et al*., 2015; Ngo *et al*., 2016) [19].

There are efforts to ease the insertion of all types of IUDs; some health practitioner appointed to Misotac [misoprostol], to females who want to insert IUD to facilitate the insertion. Misoprostol is a synthetic [PGE1] analogue, could be used sublingually, vaginally, orally or rectally. Uterine contractions, cervical changes and ripening, facilitation of trans-cervical procedures are the actions of misoprostol (Elgharbawy *et al*., 2020) [20]. Nevertheless, the use of misoprostol has, been associated with adverse reactions such as fever, shivering, mild diarrhea, nausea, and vomiting (Samy *et al*., 2020).

There were no clear prevalence figures for the retroverted uterus in gynecological patients. One study determined a prevalence rate of 19% in a general gynecological patient population (Haylen, 2006) [21] and it was recently reported that Approximately 11-15% of women have a retroverted uterus (Yılmaz *et al*., 21016; Clare, 2020) [22].

Despite IUD insertion is relatively a quick (5-10 minutes) procedure, each step of it can bring about variable extents of pain. Sources of pain comprise sounding of uterus, forward advancement of IUD inserter into uterine cavity, and post procedural pain (Abbas *et al*., 2017) [23].

In agreement with our results, Ashour, A. S. A and his collegues 2020 in recent study that aimed to compare the efficacy of vaginal misoprostol, vaginal dinoprostone, and placebo administered 3 hours before IUD in facilitating IUD insertion and decreasing IUD insertion pain found that both vaginal misoprostol and vaginal dinoprostone effectively reduced pain during sound insertion and copper IUD insertion compared to placebo.

Also, they reported that vaginal dinoprostone was effective in reducing pain during 10 minutes after the procedure. They reported a nearly similar results to ours, no statistically difference and the VAS score during sound insertion (2.4 ± 1. 7versus 2.0 ± 1.3), IUD insertion (3.1 ± 1.83 versus 2.4 ± 1.08), and 10 minutes after insertion (2.7± 2.4 versus 2.0 ± 1.5) in groups A&B respectively with no significant differences in pain scores were found between the misoprostol and dinoprostone groups during sound insertion (P = 0.7), IUD insertion (P =0.3), and 10 minutes after insertion (P = 0.4)

In another studies comparing misoprostol to placebo Elgharbawy and his co-workers in 2020(24) revealed that, the use of misoprostol to facilitate IUCD insertion is somewhat better than placebo.

Moreover, Mohammed *et al*., 2018 [25] reported that pain during insertion was improved and was significantly lower with misoprostol.

Another study by Abd ELhassib *et al*. 2021 who aim to compare the role of vaginal misoprostol versus placebo before intrauterine device insertion reported that misoprostol decreasing pain during sounding of uterus significantly p value less than.001.

Also, Scavuzzi and his colleuges, 2009 [26] who randomized females to obtain two tablets of misoprostol, or placebo, vaginally, one hour prior to insertion did not show any significant difference in patient reported pain.

Prior findings by Scavuzzi *et al*., 2013 [27] reinforced on beneficial effect of misoprostol inserted prior to IUD insertion in nulligravida in reducing moderate-to-severe pain at IUD insertion (risk ratio 0.56; 95% confidence interval 0.41-0.76), Yet, many other studies reported no benefit from premedication with misoprostol in nullipara and showed that misoprostol may even increase pain associated with IUD insertion procedures (Swenson *et al*., 2012; Lathrop *et al*., 2013; Espey *et al*., 2014). This discrepancy in results could be due to the difference in route of misoprostol administration between those studies (buccal misoprostol) and our study (vaginal misoprostol).

For reducing pain, the Samy *et al*., 2019 [28] network metanalysis showed that dinoprostone effectively reducing pain perception during diagnostic office hysteroscopy.

Other research worked like Samy *et al*., 2020 and the meta-analysis conducted via Abu-Zaid *et al*., 2021 reported that overall effect estimate revealed significantly reduced pain at uterine sounding in the dinoprostone versus placebo group (SMD=-0.88, 95% CI [-1.54, -0.22], p=0.009) reduced pain at IUD insertion in the dinoprostone versus placebo group (SMD=-1.18, 95% CI [-1.74, -0.61], *p* <0.001).

In addition, this results revealed that there was no significant difference in the Ease of insertion score among both studied groups (P value =.075) with the dinoprostone group slightly better score (2.52± 1. 64 versus 1.97 ± 1.32) in groups A&B respectively. But high easy insertion cases (60% and 58%) and moderate insertion cases (20% and 18%) between two groups with decrease difficult insertion cases (12% and 10%) this confirm both durgs easing IUD insertion. Also the dinoprostone group showed a fewer 2 (4%) number of cases who needed additional analgesic than group A with a double number of cases but without significant difference 4 (8%) (P = 399).

Moreover, results of the current study showed that there was a significant difference between both groups regarding satisfaction level value 0.002 that was better in dinoprostone group (8.54± 1.08) than misoprostol (7.12± 2.51) also satisfaction scale is <0.001 with (84)% satisfactory cases in Dinoprostone group to (48%) cases in Misoprostol group.

In concordance to our results, Samy and his colleuges, 2020 [29] published that both misoprostol and dinoprostone resulted in significantly easier copper IUD insertion than placebo but misoprostol group had an ease of insertion score similar to that of the dinoprostone (the reported ease of insertion scores were 2.4 ± 1.7 or the former and 2 ± 1.5 for the latter). They also declared that Satisfaction scores in the misoprostol and dinoprostone groups were significantly higher than in the placebo and the satisfaction level was significantly higher in the dinoprostone group than in the misoprostol group (P =.012) (the reported satisfaction scores were 7 ± 2.7 or the former and 8.3 ± 1.8 for the latter). Also, 3 (7.0%) in their study in misoprostol group needed extra- analgesia versus 2(4.7%) in dinoprostone cases with no statistically significant value. No procedure-related complications such as uterine perforation, or vasovagal reaction were reported in their groups like our study.

Furthermore, Rasheedy *et al*., 2019 [30] reported that, vaginal misoprostol prior to IUCD insertion in parous females with previous failure increased the success rate, particularly in females with previous caesarean section.

Women who delivered via cesarean section, pretreatment with 400 mg vaginal misoprostol increased success and decreased pain of IUD insertion, and clinicians reported easier IUD insertion (Abdellah *et al*., 2017).

Whereas Ibrahim *et al*., 2013 [31] in their study that included women who had delivered only by elective cesarean Delivery showed that misoprostol does not increase the ease of insertion or decrease the pain scores in spite of more cases of failed IUD insertion in the control group than the misoprostol group (400 mg sublingual misoprostol did not facilitate the procedure and caused undesirable side-effects). The difference in the route and time of administration of misoprostol may be behind the difference in our results.

Previous studies found that misoprostol did not improve the ease of IUD insertion in nulliparous women (Swenson *et al*., 2012; Lathrop E *et al*., 2013; Espey *et al*., 2014) [32].

However, in Samy *et al*., 2019 study, dinoprostone facilitated the IUD insertion by providers in nullipara. In another randomized controlled trial, Samy *et al*., 2020 evaluated safety and efficacy of self-administered vaginal dinoprostone and found that women's satisfaction, provider-reported ease of insertion, and need for additional analgesia were significantly better among dinoprostone users, with mild tolerable side effects compared to placebo.

Other research works like Samy *et al*., 2020 [33] and the meta-analysis conducted via Abu-Zaid *et al*., 2021 reported that the overall effect estimate revealed significantly increased patient satisfaction in the dinoprostone versus placebo group (SMD=1.41, 95% CI [0.62, 2.20], with significantly increased ease of IUD insertion in the dinoprostone versus placebo group (SMD=- 1.17, 95% CI [-1.62, -0.73], p<0.001). Also Abd ELhassib *et al*. 2021 reported misoprostol made insertion significally easier and reduced rate of failure of insertion.

The used dosage of misoprostol (200 mg not 40 0mg) was in agreement with our results, Singh *et al*., 1998 found that increasing the dose of vaginal misoprostol to 400 mcg has not improved the effect on cervical dilatation before evacuation, but it has increased side effects, mainly diarrhea and shivering. The same was observed by Singh *et al*., 2009 that vaginal misoprostol 400 mcg before diagnostic hysteroscopy did not increase cervical dilation, patient satisfaction and no decrease in need for analgesia.

Regarding side effects of both studied medications, this results revealed that there was the dinoprostone group had lesser reported side effects than misoprostol overall. Abdominal cramps were the most frequently encountered side effect but the frequency was lower in dinoprostone group 7 (14%) than misoprostol group 13 (26%) (P =.399). Moreover, other reported side effects that was lower in dinoprostone group than misoprostol group were nausea [4 (8%) & 6 (12%)], vomiting [3 (6%) & 5 (10%)], fever [2 (4%) & 4 (8%)], & both diarrhea and shivering 1 (2%) & 3 (6%)] for dinoprostone and misoprostol in order but all were with no statistically significant difference.

The relatively lower side effect profile of misoprostol and dinoprostone in our study compared to previous studies could be attributed to the low dose of misoprostol (200 mg) and dinoprostone (3 mg) used in this study, and our preference for using the vaginal route of administration which is known to have lower side effects than other routes of administration.

The most striking finding in all studies that women used misoprostol experienced more unwanted adverse effects reaching up to 61% of study participants as abdominal cramps, nausea, vomiting, shivering and diarrhea (Dijkhuizen *et al*., 2011; Edelman *et al*., 2011; Scavuzzi *et al*., 2013; Khalaf *et al*., 2017).

Other studies reported a higher side effect profile with misoprostol use, such as Samy *et al*., 2020 on comparing the same studied medications reported that the most frequent side effect was abdominal cramping, and the highest incidence was in the misoprostol group compared with the Dinoprostone groups.

In the Abdellah *et al*., 2017 [34], study; abdominal cramping was higher in misoprostol group more than placebo one (22.9% vs. 4.3%, p=.0001) and shivering (14.3% vs. 2.9%, p=.001) and In agreement to this work were the most reported side effects in the misoprostol group This coincides with the study of Dijkhuizen *et al*., 2011, [35] when used misoprostol in the same dose, route and time of administration prior to IUD insertion.

Tassi *et al*., 2020 [36] meta-analysis found higher side effects and nausea with misoprostol premedication before IUD insertion.)

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Conclusions

Both Dinoprostone and Misoprostol were effective in decreasing pain and easing insertion of Copper IUD in women with anticipated difficult insertion. However, more satisfaction lesser, adverse effects in dinoprostone group, we recommend misoprostol as is less cost than dinoprostone and stable at room temperature. This study further supports the clinical using of dinoprostone in an additional-obstetric indication.

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Nil

Conflict of Interest

Nil

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