

# Comparison of the cervical priming effect of different medical methods in postmenopausal women before the removal of the intrauterine devices

## Abstract

Remove of intrauterine device (IUD) in postmenopausal women frequently require cervical dilation. Many medications have been clinical used to ripen the cervix prior to the procedure. To improve IUD removal procedure following the menopause and decrease the risk of complications, we have compared several commonly used agents to evaluate their safety and effectiveness in terms of cervical softening before IUD removal in postmenopausal women. Postmenopausal women (n=244) who came to remove the intrauterine device during the years of 2011-2012 have been randomly assigned into five groups. Four medicines, Progynova, Misoprostol, Carboprost and Mifepristone were given to four groups respectively, with the fifth group serve as a control group without taking any medication. Our study indicates that estrogen and prostaglandin F<sub>2α</sub> have shown a better cervical softening result in the postmenopausal women compared to the other two medicines. All the four medicines can be safely used in postmenopausal patients without contraindications in cervical preparation prior intrauterine procedures.

**Keywords:** Cervical priming, Postmenopausal, Progynova, Misoprostol, Carboprost and mifepristone

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**Qing Lin, HuiYing Wang**

Department of Obstetrics and Gynaecology, Capital Medical University, China

**Correspondence:** Qing Lin, Department of Obstetrics and Gynaecology, Beijing Friendship Hospital, Capital Medical University, 95 Yong'an Rd, Xicheng, Beijing, China, 100050, Tel 8613801118981, Email qing.lin1008@gmail.com

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## Introduction

The intrauterine device (IUD) is the most widely used reversible forms of contraception in the world.<sup>1</sup> Given its excellent efficacy and long-acting properties, IUD remains the most simple, cost-effective contraceptive method that is widely used in China. Ideally, the IUD should be removed soon after the menopause, however, many women with an IUD fail to remove it following the menopause for a variety of reasons, and the longer it remains in the uterus, the more difficult it becomes with removal because of the atrophy of the vagina, cervix and uterine body, and the cervix may become firmly closed and rigid. Many patients require cervical dilatation prior to IUD extraction, especially in patients with rigid cervix, cervical adhesions and IUD deformation. However, in women with a firmly closed and rigid cervix, dilatation can lead to considerable traumatization of the tissue. Several selected medical agents have been widely used for ripening of the cervix in early pregnancy before surgical abortion,<sup>2</sup> later in pregnancy to induce labor<sup>3</sup> and in non-pregnant women if intrauterine surgery is indicated.<sup>4</sup> To improve IUD removal following the menopause and decrease the risk of complications, we have compared several commonly used agents to evaluate their effectiveness and safety for cervical softening before IUD removal in postmenopausal women.

## Materials and methods

### Patients

Postmenopausal women (defined as at least 1 year after the last menstrual period/menstruation) (n=244) who came to our hospital to remove the intrauterine device during the years of 2011-2012; All the patients were given a thorough preoperative examination such as blood tests, and a routine ultrasonic examination to determine the IUD location in the uterine cavity, and to rule out any other abnormal intrauterine findings. Patients with a medical contraindication of

using mifepristone, prostaglandin, misoprostol and estrogen were excluded from this study, such as patients with a history of allergy to the medicine, with chronic adrenal failure, coagulopathy or current therapy with anticoagulants, patients with active cardiac, pulmonary, renal or hepatic disease, or with estrogen dependent tumors etc. All patients were evaluated by the author (Q.Lin.) in Beijing Friendship Hospital. Institutional review board approval was obtained from Beijing Friendship Hospital and Capital Medical University. All patients gave written consent.

### Research methods

Patients are divided into 5 groups according to the time they came to seek the treatment. Group A patients took Progynova, an estradiol valerate tablets, 3mg each evening starting 7 days before the procedure for 7 days. Group B patients were given 400µg Misoprostol vaginally 2 hours before performing the procedure; Group C had vagina Carboprost, a prostaglandin F<sub>2α</sub> suppository, 0.5mg, 2 hours before the operation. Group D took Mifepristone 150mg once 2 days before the procedure; Group E patients did not use any medicine. All the procedures are performed by the same doctor.

### Procedures

- Cervical dilatation:** cervical dilatation was measured by passing Hegar dilators through the cervix in ascending order, starting with a size of No. 4 till the No. 6.5 Hegar dilator can easily pass through the cervix [5-7]. The size of the largest dilator passed into the internal cervical os without subjective resistance felt by the operator was recorded as the preoperative degree of dilatation (or the resistance of the cervical dilation).
- The time of the cervix dilatation:** the time used to dilate the cervix to No. 6.5 Hegar dilator was recorded by the operator.

- c. **The time spent for IUD extraction:** The operation time was recorded start from the beginning of the cervical dilation to the time that the IUD was taken out.
- d. **Blood loss during the operation:** The amount of blood lost during the operation was recorded. A container was placed under the hip of the patient to collect all the blood for postoperative measurement.
- e. **IUD:** The detail about the integrity of the IUD was recorded. If there was any fracture or damage of IUD, then an x-ray was performed to rule out any IUD residue. The biopsies of endometrial tissues were sent for regular pathological examination.

### Statistical methods

Statistical analysis was performed using SPSS11.5. Homogeneity of variance of each set of data was examined. If the data sets have similar variables, the result was presented as mean±standard deviation. The statistical significance of differences between the means of five groups was determined by using One Way ANOVA. The difference between two groups was assessed by LSD(least significant difference). When the variance between data sets was significantly different, the result was then presented as the median value of “the minimum value –the maximum value”, and the difference between the five groups was analyzed by Kruskal-Wallis Test, between two groups was by Mann-Whitney U Test. P<0.05 was considered statistical significant.

### Result

- i. General comparison of the five groups
- ii. The patients’ age, postmenopausal duration, previous pregnancy history, uterine volume and depth etc., were compared. Patients’ age was from 45 y to 72 y (54.47±4.15), postmenopausal duration is 1 to 20 years, the average is 4.38±3.48 years, IUD installation duration is 8 to 35 years, the average is 23.56±4.06 years and there was no significant difference between the five groups (Table 1).

- iii. **Comparison of data related to IUD removal operations:** All the operations of IUD extraction were successful. No perforation or other serious complications happened in all the patients. In the cases that the IUD has shown severe damage, postoperative pelvic X-ray and ultrasound examination was performed to rule out the IUD residue.
- iv. The detail parameters of the operations in the five groups were compared in Table 2. Group A (Progynova user) had the lowest cervical resistance (Higher dilator number) and the least time that needed on cervical dilation when compared with other groups (P<0.001); It also had less IUD removal time (P<0.05) compared with other groups, except Group C (Carboprost). There is no difference of cervical resistance among groups B, C, D, and E, but the dilation time of group C is less than groups B, D and E (P<0.001). Group B (Misoprostol) and D had no difference on cervical resistance, dilation time and IUD removal time compared to the control group E.
- v. **Pathology results:** the endometrial biopsy result was listed in Table 3. Most cases showed either the proliferative phase endometrium (mainly group A patients, P<0.05) or atrophy or foreign body reaction. No endometrial cancer or precancerous lesions were present in any patient. 31 patients were listed under other circumstances, included: 13 cases of uterine smooth muscle, 8 cases of small amount of endometrial glands, 5 cases of cervical columnar cells, 4 cases of scattered squamous cells; 1 case of endometrial polyps.
- vi. **Side effect and follow-up:** 9 cases have shown sore and mild breast engorgement in Progynova group; 2 cases reported bleeding and nausea in Misoprostol group; in Carboprost group, 17 cases reported of abdominal pain and nausea, 13 cases had diarrhea, 4 cases with preoperative vaginal bleeding; no major complain in Mifepristone group. None of the patients with above complains required any treatment. Ultrasonic follow-ups were given to the patients with proliferative endometrium and polyps one month post operation, no abnormal findings presented.

**Table 1** Summary of general information of all cases

Group	Case No.	Age	Postmenopausal duration (year)	Carrying IUD time (year)	C-section history	Pregnancy	Uterine volume (cm <sup>3</sup> )	Uterine depth (cm)
A(Progynova)	56	54.77±4.29	4(1~16)	24.05±4.81	11	2(1~5)	10.75±1.76	7(6~9)
B(Misoprostal)	40	53.60±3.84	3(1~8)	22.50±3.88	15	2(1~3)	10.58±2.01	7(6~9)
C(Carboprost)	40	55.85±5.57	4(1~20)	24.4±3.02	13	2(1~4)	10.95±1.99	7(6~7)
D(Mifepristal)	40	55.23±4.14	3(1~10)	23.48±4.13	12	2(1~5)	10.79±1.64	6.75(6~8)
E(Control)	68	53.76±3.80	3(1~14)	23.34±3.94	12	2(1~6)	11.46±1.85	7(6~8)
F(χ <sup>2</sup> )value		F=2.244	χ <sup>2</sup> =6.322	F=1.379	χ <sup>2</sup> =7.429	χ <sup>2</sup> =5.346	F=1.936	χ <sup>2</sup> =8.008
P value		0.065	0.176	0.242	0.115	0.254	0.105	0.091

**Table 2** Comparison between operations

Group	Case no.	Cervical resistance (dilator no.)	Time spent for cervical dialation (sec.)	Time spent for iud extraction (sec.)	Embedded iud case (no.)	Blood lose (ml)
A(Progynova)	56	6(4~7.5)	60(6~420)	180(10~900)	21	10(3~20)
B(Misoprostal)	40	5(4~6)	120(40~1200)	360(90~1500)	25	10(5~10)
C(Carboprost)	40	5.5 (4.5~6.5)	90(40~240)	180(60~480)	26	10(5~10)
D(Mifepristal)	40	5(4~6)	120(30~900)	345(60~2400)	23	10(5~20)
E(Control)	68	5(4~7)	120(10~1200)	300(60~1800)	28	5(0~20)
χ <sup>2</sup> value		χ <sup>2</sup> =60.683	χ <sup>2</sup> =35.123	χ <sup>2</sup> =18.976	χ <sup>2</sup> =12.602	χ <sup>2</sup> =12.385
P value		0	0	0	0.013	0.156
A-B		Z=-6.585,P=0.000	Z=-4.390,P=0.000	Z=-4.125,P=0.000	χ <sup>2</sup> =5.843,P=0.016	Z=-1.829,P=0.067
A-C		Z=-3.784,P=0.000	Z=-1.314,P=0.189	Z=-0.483,P=0.629	χ <sup>2</sup> =7.061,P=0.008	Z=-0.978,P=0.328

Table continued...

Group	Case no.	Cervical resistance (dilatator no.)	Time spent for cervical dialation (sec.)	Time spent for iud extraction (sec.)	Embedded iud case (no.)	Blood lose (ml)
A-D		Z=-5.645,P=0.000	Z=-3.638,P=0.000	Z=-1.957,P=0.050	$\chi^2=3.759,P=0.053$	Z=-0.366,P=0.714
A-E		Z=-5.485,P=0.000	Z=-3.7815,P=0.000	Z=-2.103,P=0.035	$\chi^2=0.174,P=0.677$	Z=-1.606,P=0.108
B-C		Z=-3.738,P=0.000	Z=-4.157,P=0.000	Z=-3.138,P=0.002	$\chi^2=0.054,P=0.816$	Z=-3.283,P=0.001
B-D		Z=-1.415,P=0.157	Z=-1.334,P=0.182	Z=-1.702,P=0.089	$\chi^2=0.208,P=0.648$	Z=-2.232,P=0.026
B-E		Z=-1.688,P=0.091	Z=-1.386,P=0.166	Z=-2.505,P=0.012	$\chi^2=4.582,P=0.032$	Z=-3.237,P=0.001
C-D		Z=-2.487,P=0.013	Z=-2.521,P=0.012	Z=-1.219,P=0.223	$\chi^2=0.474,P=0.491$	Z=-0.502,P=0.616
C-E		Z=-2.116,P=0.034	Z=-3.575,P=0.000	Z=-1.439,P=0.150	$\chi^2=5.718,P=0.017$	Z=-0.646,P=0.518
D-E		Z=-0.270,P=0.787	Z=-0.387,P=0.699	Z=-0.520,P=0.603	$\chi^2=2.693,P=0.101$	Z=-1.135,P=0.256

Table 3 Pathological result endometrium biopsy

Group	Case no.	Proliferative phase (case no.)	Atrophy or foreign body reaction	Others	No tissue content
A(progynova)	56	38	7	11	0
B(misoprostal)	40	18	16	6	0
C(carboprost)	40	11	29	0	0
D(mifefristal)	40	12	27	1	0
E(control)	68	11	41	13	3
$\chi^2$ value		70.133			
P value		0			

## Discussion

Cervical dilation is a prerequisite prior to any procedures in the uterine cavity, especially for postmenopausal women. After menopause, due to the low level of estrogen and progesterone, collagenase produced by cervical tissue is reduced, and lead to the increased level of collagen tissue, the cervix becomes atrophic and hard, the cervical inner mouth narrows and lost elasticity, all these make the cervical dilation difficult. In our study, we compared four commonly used cervical softening medicines that used in patients underwent menopause for at least one year that request the removal of the IUD.

These medicines had shown favorable results and remarkable effects in numerous studies for cervical dilation. Most of the studies were focused on a single medicine or the effect of a medicine on cervix softening at different doses; some studies have also tested the synchronized effect of more than one medicine. However, to our knowledge, there are no studies compared the effect of different medicines on their function of softening the cervix so far, and in our study, we compared four medicines on their effects in cervix dilation on menopausal patients at the time of performing IUD removal procedure.

Progynova (Estrogen) group has the best result in terms of the cervical resistance, dilation time and IUD extraction time, etc. However, estrogen application can be contraindicated in some patients, it may cause severe side effect, such as thrombotic diseases in some high-risk patients, like patients with endometrial carcinoma or estrogen contraindications.<sup>8-10</sup> Therefore, it cannot apply to all postmenopausal women.

Carboprost is a prostaglandin F2 $\alpha$  which is invented and produced from China and is widely used in postpartum hemorrhage and softening of the cervix.<sup>11</sup> Study by Wang et al.<sup>12</sup> indicated, that Carboprost can inhibit collagen synthesis and promote collagen dissolution.<sup>12</sup> In our study showed that the cervical softening effect of the Carboprost group is better than the mifepristone, the misoprostol and the control group.

Misoprostol is a synthetic prostaglandin E1 analogue that can

stimulate the cervical fibroblasts, accelerate the decomposition activity of collagenase and elastase on collagen, therefore, soften the cervical tissue. But our study showed no significant difference between the Misoprostol group and the control group. It is possibly due to vaginal application method used in this study. Because the Misoprostol pill in this study takes longer time to fully dissolve in the vagina, most of the time the whole tablet was still visible during operation. Many reports<sup>13,14</sup> have shown an excellent effect on vaginal applied Misoprostol when observed after 2 hours; Lou et al.<sup>15</sup> in their study of using Misoprostol in the elective terminations showed Misoprostol reached the best effect at 3 hours. Hou et al.<sup>16</sup> reviewed published papers from 1980 to 2011 on medicines promoting postmenopausal cervical maturation, results showed that the effective time for sublingual misoprostol is 2-3 to 24 hours. In our study, 2 hours seems not sufficient for vaginal misoprostol to take its effect, it is possible due to the fact that the pill is designed for oral use and postmenopausal women usually are lack of vaginal secretion so it took even longer for the pill to dissolve. Some studies showed that Misoprostol increased side effect, although it did effectively improve the cervical dilation,<sup>17</sup> however, others also point out that there was no enough evidence to support the benefit of using misoprostol on cervical dilation in postmenopausal women.<sup>18</sup> Nevertheless, our study did not show significant improvement on cervical softening by using misoprostol.

Mifepristone is a synthetic progesterone antagonist. It competes with progesterone for receptors. During pregnancy, it can antagonize the inhibitory effect of progesterone in degradation of cervical collagen fiber, interfere the prostaglandin catabolism, decomposes the cervical collagen fiber and therefore promotes the cervical maturation.<sup>19</sup> In postmenopausal women, although the progesterone level is low, it is reported that mifepristone may stimulate endogenous prostaglandin (PG) production, which promotes the decomposition of the collagen fibers and softens the cervix, and it also increases the sensitivity of the uterine muscle to PG [20]. So, it is frequently used together with prostaglandin to achieve a better result in softening the cervical tissue. In our study, mifepristone alone didn't show significant effect on cervical maturation when compared with the control group in postmenopausal women.

Then endometrial biopsy from the patients in this study showed that the estrogen group has the highest number of proliferative endometrium, but no complex proliferation and precancerous lesions found. All the tested proliferative endometrium went back to the normal thickness at the one month follow-up. No serious complications have been found in any of the groups.

In summary, our study indicates that estrogen and prostaglandin F2 $\alpha$  have shown a better cervical softening result in the postmenopausal women compared to the other two medicines. All the four medicines can be safely used in postmenopausal patients without contraindications in cervical preparation prior intrauterine procedures. However, they all have their own limitations and should be chosen according to the actual situation of the patient in the clinical application.

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None.

## Conflicts of interest

None.

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