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Original Research

Does Vaginal Estriol or Hyaluronic Acid Facilitate Office Hysteroscopy in Peri and Postmenopause? A Prospective Cohort Study

Iwona Gawron[1,*], Rafał Baran[2], Kamil Derbisz[2], Andrzej Zmaczyński[1], Robert Jach[1], Miłosz Pietrus[1]

[1]Department of Gynecology and Obstetrics, Faculty of Medicine, Jagiellonian University Medical College, 31-501 Krakow, Poland
[2]Clinical Department of Gynecological Endocrinology and Gynecology, University Hospital in Krakow, 31-501 Krakow, Poland
*Correspondence: iwona.gawron@uj.edu.pl (Iwona Gawron)
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Abstract

Background: Pain accompanying office hysteroscopy, possibly aggravated by urogenital atrophy, is the most common reason for its discontinuation. The aim was to evaluate the effectiveness of vaginal estriol and hyaluronic acid to facilitate the office hysteroscopy in peri and postmenopausal women. **Methods**: A prospective cohort study involved women aged 45–90 years subjected to office hysteroscopy. Women were assigned to three study arms: (A) 0.5 mg of estriol in vaginal cream twice daily for 10 days pre-procedure, (B) 5 mg of hyaluronic acid in vaginal gel twice daily for 10 days pre-procedure, (C) no medication. The following endpoints were compared: pain accompanying the procedure, need for cervical dilation, time of cervical passage, incidence of severe urogenital atrophy, and vaso-vagal reaction. **Results**: There were no significant differences between the arms in terms of pain intensity during (p = 0.93) and after the procedure (p = 0.17), need for cervical dilation (p = 0.5), cervical passage time (p = 0.1), severe urogenital atrophy (p = 0.15), and vaso-vagal reaction (p = 0.29). **Conclusions**: Despite unfavorable conditions in peri and postmenopausal women, cervical preparation in the above regimens did not seem to bring clinically significant benefits. **Clinical Trial Registration**: The study was registered under the number NCT05783479 in the Protocol Registration and Results System database (https://clinicaltrials.gov/). The database used for the study was made available in Harvard Dataverse (https://doi.org/10.7910/DVN/HSWURD).

Keywords: menopause; office hysteroscopy; estriol; hyaluronic acid

1. Introduction

Hysteroscopy is one of the basic diagnostic and therapeutic tools in gynecological practice [1,2]. An increasingly popular option in the management of uterine pathology, abnormal uterine bleeding (AUB) and postmenopausal bleeding (PMB) is office hysteroscopy (OF) [3], which enables excision of certain focal lesions or targeted endometrial biopsy [4]. Outpatient procedures do not require general anesthesia or using an operating room, bringing benefits in terms of shorter recovery time, fewer complications, fewer staff and equipment needed, and hence leading to a reduced economic burden on the healthcare sector [5]. While OF is widely accepted by physicians and patients, it has several disadvantages, the first of which is pain, being the most common reason for discontinuation of the procedure [6]. Pain accompanying OF is caused by several factors: instrumentalization of the cervix (dilation of the canal, insertion of a hysteroscope), distension of the uterine cavity (dilating medium), and peritoneal irritation (accumulation of the dilating medium in the peritoneal cavity) [6,7]. The ongoing minimization of hysteroscopic instruments and the evolution of surgical technique are aimed at providing patients with better comfort by reducing pain while maximizing therapeutic effects [8,9]. Various modalities are used to relieve the pain experienced during and after hysteroscopy, but no consensus has yet been reached on the preferred method [6,10,11]. Half of the adverse effects of hysteroscopy, such as pain, cervical laceration, perforation of the uterus and false canal, occur during cervical passage [12]. Difficult passage through the cervix in postmenopausal women is caused by its reduced elasticity and fibrosis associated with hormonal changes after menopause [13,14]. Blind dilatation of the cervical canal, its atresia or tortuosity may increase the risk of iatrogenic damage to the cervix [12]. Severe pain caused by cervical stenosis is one of the main reasons for discontinuation of OF. To avoid negative consequences of abandoning the procedure, such as delayed oncological diagnosis, various methods of pharmacological and mechanical preparation of the cervix were tested in previous research [15], mainly prostaglandins. Contradictory results were obtained, on one hand emphasizing the potential benefit of using prostaglandins (reduced pain, reduced percentage of postponing the procedure), on the other hand indicating an increased risk of complications (vaginal bleeding, abdominal pain and gastrointestinal disorders) [16–19]. It has therefore been hypothesized that preoperative local administration of estriol, registered for treatment of vaginal atrophy caused by estrogen deficiency and facilitation of healing after vaginal surgeries, and hyaluronic acid registered to support the healing and

regeneration of the vaginal skin, may have a beneficial effect on the patient's comfort and the effectiveness of OF, with minimal local side effects and no systemic action. The aim of the study was to evaluate the effectiveness of estriol in vaginal cream, and hyaluronic acid in vaginal gel compared to no intervention in cervical preparation for OF in peri and postmenopausal women. To achieve the study objectives, the following endpoints were recorded and compared across the three arms of the study: cervical passage time, intensity of pain during and after the procedure, need for cervical dilation, occurrence of vaso-vagal reaction, rate of OF abandonment and rate of other complications (false canal, uterine perforation).

2. Materials and Methods

A prospective cohort single tertiary-center open-label study was conducted after obtaining a positive opinion of the Jagiellonian University Bioethics Committee (no. 1072.6120.128.2021). All women gave informed written consent to participate in the research. The study group consisted of peri and postmenopausal women subjected to OF by vaginoscopic approach. The inclusion criteria were age 45–90 years, and confirmed indications for OF. The exclusion criteria were: (i) medication allergy, (ii) vaginal surgeries within 3 months prior to OF, and (iii) history of cervical conization or amputation. The precondition for OF was a normal cervical cytology result and a physiological vaginal biocenosis. During the pre-procedure medical consultation women were assigned to three study arms depending on the treatment they chose: (i) estriol (Oekolp®, Dr. Kade GmbH, Berlin, Germany) 0.5 mg in vaginal cream twice daily for 10 days pre-OF, (ii) hyaluronic acid (Mucovagin®, Verco, Warsaw, Poland) 5 mg in vaginal gel twice daily for 10 days pre-OF, (iii) no treatment (control). Women who did not comply with the instructions (inappropriate duration of therapy, postponing the procedure) were excluded in the course of the research. The study population was characterized in terms of demographic and clinical data. Intensity of pain during OF and post-procedure in Numeric Rating Scale (NRS) [20], time of cervical passage (in seconds, sec.) obtained from the video recording of the procedure, need for cervical dilatation, incidents of OF abandonment, false canal, perforation of the uterus and vaso-vagal reaction were noted and then compared in three arms of the study in order to achieve the assumed objectives. The study was registered under the number NCT05783479 in the Protocol Registration and Results System database (https://clinicaltrials.gov/). The database used for the study was made available in Harvard Dataverse (https://doi.org/10.7910/DVN/HSWURD).

2.1 Qualification for Surgical Treatment

Medical procedures commonly accepted as routine in reference centers for endoscopic diagnostics were applied to women of the study population. The legitimacy of these procedures, safety and the adopted qualification criteria have been confirmed by previous scientific research and are widely used in practice. After meeting the inclusion criteria and obtaining informed consent for treatment, women were qualified for OF by a specialist in obstetrics and gynecology. The applied diagnostic procedures included taking past medical history, vaginal speculum and bimanual gynecological examination, vaginal biocenosis examination, and pelvic ultrasonography. During the gynecological examination, signs of urogenital atrophy were noted, such as: dryness, redness or whitish discoloration and loss of elasticity of the vaginal skin, fragile and unrugated epithelium, introital stenosis and vaginal shortening or narrowing, minor lacerations near the vaginal opening and decreased size of the labia. Features of atrophy in a cervical cytology smear, such as increase in proportion of parabasal cells, and pH >5 in the vaginal vault assessed as part of the vaginal biocenosis study, were searched for in the genital smear results. In menstruating women, hysteroscopy was performed in the follicular phase or regardless of the phase of the cycle, except in case of menstrual bleeding, if the menstruation was irregular. All women received ketoprofen (Ketonal, Sandoz GmBH, Kundl, Austria) 100 mg intravenously up to one hour before surgery and infiltration anesthesia with 20 mL of 1% lidocaine (Lidocaine 1% Fresenius Kabi, Fresenius Kabi Polska, Warsaw, Polnad) at the time of surgery. Oral consent for imaging studies and informed written consent for OF and video recording of the procedure were obtained.

2.2 Hysteroscopy

OF was performed by vaginoscopic approach using a Karl Storz Bettocchi® (KARL STORZ SE & Co. KG, Tuttlingen, Germany) rigid hysteroscope with an outer sheath diameter of 5 mm, a telescope of 2.9 mm diameter with a 30° angled lens, and an operating channel for instruments with a diameter of 5 Fr. A 0.9% NaCl solution at a maximum pressure of 80–100 mmHg was used as the medium. A thorough inspection of the uterine cavity was performed during the procedure. The surgeon provided ongoing information about the course of OF during the procedure and gave advance warning when the pain could be more intense. Resection of the focal lesion was performed using blunt scissors and/or a bipolar needle electrode and biopsy forceps. Endometrial biopsy was performed using biopsy forceps. Adhesions were excised with blunt scissors. If it was necessary to overcome cervical stenosis, scissors, forceps or bipolar electrode were used. Hysteroscopy was performed by a specialist in obstetrics and gynecology, or by a supervised trainee physician. The surgical procedure was archived using intraoperative video recording.

2.3 Statistical Analysis

Descriptive statistics was used to characterize the population. Categorical variables were summarized as number of cases (n), frequency (n/N) and percentage (%). Continu-

Table 1. Characteristics of the population across the three arms of the study in relation to selected quantitative variables (using the Kruskal-Wallis difference test) and qualitative variables (using the Chi-square test of independence).

Quantitative variable		Arm A (Estriol)		Arm B (Hyaluronic acid)		Arm C (Control)		Overall		*p*
		M	SD	M	SD	M	SD	M	SD	
Age (years)		55.26	10.10	55.95	9.27	54.55	8.75	55.01	9.11	0.844
BMI (kg/m^2)		25.55	4.71	27.58	5.75	26.97	5.26	26.12	5.11	0.339
Vaginal deliveries (n)		1.52	0.99	1.25	0.91	1.51	0.93	1.46	0.94	0.563
Endometrial thickness on TVS (mm)		8.28	5.07	8.25	4.27	7.36	4.21	7.77	4.42	0.565
Qualitative variable		**Arm A (Estriol)**		**Arm B (Hyaluronic acid)**		**Arm C (Control)**		**Overall**		***p***
		N	%	N	%	N	%	N	%	
Menopause	Premenopause	12	52.2%	7	35.0%	27	50.9%	46	47.9%	0.428
	Postmenopause	11	47.8%	13	65.0%	26	49.1%	50	52.1%	
	Total	23	100.0%	20	100.0%	53	100.0%	96	100.0%	
Estrogen plus progestogen therapy (EPT)	No	17	73.9%	20	100.0%	43	81.1%	80	83.3%	0.059
	Yes	6	26.1%	0	0.0%	10	18.9%	16	16.7%	
	Total	23	100.0%	20	100.0%	53	100.0%	96	100.0%	
Previous procedures with cervical dilatation	No	15	65.2%	12	60.0%	40	75.5%	67	69.8%	0.377
	Yes	8	34.8%	8	40.0%	13	24.5%	29	30.2%	
	Total	23	100.0%	20	100.0%	53	100.0%	96	100.0%	
Abnormal uterine/postmenopausal bleeding (AUB/PMB)	No	15	65.2%	11	55.0%	32	60.4%	58	60.4%	0.792
	Yes	8	34.8%	9	45.0%	21	39.6%	38	39.6%	
	Total	23	100.0%	20	100.0%	53	100.0%	96	100.0%	
Uterine polyp on ultrasound	No	2	8.7%	8	40.0%	17	32.1%	27	28.1%	0.047
	Yes	21	91.3%	12	60.0%	36	67.9%	69	71.9%	
	Total	23	100.0%	20	100.0%	53	100.0%	96	100.0%	
Polypoid/heterogeneous endometrium in ultrasound	No	21	91.3%	12	60.0%	36	67.9%	69	71.9%	0.041
	Yes	2	8.7%	8	40.0%	17	32.1%	27	28.1%	
	Total	23	100.0%	20	100.0%	53	100.0%	96	100.0%	
Severe urogenital atrophy	No	20	87.0%	13	65.0%	44	83.0%	77	80.2%	0.147
	Yes	3	13.0%	7	35.0%	9	17.0%	19	19.8%	
	Total	23	100.0%	20	100.0%	53	100.0%	96	100.0%	

M, mean; SD, standard deviation; *p*, probability value; BMI, body mass index; n, number; TVS, transvaginal sonography; N, number of cases.

Table 2. Comparison of outcome measures across three study arms using the Kruskal-Wallis test of differences (for quantitative variables) and the Chi-square test of independence (for qualitative variables) across three study arms.

Quantitative variable		Arm A (Estriol)		Arm B (Hyaluronic acid)		Arm C (Control)		Total		*p*
		M	SD	M	SD	M	SD	M	SD	
Cervical passage time (sec.)		135.30	103.62	223.25	190.17	137.62	107.81	154.91	131.62	0.113
Pain during procedure (NRS)		4.87	2.87	5.10	2.79	4.92	2.29	4.95	2.52	0.933
Post-procedure pain (NRS)		0.43	1.24	0.90	1.37	1.02	1.89	0.85	1.65	0.173
Qualitative variable		**Arm A (Estriol)**		**Arm B (Hyaluronic acid)**		**Arm C (Control)**		**Overall**		***p***
		N	%	N	%	N	%	N	%	
Need for cervical dilation	No	14	60.9%	10	50.0%	34	64.2%	58	60.4%	0.544
	Yes	9	39.1%	10	50.0%	19	35.8%	38	39.6%	
	Total	23	100.0%	20	100.0%	53	100.0%	96	100.0%	
Vaso-vagal reaction	No	23	100.0	20	100.0%	50	94.3	93	96.9%	0.285
	Yes	0	0.0	0	0.0	3	5.7	3	3.1%	
	Total	23	100.0	20	100.0%	53	100.0	96	100.0%	

M, mean; SD, standard deviation; *p*, probability value; NRS, Numeric Rating Scale; N, number of cases.

ous variables were presented using means and standard deviations, and medians. The maximum and minimum values of the variables were also provided. The normality of the distribution was checked using the Shapiro-Wilk test. Due to the non-normal distribution, non-parametric analyzes were used. The variables were analyzed using Chi-squared test of independence, Mann-Whitney U test and Kruskal-Wallis test of differences, and Spearman's Rho correlation assessment. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using IBM® SPSS® Statistics 28.0.1 software (Armonk, NY, USA).

3. Results

The study included 110 women, of which 14 were excluded due to non-compliance. Of the remaining 96 women, 23 received estriol, 20 received hyaluronic acid, and 53 received no medication. The procedure was performed due to asymptomatic uterine polyp in 44/96 (45.8%) women, AUB/PMB with underlying uterine polyp in 25/96 (26%) women, abnormal endometrial ultrasound image in 14/96 (14.6%) women, and AUB/PMB and abnormal endometrial ultrasound in 13/96 (13.5%) women. The distribution of quantitative and qualitative variables characterizing the population across the three study arms is presented in Table 1.

The women did not differ in terms of age, body mass index (BMI), parity, endometrial width, menopausal status, systemic postmenopausal estrogen plus progestogen therapy (EPT) use, history of cervical dilation, history of AUB/PMB, and severe urogenital atrophy between the three study arms. In arm A, the diagnosis of endometrial polyp was significantly more frequent than in arm B and C, while the diagnosis of polypoid endometrium was significantly less frequent than in arm B and C. Quantitative and qualitative outcome measures across the three study arms are presented in Table 2. The use of the medication for cervical preparation and its type had no effect on time of cervical passage and intensity of pain during and after OF. There were no differences in the need for cervical dilation or the occurrence of vaso-vagal reaction among the studied women, depending on the drug used and its type.

Furthermore, additional calculations were conducted to determine how the characteristics of the examined women influenced the course of the procedure. When analyzing the effect of variables such as menopausal status, EPT use, prior cervical dilation on the need for cervical dilation, presence of severe urogenital atrophy and vaso-vagal reactions, the Chi-square test showed that postmenopausal women needed cervical dilation more often than premenopausal (26/50, 52% *vs.* 12/46, 26.1%, $p = 0.012$), and more often demonstrated symptoms of severe urogenital atrophy (18/50, 36% *vs.* 1/46, 2.2%, $p < 0.001$). Moreover, women not using EPT were more likely to have severe urogenital atrophy than those who were treated (19/80, 23.8% *vs.* 0/16, 0%, $p = 0.036$), whereas prior cervical dilatation had no effect on the course of the current procedure. Based on Spearman's Rho correlation analysis, there was no significant association between age, BMI, parity or endometrial width and cervical passage time or OF-related pain ($p > 0.05$ for each combination of variables). No significant impact of menopause on cervical passage time (176.4 sec. in postmenopausal *vs.* 131.6 sec. in premenopausal, $p = 0.062$) and intensity of pain during (5.14 in postmenopausal *vs.* 4.74 in premenopausal, $p = 0.34$) and after OF (0.58 in postmenopausal *vs.* 1.15 in premenopausal, $p = 0.23$) was revealed using the Mann-Whitney U difference test and subsequent median analysis. Women using EPT compared to untreated women also did not differ in terms of the mean cervical passage time (157.06 sec. *vs.* 154.48 sec., $p = 0.67$) and intensity of pain during (6.69 *vs.* 4.8, $p = 0.16$) and after OF (1.19 *vs.* 0.79, p

= 0.4). Similarly, women who had undergone instrumental cervical dilation in the past did not differ from women who had not undergone this procedure in terms of the mean cervical passage time (172.24 sec. *vs*. 147.4 sec., $p = 0.45$) or intensity of pain during (5.14 *vs*. 4.87, $p = 0.63$) and after OF (1.41 *vs*. 0.61, $p = 0.27$).

Finally, the impact of the indications for OF on its course was also assessed. There was no association between the ultrasound diagnosis of a polyp or an abnormal endometrial appearance and the need for cervical dilation, severe urogenital atrophy, and vaso-vagal reaction in the Chi-squared test ($p > 0.05$ for each pair of variables). Similarly, above indications had no effect on cervical passage time or pain during and after OF in the Mann-Whitney U test ($p > 0.05$ for each pair of variables). In contrast, women without AUB/PMB were more likely to have severe urogenital atrophy (17/58, 29.3% *vs*. 2/38, 5.3%, $p = 0.004$), and women with AUB/PMB experienced more intense pain after the procedure (1.5 *vs*. 0.43, $p = 0.002$). In 2 cases, both in the control group, the procedure was abandoned due to failed cervical canal penetration (2/96, 2.1%). Of the adverse events, there were 3 cases of vaso-vagal reaction (3/96, 3.1%) and 1 case of false entry into the cesarean scar niche, all in the control group (1/96, 1%). There were no cases of uterine perforation or false canal. There were no adverse effects of the drugs used in the study.

4. Discussion

Preparation of the cervix for hysteroscopy is not a mandatory element of the procedure, but it may be considered in a selected group of women who are at an increased risk of cervical stenosis or severe pain [1]. Such a group may include peri and postmenopausal women with symptoms of estrogen deficiency in the lower urogenital tract. Various methods of cervical preparation have been described in the literature, of which the combination of vaginal estrogen with misoprostol, unlike misoprostol alone [21], significantly facilitated the procedure and reduced pain in postmenopausal women [13,22,23], but also caused complications such as abdominal pain, vaginal bleeding, and increased body temperature [17]. The effect of estrogen alone, however, has not yet been verified [13]. Abdominal pain and bleeding prolong the duration of the procedure, and thus increase the level of anxiety and patient's discomfort. In order to avoid the side effects of prostaglandins, the effectiveness of estriol, hyaluronic acid and placebo was compared. No significant differences were found in the studied endpoints across the three study arms, including cervical passage time, intensity of pain during and after the procedure, need for cervical dilation, occurrence of vaso-vagal reaction, rate of OF abandonment and rate of other complications, such as false canal or uterine perforation. It was previously assumed that cervical canal stenosis resulting from urogenital atrophy, and the need to overcome it influenced the course of the procedure [22]. However, the results of the study showed that although postmenopausal women more often demonstrated symptoms of severe urogenital atrophy and needed cervical dilation more often than premenopausal women, there was no effect of menopause on cervical passage time or pain during and after OF. Similarly, there was no correlation between age and the passage time of the cervical canal, or the intensity of pain during and after OF. In the absence of a negative impact of postmenopausal status or advancing age on the examined OF-related parameters in the studied population, preparation of the cervix in the study population was not found to have a beneficial effect on the course of the procedure. Considering the fact that all women had endometrial damage (excision of the focal lesion, multiple endometrial biopsy), the fact that the polyp was more frequent in arm A than in arms B and C did not seem to have a significant impact on pain or other parameters. The results did not support a measurable benefit from the routine use of cervical preparation with vaginal estriol or hyaluronic acid in the studied regimens compared to no medication in women of peri and postmenopausal age. Limitations of the study include small sample size, lack of randomization, and lack of blinding. Due to internal medico-legal regulations of the hospital, it was not possible to conduct a randomized double-blinded study. The strength of the study is that the data have come from a center specializing in endoscopic surgery, where the majority of focal lesions of the uterine cavity are removed using operative office hysteroscopy by vaginoscopic approach, and therefore reflect real clinical practice.

5. Conclusions

In the absence of evidence on the effectiveness of cervical preparation in the studied regimens, the decision on its implementation and type should be made on the basis of individual risk factors for hysteroscopy complications, i.e., local condition of the lower urogenital tract tissues, menopausal status, age, parity, previous vaginal procedures, assumed pain tolerance, and the woman's preferences. Future studies may evaluate modifications to these protocols in terms of dose and duration of treatment.

Abbreviations

AUB, abnormal uterine bleeding; PMB, postmenopausal bleeding; OF, office hysteroscopy; NRS, Numeric Rating Scale; EPT, estrogen plus progestogen therapy; BMI, body mass index.

Availability of Data and Materials

The database used for the study was made available in Harvard Dataverse (https://doi.org/10.7910/DVN/HSWURD).

Author Contributions

Conceptualization and study design: IG, RJ. Methodology: IG, KD, MP. Investigations and data curation: IG, RB, AZ, KD. Statistical analysis: KD, IG. Writing, reviewing and editing: IG, MP. Drafting and supervision: IG, MP, RJ. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board. A positive opinion of the Jagiellonian University Bioethics Committee (no. 1072.6120.128.2021) was obtained prior to the start of the study. Written informed consent was obtained from all women involved in the study.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] The Use of Hysteroscopy for the Diagnosis and Treatment of Intrauterine Pathology: ACOG Committee Opinion, Number 800. Obstetrics and Gynecology. 2020; 135: e138–e148.

[2] ACOG Technology Assessment No. 13: Hysteroscopy. Obstetrics and Gynecology. 2018; 131: 1.

[3] Salazar CA, Isaacson KB. Office Operative Hysteroscopy: An Update. Journal of Minimally Invasive Gynecology. 2018; 25: 199–208.

[4] Giampaolino P, Della Corte L, Di Filippo C, Mercorio A, Vitale SG, Bifulco G. Office hysteroscopy in the management of women with postmenopausal bleeding. Climacteric. 2020; 23: 369–375.

[5] Wortman M, Carroll K. Office-Based Gynecologic Surgery (OBGS): Past, Present, and Future: Part II. Surgical Technology International. 2020; 36: 159–177.

[6] Ahmad G, Saluja S, O'Flynn H, Sorrentino A, Leach D, Watson A. Pain relief for outpatient hysteroscopy. The Cochrane Database of Systematic Reviews. 2017; CD007710.

[7] Zupi E, Luciano AA, Valli E, Marconi D, Maneschi F, Romanini C. The use of topical anesthesia in diagnostic hysteroscopy and endometrial biopsy. Fertility and Sterility. 1995; 63: 414–416.

[8] De Silva PM, Carnegy A, Smith PP, Clark TJ. Vaginoscopy for office hysteroscopy: A systematic review & meta-analysis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2020; 252: 278–285.

[9] Di Spiezio Sardo A, Giampaolino P, Manzi A, De Angelis MC, Zizolfi B, Alonso L, *et al*. The Invisible External Cervical Os. Tips and Tricks to Overcome this Challenge during In-Office Hysteroscopy. Journal of Minimally Invasive Gynecology. 2021; 28: 172–173.

[10] Tangsiriwatthana T, Sangkomkamhang US, Lumbiganon P, Laopaiboon M. Paracervical local anaesthesia for cervical dilatation and uterine intervention. The Cochrane Database of Systematic Reviews. 2013; CD005056.

[11] De Silva PM, Mahmud A, Smith PP, Clark TJ. Analgesia for Office Hysteroscopy: A Systematic Review and Meta-analysis. Journal of Minimally Invasive Gynecology. 2020; 27: 1034–1047.

[12] Jansen FW, Vredevoogd CB, van Ulzen K, Hermans J, Trimbos JB, Trimbos-Kemper TC. Complications of hysteroscopy: a prospective, multicenter study. Obstetrics and Gynecology. 2000; 96: 266–270.

[13] Casadei L, Piccolo E, Manicuti C, Cardinale S, Collamarini M, Piccione E. Role of vaginal estradiol pretreatment combined with vaginal misoprostol for cervical ripening before operative hysteroscopy in postmenopausal women. Obstetrics & Gynecology Science. 2016; 59: 220–226.

[14] Wood MA, Kerrigan KL, Burns MK, Glenn TL, Ludwin A, Christianson MS, *et al*. Overcoming the Challenging Cervix: Identification and Techniques to Access the Uterine Cavity. Obstetrical & Gynecological Survey. 2018; 73: 641–649.

[15] Genovese F, D'Urso G, Di Guardo F, Insalaco G, Tuscano A, Ciotta L, *et al*. Failed diagnostic hysteroscopy: Analysis of 62 cases. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2020; 245: 193–197.

[16] De Silva PM, Wilson L, Carnegy A, Smith PP, Clark TJ. Cervical dilatation and preparation prior to outpatient hysteroscopy: a systematic review and meta-analysis. BJOG: an International Journal of Obstetrics and Gynaecology. 2021; 128: 1112–1123.

[17] Al-Fozan H, Firwana B, Al Kadri H, Hassan S, Tulandi T. Preoperative ripening of the cervix before operative hysteroscopy. The Cochrane Database of Systematic Reviews. 2015; CD005998.

[18] Abdelhakim AM, Gadallah AH, Abbas AM. Efficacy and safety of oral vs vaginal misoprostol for cervical priming before hysteroscopy: A systematic review and meta-analysis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2019; 243: 111–119.

[19] Cooper NAM, Smith P, Khan KS, Clark TJ. Does cervical preparation before outpatient hysteroscopy reduce women's pain experience? A systematic review. BJOG: an International Journal of Obstetrics and Gynaecology. 2011; 118: 1292–1301.

[20] Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EKB, *et al*. Assessment of pain. British Journal of Anaesthesia. 2008; 101: 17–24.

[21] Ngai SW, Chan YM, Ho PC. The use of misoprostol prior to hysteroscopy in postmenopausal women. Human Reproduction. 2001; 16: 1486–1488.

[22] Oppegaard KS, Lieng M, Berg A, Istre O, Qvigstad E, Nesheim BI. A combination of misoprostol and estradiol for preoperative cervical ripening in postmenopausal women: a randomised controlled trial. BJOG: an International Journal of Obstetrics and Gynaecology. 2010; 117: 53–61.

[23] Bettocchi S, Bramante S, Bifulco G, Spinelli M, Ceci O, Fascilla FD, *et al*. Challenging the cervix: strategies to overcome the anatomic impediments to hysteroscopy: analysis of 31,052 office hysteroscopies. Fertility and Sterility. 2016; 105: e16–e17.