The Egyptian Journal of Hospital Medicine (April 2018) Vol. 71(1), Page 2287-2293

Dinoprostone Versus Misoprostol for Cervical Ripening before Diagnostic Hysteroscopy in Nulliparous Women: A Randomized Controlled Trial

Ayman Abd El-Razek Abulnour*, Mohamed El-Mandooh Mohamed*,
Waleed Mohamed Khalaf*, Shady Ali Tarek**
*Obstetrics & Gynecology Department, Ain Shams University;
** M.B.B.Ch. October University
Corresponding author: Shady Ali Tarek,email: shaditarek@gmail.com, mobile:00201226600770

ABSTRACT

Background: Hysteroscopy has revolutionized the field of Gynecology and the management of many gynecological conditions. It has now become a standard part in the diagnosis of postmenopausal bleeding by the gynecological surgeons. Cost, convenience, accuracy, and patient acceptability of these procedures are clearly superior to those of traditional surgeries. As gynecologists have grown better acquainted with the benefits and techniques of operative hysteroscopy, it has become the method of choice for treatment of intrauterine pathology.

Cervical ripening is a complicated process, being mediated by cytokines, growth factors, hormones and other biochemical compounds.

Both dinoglandin and Misoprostol can be used for cervical ripening before introduction of hysteroscopy and hence reduce the incidence of complications.

Objects: This study aims to assess the efficacy of dinoprostone compared to misoprostol in cervical ripening in nulliparous women undergoing diagnostic hysteroscopy.

Methodology: a randomized controlled clinical trial comparing dinoprostone versus misoprostol for cervical ripening before diagnostic hysteroscopy in nulliparous women, it included 2 groups, 33 patients each. In the first group named (group D) dinoprostone 3 mg was applied vaginally 6 hours before diagnostic hysteroscopic procedure while in the second group named (group M) 400 mcg misoprostol was applied vaginally at the same timing.

Results: There was no statistically significant difference between the groups that received misoprostol or dinoprostone with regard to age, duration of marriage, medical disorder, history of gynecological operations and type of gynecological operations. However, the use of misoprostol caused slightly less pain compared to dinoprostone but more side effects occurred with the use of misoprostol.

Conclusion: There was no significant difference between dinoprostone and misoprostol in priming of cervix before diagnostic hysteroscopy in nulliparous women regarding ease of hysteroscope entry, pain or side effects.

Keywords: Dinoprostone, Misoprostol, Diagnostic hysteroscopy

INTRODUCTION

Hysteroscopy is one of the diagnostic methods that developed recently in gynecology. The whole uterine cavity is explored through hysteroscope. In the presense of any pathologic lesion, biopsy is taken and treatment is performed through hysteroscopy if needed (e.g. removal of submucosal myoma or endometrial polyp). Hysteroscopy has been proved to be a totally reliable method for the study of postmenopausal bleeding[(1)]. Although hysteroscopy has been identified as a safe and less invasive procedure, some complications such as cervical tear, bleeding, uterine perforation, pain and discomfort may occur during the procedure. Many women need dilatation prior to hysteroscopy to make the procedure more simple[(2)].

The incidence of these complications may decline if we use cervical ripening before the procedure. Cervical ripening is a complicated process, being mediated by hormones, cytokines, growth factors and other biochemical compounds.

For easy passage of hysteroscope, cervical ripening and cervical canal widening to a specific diameter should be done[(3)].

Many methods including medications have been introduced for cervical ripening. The most commonly used medication is misoprostol, a synthetic prostaglandin E1 (PGE1) analogue that is administered frequently in obstetrics and gynecology for cervical ripening, medical abortion, induction of labor, dilatation and curettage, endometrial biopsy, intrauterine device insertion, postpartum hemorrhage and myomectomy[(4)].

Prostaglandins have been widely used for induction of labor, particularly if the cervix is not 'favorable'. Prostaglandin E2 (PGE2 or dinoprostone) appears to be the prostaglandin of choice when used vaginally in the form of tablets, gel or pessaries. Oral prostaglandins administration is less effective and has been virtually abandoned, mainly due to its side effects on gastrointestinal

Received: 11/12/2017 DOI: 10.12816/0045305
Accepted: 21/12/2017

tract. However, after the introduction of a new synthetic prostaglandin E1 analogue – misoprostol interest in oral prostaglandins has increased[5].

Misoprostol was first used for prevention of peptic ulcer from the use of non-steroidal anti-inflammatory drugs[6]. It has been argued that administration of misoprostol before hysteroscopy makes cervical passage easier and decreases the risk of cervicouterine complications[7].

AIM OF THE WORK

This study aims to assess the efficacy of dinoprostone compared to misoprostol in cervical ripening in nulliparous women undergoing diagnostic hysteroscopy.

PATIENTS AND METHODS

Study setting: This study was conducted in Ain Shams University Maternity Hospital, Hysteroscopy Unit. **The study was approved by the Ethics Board of Ain Shams University.**

Study design: A randomized controlled trial.

Study Population:

Sample size: A sample of 66 women were included in the study and were divided equally and randomly into two groups; group M received 400 mcg misoprostol vaginally 6 hours before their diagnostic hysteroscopy and group D received 3 mg dinoprostone vaginally 6 hours before their diagnostic hysteroscopy.

Sample Size Justification: Sample size was calculated using STATA® version 11 program, setting the type-1 error (α) at 0.05 and the power (1-β) at 0.7. Results from a previous study showed that mean cervical width for misoprostol was 5.43±0.43 mm while for dinoprostone it was 5.83±0.64 mm. Calculation according to these values produced a minimal sample size of 33 cases in each group.

Reference for program: StataCorp. 2001. Statistical Software: Release 7.0. College Station, TX: Stata Corporation.

Inclusion criteria

1. Nulliparous women.
2. Diagnostic hysteroscopy indications e.g. confirmation of abnormal test findings (abnormal hysterosalpingogram or thickened endometrial lining on sonography), suspected Müllerian anomalies or infertility.

Exclusion criteria

1. Women with previous vaginal delivery.
2. Women with previous caesarean section.
3. Women with previous dilatation and curettage.
4. Women with cervical lesions e.g. tears or polyps.
5. Contraindications for prostaglandin such as hypersensitivity, bronchial asthma, glaucoma, low blood pressure, heart disease, diabetes and liver disease.
6.

METHODS

All women participating were subjected to the following:

1. Counseling about all the steps of the study with full explanation of the procedure.
2. Informed consent obtained.
3. Careful history taking regarding personal, last menstrual period, obstetric, medical and surgical histories.
4. Complete physical examination to exclude any disorders that may interfere with the results.
5. In this study 66 women were included in the study and distributed randomly into two groups;

Group (M)

- Thirty-three women received 400 mcg misoprostol vaginally 6 hours before their diagnostic hysteroscopy.

Group (D)

- Thirty-three women received 3 mg dinoprostone vaginally 6 hours before their diagnostic hysteroscopy.
- Office hysteroscope (Karl Storz bettocchi hysteroscope) with an outer sheath diameter 5 mm, inner sheath diameter 4.3 mm and scope diameter 2.9 mm was inserted through the cervical canal to view the uterine cavity for 20-30 seconds maximum.

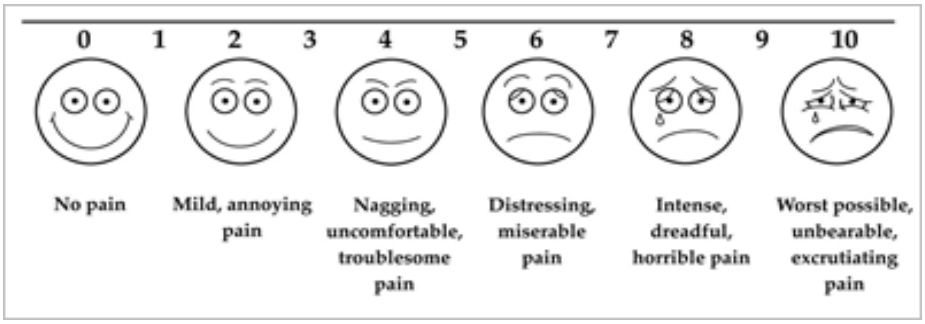
Outcomes:

Primary outcome:

Office hysteroscope entry was evaluated using Likert scale, which is a method of ascribing quantitative value to qualitative data, to make it amenable to statistical analysis. A numerical value is assigned to each potential choice and a mean figure for all the responses is computed at the end of the evaluation. The final average score represents overall level of accomplishment or attitude toward the subject matter and in this study the scale was as follows; easy entry, hard entry, failed entry.

Secondary outcomes

Pain assessment was evaluated at the end of the procedure using visual analogue scale, which is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. It is often used in epidemiologic and clinical research to measure the intensity or frequency of various symptoms. For example, the amount of pain that a patient feels ranges across a continuum from none to an extreme amount of pain [8].



Side effects will be assessed as diarrhea, nausea, vomiting, fever, and abdominal pain.

Data Management and Analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science **((IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).** Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics

1. Mean, standard deviation (SD) and range for parametric numerical data, while median and interquartile range (IQR) for non-parametric numerical data.
2. Frequency and percentage of non-numerical data.

Analytical statistics

1.**Student t** test was used to assess the statistical significance of the difference between two study group means.

2. Mann Whitney Test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups.

3. Chi-Square test was used to examine the relationship between two qualitative variables

4. Fisher's exact test: was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells

P- value: level of significance

-P>0.05: Non significant (NS).

-P< 0.05: Significant (S).

-P<0.01: Highly significant (HS).

RESULTS

In this study, a sample of 66 women were included and divided equally and randomly in to two groups; group M received 400 mcg misoprostol vaginally 6 hours before their diagnostic hysteroscopy and group D received 3 mg dinoprostone vaginally 6 hours before their diagnostic hysteroscopy.

Table (1): Comparison between two groups as regard to personal and gynecological history

		Group				P	Sig
		Dinoprostone		Misoprostol			
		Mean	±SD	Mean	±SD		
Age (years)		23.15	±3.34	22.39	±2.12	>0.05*	NS
Duration of marriage (years)		2.03	±0.93	2.29	±1.05	>0.05*	NS
Medical disorders	No	32	97.0%	33	100.0%	>0.05**	NS
	Yes	1	3.0%	0	0.0%		
History of gynecological operations	No	31	93.9%	29	87.9%	>0.05**	NS
	Yes	2	6.1%	4	12.1%		
Type of gynecological operations	No	31	93.9%	29	87.9%	>0.05**	NS
	Myomectomy	1	3.0%	1	3.0%		
	Laparoscopy	1	3.0%	3	9.1%		

*Student t test **Fisher exact test

There was no significant difference between the two study groups as regard to personal and gynecological history.

Table (2): Comparison between two groups as regard to procedure outcome and mode of hysteroscopic entry

		Group				P	Sig
		Dinoprostone		Misoprostol			
		N.	%	N.	%		
Failure	Failed	5	15.2%	3	9.1%	>0.05**	NS
	Succeeded	28	84.8%	30	90.9%		
Hysteroscopic entry	Easy	15	53.6%	19	63.3%	>0.05*	NS
	Hard	13	46.4%	11	36.7%		

**Fisher exact test

***Chi-Square Tests**

There was no significant difference between the two study groups as regard to procedure outcome; as 84.8% of group D succeeded compared to 90.9% of group M cases. Similarly, no significant difference was found between the two study groups as regard to mode of hysteroscopic entry; as 53.6% of group D was easy entry compared to 63.3% of group M.

Table (3): Comparisons between two groups as regard to procedure duration, pain and need for anesthesia

		Group						P	Sig
		Dinoprostone			Misoprostol				
		Mean	±SD	Median	Mean	±SD	Median		
Duration of operation (mins)		13.79	±2.85	14.00	12.85	±2.58	13.0	>0.05*	NS
Visual analogue scale		5.15	±2.09	5.00	4.33	±1.96	4.00	0.05**	NS
Need for	**No**	28	84.8%		30	90.9%		0.05***	NS
		5	15.2%		3	9.1%			

*Student t test ** Mann Whitney test ***Fisher exact test

There was no significant difference between the two study groups as regard to mean procedure duration, as it was 13.7±2.85 minutes for group D compared to 12.85± 2.58 minutes for group M. Also, no significant differences between the two study groups as regard to pain score, and in the need for anesthesia.

Table (4): Comparisons between two groups as regard to side effects

		Group				*P*	*Sig*
		Dinoprostone		Misoprostol			
		N	%	N	%		
Diarrhea	No	33	100.0%	33	100.0%	>0.05**	NS
	Yes	0	0.0%	0	0.0%		
Nausea	No	31	93.9%	30	90.9%	>0.05**	NS
	Yes	2	6.1%	3	9.1%		
Vomiting	No	33	100.0%	32	97.0%	>0.05**	NS
	Yes	0	0.0%	1	3.0%		
Fever	No	32	97.0%	31	93.9%	>0.05**	NS
	Yes	1	3.0%	2	6.1%		
Abdominal pain	No	28	84.8%	26	78.8%	>0.05*	NS
	Yes	5	15.2%	7	21.2%		
Complications	No	33	100.0%	33	100.0%	>0.05**	NS
	Yes	0	0.0%	0	0.0%		

****Fisher exact test** ***Chi-Square Tests**

There was no significant difference between the two study groups as regard to side effects.

Table (5): Comparison between failed and succeeded cases as regard to personal and intraoperative characteristics

		Outcome						P	Sig
		Failed			Succeeded				
		Mean	±SD	Median	Mean	±SD	Median		
Age (years)		22.13	±2.30	21.50	22.86	±2.87	22.00	>0.05	NS
Duration of marriage (years)		2.31	±0.96	2.00	2.14	±1.00	2.00	>0.05	NS
Duration of operation (mins)		17.25	±0.46	17.00	12.78	±2.46	13.00	<0.001	HS
Visual analogue scale		7.88	±2.03	8.00	4.31	±1.66	4.00	<0.001	HS
Need for anesthesia	**No (N %)**	0	0.0%		58	100.0%		<0.001	HS
	Yes (N %)	8	100.0%		0	0.0%			

*Student t test **Fisher exact test

There was no significant difference between the failed and succeeded cases as regard to cases' mean age and mean duration of marriage, however, a significant difference was found between the failed and succeeded cases regarding procedural duration and pain score, as they were both higher among failed group. Similarly, need for anesthesia was significantly more frequent among the failed group.

Table (6): Comparison between failed and succeeded cases as regard to medical and gynecological characteristics

		Failure				P	Sig
		Failed		Succeeded			
		N	%	N	%		
Medical disorders	No	8	100.0%	57	98.3%	>0.05	NS
	Yes	0	0.0%	1	1.7%		
History of gynecological operations	No	8	100.0%	52	89.7%	>0.05	NS
	Yes	0	0.0%	6	10.3%		

****Fisher exact test** ***Chi-Square Tests**

There was no significant difference between the failed and succeeded cases as regard to medical and gynecological history.

Table (7): Comparison between failed and succeeded cases as regard to occurrence of side effects

		Failure				P	Sig
		Failed		Succeeded			
		N	%	N	%		
Diarrhea	No	8	100.0%	58	100.0%	>0.05**	NS
	Yes	0	0.0%	0	0.0%		
Nausea	No	6	75.0%	55	94.8%	>0.05**	NS
	Yes	2	25.0%	3	5.2%		
Vomiting	No	8	100.0%	57	98.3%	>0.05**	NS
	Yes	0	0.0%	1	1.7%		
Fever	No	8	100.0%	55	94.8%	>0.05**	NS
	Yes	0	0.0%	3	5.2%		
Abdominal pain	No	6	75.0%	48	82.8%	>0.05**	NS
	Yes	2	25.0%	10	17.2%		
Complications	No	8	100.0%	58	100.0%	>0.05**	NS
	Yes	0	0.0%	0	0.0%		

**Fisher exact test *Chi-Square Tests

There was no significant difference between the failed and succeeded cases as regard to occurrence of side effects.

DISCUSSION

Hysteroscopy is considered the gold standard for uterine cavity evaluation because it allows for direct visualization. Diagnostic hysteroscopy may be performed in the office using a small-diameter hysteroscope and saline distension, often without need for anesthesia [(9)].

Almost 50% of hysteroscopic complications are related to difficulty with cervical entry. Potential complications include cervical tears, creation of a false passage, perforation, bleeding, or simply difficulty in entering the internal os (between the cervix and the uterus) with the hysteroscope.[(10)] Using efficient method to facilitate an easier uncomplicated entry during the hysteroscopic procedure could substantially minimize the risk of complications [(11)]. Cervical ripening agents include oral or vaginal prostaglandin, which can be synthetic (e.g. misoprostol) or natural (e.g. dinoprostone) and vaginal osmotic dilators, which can be naturally occurring (e.g. laminaria) or synthetic [(10)]. Prostaglandins have been considered to be the central mediators in cervical ripening by inducing collagenolytic activity and synthesis of proteoglycans [(12)], misoprostol is a prostaglandin El analogue, like PGE2, is capable of facilitation of metalloproteinase (MMP) containing leukocyte and monocyte influx into the cervix [(13)], originally approved by the Food and Drug Administration (FDA) [(14)]. It can be administered either sublingually[(15)] or vaginally [(16)]. It is inexpensive, has short half life, easily stored, and is widely available, being registered in more than 80 countries, it has been tested in randomized controlled trials (RCTs), these studies have shown that preoperative cervical ripening with misoprostol decreased both intraoperative morbidity and duration of hysteroscopy [(17)].

Currently, misoprostol is the drug of choice for cervical ripening; previous randomized studies have shown that preoperative cervical ripening with misoprostol decreased both intraoperative morbidity and duration of hysteroscopy [(18)]. Although both the sublingual **Mulayim *et al*** [(15)] and vaginal **Darwish *et al*** [(19)] routes have been proven to be effective for cervical priming before hysteroscopy, the optimal regimen and dose of misoprostol remains to be determined. This is a randomized controlled clinical trial comparing dinoprostone versus misoprostol for cervical ripening before diagnostic hysteroscopy in nulliparous women, it included 2 groups, 33 patients each. In the first group named (group D) dinoprostone 3 mg was applied vaginally 6 hours before diagnostic hysteroscopic procedure while in the second group named (group M) 400 mcg misoprostol was applied vaginally at the same timing. There was no statistically significant difference between the groups that received misoprostol or dinoprostone with regard to age, duration of marriage, medical disorder, history of gynecological operations and type of gynecological operations. In the current study, we have found that there was no significant difference between the two study groups as regard to procedure outcome; as 84.8% of group D succeeded compared to 90.9% of group M cases. Similarly, no significant difference was found between the two study groups as regard to mode of hysteroscopic entry; as 53.6% of group D was easy entry compared to 63.3% of group M.

This is a disagreement with **Inal *et al*** [(20)], they found that the use of vaginal dinoprostone is more effective than misoprostol for cervical ripening in nulliparous women before diagnostic hysteroscopy and the study showed that dinoprostone provides a higher level of cervical priming.

Also, our results agreed with **Preutthipan and Herabutya**[(21)] to an extent, as they found that the use of vaginal misoprostol is more effective than dinoprostone for cervical priming, but in our study this superiority did not reach a statistical significance.

In the current study, there was no significant difference between the two study groups as regard to mean procedure duration, as it was 13.7±2.85 minutes for group D compared to 12.85± 2.58 minutes for group M. Also, no significant differences between the two study groups as regard to pain score as it was 5.15±2.09 for group D compared to 4.33±1.96 for group M, and in the need for anesthesia there was also no significant differences as it was 15.2% for group D compared to 9.1% for group M. In the **Inal *et al*** [(20)] study there was an agreement regarding procedure duration as there was no significant differences between the two study groups but there was a disagreement regarding the need for anesthesia and cervical dilatation as it was 30% for the dinoprostone group compared to 56.7% for the misoprostol group.

In the **Preutthipan and Herabutya** [(21)] study there was an agreement with the current study and **Inal *et al*** [(20)] regarding procedure duration as there was no significant differences between the two study groups, but there was a disagreement between **Preutthipan and Herabutya** [(22)] and the current study regarding the need for anesthesia and cervical dilatation as it was 80.4% for the dinoprostone group compared to 70.4% for the misoprostol group.

The pain assessment using the visual analogue scale was not studied by **Inal *et al*** [(20)] **or Preutthipan and Herabutya** [(21)] in their studies.

In the current study as regard to side effects, 2 patients complained from nausea in group D (6.1%) compared to 3 patients in group M (9.1%), none of the patients complained from vomiting in group D (0%) compared to 1 patient in group M (3%), 1 patient

complained of fever in group D (3%) compared to 2 patients in group M (6.1%), 5 patients complained from abdominal pain in group D (15.2%) compared to 7 patients in group M (21.2%) and none of the patients complained from diarrhea in both study groups. As a conclusion, there was no significant differences between the two study groups regarding all these side effects. The current study was supported by **Inal *et al* [(20)]** as there was no significant differences between the two study groups regarding side effects. **Preutthipan and Herabutya [(21)]** suggested that there were more side effects in the misoprostol group. The significant difference of side effects between the two groups were abdominal pain, vaginal bleeding, and feeling feverish, which occurred in 36.2%, 29.6%, and 7.2% in the misoprostol group compared to 21.5%, 16.5%, and 1.3%, respectively, in the dinoprostone group.

CONCLUSION

There was no significant difference between dinoprostone and misoprostol in priming of cervix before diagnostic hysteroscopy in nulliparous women regarding ease of hysteroscope entry, pain or side effects.

REFERENCES

1. **Caserta D, Toro G, Porretta M (2007):** Hysteroscopic versus histologic diagnosis: Study of 222 cases of abnormal uterine hemorrhage. Minerva. Ginecol., 51: 169 -172.
2. **Jansen FW, Vredevoogd CB, Van Ulzen K (2005):** Complications of hysteroscopy: a prospective multicenter study. Obstet. Gynecol., 96:266–270.
3. **Bradley LD (2002):** Complications in hysetroscopy: prevention, treatment and legal risk. Curr. Opin. Obstet. Gyncol., 14: 409-415.
4. **Song T, Kim MK, Kim ML *et al* (2014):** Effectiveness of different routes of misoprostol administration before operative hysteroscopy: a randomized, controlled trial. Fertil. Steril., 102:519–524.
5. **Alfirevic Z, Aflaifel N. (2014):** Oral misoprostol for induction of labour. Cochrane Database Syst. Rev., 6:CD001338.
6. **Choksuchat C. (2010):** Clinical use of misoprostol in nonpregnant women: reviewarticle. J. Minim. Invasive. Gynecol., 17:449–455.
7. **Crane JM, Healey S. (2006):** Use of misoprostol before hysteroscopy: A systematic review. J. Obstet. Gynecol. Can., 28:373–379.
8. **Gould *D* (2001): Visual Analogue Scale (VAS).** Journal of Clinical Nursing , 10:697-706
9. **Shukla P, Kalpana Y, Sakshi M (2016):** Hysteroscopic evaluation of uterine cavity in cases of infertility and its correlation with transvaginal ultrasound and hysteron-salpingograph**y.** Int. J. Reprod. Contracept. Obstet. Gynecol., 5(11):3843-3848.
10. **Al-Fozan H, Fergana B, Al Kadri H *et al*. (2015):** Preoperative ripening of the cervix before operative hysteroscopy. Cochrane Database of Systematic Reviews, 4(1): CD005998.
11. **El-Toukhy T, Sunkara SK, Coomarasamy A *et al*. (2008):** Outpatient hysteroscopy and subsequent IVF cycle outcome: a systematic review and meta-analysis. Reprod Biomed Online, 16 (5): 712–719.
12. **Sordia-Hernandez LH, Rosales-Tristan E, Vazquez-Mendez J *et al*. (2011):** 'Effectiveness of misoprostol for office hysteroscopy without anesthesia in infertile patients', Fertil. Steril., 95: 759-761.
13. **El-Refaey H, Calder L, Wheatley DN *et al*. (1994):** Cervical priming with prostaglandin E1 analogues, misoprostol and gemeprost. Lancet, 343:1207–1209.
14. **Tang OS, Ho PC, Ngai SW *et al*. (2001):** Vaginal misoprostol as medical treatment for first trimester spontaneous miscarriage. Human Reproduction., (7):1493–1496.
15. **Mulayim B, Celik NY, Onalan G (2010):** Sublingual misoprostol for cervical ripening before diagnostic hysteroscopy in premenopausal women: a randomized, double blind, placebo-controlled trial. Fertil. Steril., 93 (7): 2400–2404.
16. **Oppegaard KS, Nesheim BI, Istre O *et al* .(2008):** Comparison of selfadministered vaginal misoprostol versus placebo for cervical ripening prior to operative hysteroscopy using a sequential trial design. B.J.O.G., 115: 663.
17. **Bastu E, Celik C, Nehir A *et al*. (2013):** Cervical Priming Before Diagnostic Operative Hysteroscopy in Infertile Women: A Randomized, Double-Blind, Controlled Comparison of 2 Vaginal Misoprostol Doses. Int. Surg., 98: 140–144.
18. **Choksuchat C, Cheewadhanaraks S, Getpook C *et al* .(2006):** Misoprostol for cervical ripening in non-pregnant women: a randomized double-blind controlled trial of oral versus vaginal regimens. Hum. Reprod., 21: 2167–2170.
19. **Darwish AM, Ahmad AM, Mohamed AM (2004):** Cervical priming prior to operative hysteroscopy: A randomized comparison of laminaria versus misoprostol. Human reproduction, 19 : 2391 – 2394.
20. **Inal HA, Ozturk Inal ZH, Tonguc E *et al* .(2015):** 'Comparison of vaginal misoprostol and dinoprostone for cervical ripening before diagnostic hysteroscopy in nulliparous women'. Fertil. Steril., 103: 1326-1331.
21. **Preutthipan S, Herabutya Y (2005):** A randomized comparison of vaginal misoprostol and dinoprostone for cervical priming in nulliparous women before operative hysteroscopy. Fertil. Steril., 86: 990-994.
22. **Preutthipan S, Herabutya Y (2015):** Vaginal misoprostol for cervical priming before operative hysteroscopy: a randomized controlled trial. Obstet. Gynecol., 96:890–894.