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Original Article

Endometrial Preparation With Estradiol Plus Dienogest (Qlaira) for Office Hysteroscopic Polypectomy: Randomized Pilot Study

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ABSTRACT **Study Objective:** To estimate the effectiveness of Qlaira for endometrial preparation in women undergoing hysteroscopic polypectomy in the office setting.
Design: Randomized clinical pilot study (Canadian Task Force classification II-2).
Setting: Academic research environment.
Patients: Seventy-four cycling women undergoing hysteroscopic polypectomy (polyp size <1.5 cm).
Interventions: Women were randomized to be operated on during the proliferative phase (cycle day 5–7) of a spontaneous cycle (group A) or after 9 to 11 days of Qlaira intake (group B). Polypectomy was performed by using forceps and bipolar electrodes when required.
Measurements and Main Results: The quality of visualization of the uterine cavity during the procedure (visual analog score [VAS] 0–5, bad to optimal), total surgeon satisfaction (VAS 0–5, very difficult to easy to perform), and total patient satisfaction (VAS 0–5, severe pain to no pain) were compared. Endometrial thickness before and at the end of the procedure was significantly less in women in group B. Mean duration of interventions was shorter in group B than in group A. In addition, vision quality, and surgeon and patient satisfaction rates were significantly higher in women in group B.
Conclusions: At 10 days before surgery, administration of Qlaira is effective for preparation of the endometrium for hysteroscopic polypectomy in the office setting. With preoperative administration of Qlaira, the surgical procedure can be performed more easily and faster, and both surgeon and patient satisfaction rates are improved. Journal of Minimally Invasive Gynecology (2012) 19, 356–359 © 2012 AAGL. All rights reserved.

Keywords: Dienogest; Endometrial preparation; Estradiol; Hysteroscopy; Qlaira; Resectoscopy

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Hysteroscopy is considered the criterion standard for the diagnosis and treatment of endouterine diseases [1]. In fertile women operative hysteroscopy is facilitated by an endometrium that is as thin as possible. A thin endometrium makes all intrauterine maneuvers easier, ensures good visual control, reduces the operative time, increases ease of surgery, and decreases the risk of fluid intravasation [2–5]. This is particularly true in the case of office procedures in which 5F forceps or Versapoint electrodes are used. It is common experience that during office polypectomy, a few minutes after the start of the procedure, the unprepared endometrium tends to absorb the distention fluid and to become swollen, and the procedure may become difficult to accomplish. For this reason, in natural cycles, the days immediately after menstruation are considered the best

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time for hysteroscopic surgery. However, to schedule and perform interventions in the few days of the early follicular phase may produce organization problems. To avoid this temporal limit, several drugs have been proposed to minimize the endometrial thickness.

Administration of gonadotropin-releasing hormone analogues (GnRH agonist) is an effective method for endometrial preparation. Reliable thinning of the endometrial mucosa is obtained after 2 months of therapy [4–6]. However, because of cost and potency, GnRH agonists are actually overtreatment in cases of "minor" hysteroscopic surgery such as removal of endometrial polyps or uterine septae.

Because of its androgenic characteristics and capacity to reduce circulating estradiol and progesterone concentrations, danazol at a dose of 600 mg/d orally for 6 weeks produces reliable endometrial atrophy. Danazol is less expensive than GnRH agonists, but could induce unfavorable adverse effects because of its antiestrogenic activity and androgenic propensity [7]. Gestrinone, a trienic steroid with antiestrogenic and antiprogestinic activities, is capable of reducing uterine volume, menorrhagia, and endometrial thickness [8]. Recently, 14-day administration of nomegestrol acetate, a progestogen with high progestogen potency effects, was effective for rapid endometrial preparation for operative hysteroscopy [9].

Oral contraceptives also have been proposed as a simple and inexpensive treatment for obtaining a thin endometrium. Grow and Iromloo [10] reported that a monophasic combined low-dose oral contraceptive containing 150 μg desogestrel and 30 μg ethinylestradiol, when started in the early follicular phase, maintains a reliably thin endometrium: mean (SD), 4.1 (1.6) mm, as measured at ultrasonography in 100 women on day 18 of the oral conctraceptive pill pack.

In recent years, Qlaira (Bayer-Schering Pharma AG, Berlin, Germany), an oral contraceptive containing estradiol (E2) rather than ethinylestradiol and dienogest, a progestin with strong endometriotopic acitivities, has been introduced on the market. In theory, this formulation would have some advantages over traditional oral contraceptives for endometrial preparation because it combines the advantages of E2, which is about 1000 times less potent than ethinylestradiol, with those of dienogest, a specific progesterone receptor agonist with strong antiproliferative endometrial activity. In Qlaira, the composition of the differently colored tablets containing 1 or 2 active ingredients is as follows: 2 dark yellow tablets, each containing 3 mg E2 valerate; 5 medium red tablets, each containing 2 mg E2 valerate and 2 mg dienogest; and 17 light yellow tablets, each containing 2 mg E2 valerate and 3 mg dienogest.

The objective of the present study was to estimate the effectiveness of Qlaira for endometrial preparation in women undergoing hysteroscopic polypectomy in the office setting. For this reason, in a randomized study we compared the endometrial thickness, duration of the procedure, and surgeon and patient satisfaction in 2 groups of women, 1 operated on in the early follicular phase of a natural cycle and the other after 10 days of Qlaira therapy.

Materials and Methods

From April 2010 to January 2011, 74 premenopausal women referred to our department were enrolled in the study. All reported regular menstrual cycles in the last 6 months, and office polypectomy was indicated because of an echographic diagnosis of an endometrial polyp smaller than 1.5 cm. The study was approved by our institutional review board, and all women gave informed consent.

By means of a computer-generated randomization sequence, the women were randomized to undergo surgery in the early proliferative phase (cycle day 5–7) of a spontaneous cycle (group A) or after 9 to 11 days of Qlaira intake (group B). Patients were instructed to not take the first 7 tablets (2 dark yellow tablets and 5 red tablets), and to start at the beginning of menstruation with the light yellow tablets for 10 days.

Before hysteroscopy, patients underwent transvaginal ultrasonographic evaluation of the uterine cavity. Echography was performed using a 5-MHz transvaginal transducer (Aloka Prosound Co. Ltd., Tokyo, Japan) by a physician experienced in ultrasonography (V.P.). Endometrial thickness was measured as the maximal distance between the 2 myometrial interfaces on a longitudinal scan, taking care to avoid the polyp in the measurement.

Office hysteroscopies were performed via the vaginoscopic approach using a lens-based 2.9-mm outer diameter telescope equipped with a 4.5-mm outer diameter double-flow operative sheath (Karl Storz GmbH & Co. KG, Tuttlingen, Germany). Saline solution was used to distend the uterine cavity at a pressure generated by simple drop from a bag suspended 1 m above the patient. A 300-W light source with a xenon bulb and a 21-inch video color screen (Trinitron, PVM-20M2MDE; Sony Corp., Shinigawa-ku, Tokyo, Japan) were used.

All polypectomyies were performed using 5F forceps and bipolar electrodes (Gynecare Versapoint; Ethicon, Inc., Somerville, NJ) when required. All procedures were performed without anesthesia.

At the end of surgery, the duration of the procedure was calculated. In addition, surgeon satisfaction with endometrial preparation, quality of visualization of the uterine cavity, and patient pain were compared. The surgeon (E.C.), who was unaware of the treatment, was asked to score the quality of endometrial preparation and of visualization of the uterine cavity during the procedure by marking two 5-cm visual analog scales, from 0 (minimal) to 5 (maximal). Patients were also requested to score their pain using a visual analog scale, from 0, (severe pain) to 5 (no pain).

Ultrasound measurement of endometrial thickness was repeated at the end of the polypectomy.

The women were asked to report any adverse effects of treatment, and then were discharged to home within 2 hours after surgery.

Data are given as mean (SD) and 95% confidence interval (CI). Data were compared using unpaired and paired *t* tests. A p value $<.05$ was considered significant. Power analysis showed a value of 0.99 for all parameters measured.

Table 1

Percentage variation in parameters measured in 74 office hysteroscopic polypectomy procedures

Variable	Mean (SD)	95% CI	p Value
Endometrial thickness (mm)			
Before			
Group A	5.1 (0.8)	2–14	<.05
Group B	4.7 (0.7)	3–12	
After			
Group A	6.86 (0.9)	4–15	<.05
Group B	4.6 (0.7)	3–15	
Duration of surgery (min)			
Group A	8.1 (1.8)	2–14	<.05
Group B	7.5 (1.3)	4–16	
Surgeon satisfaction (VAS)			
Preparation quality			
Group A	2.51 (1.0)	1–9	<.05
Group B	3.97 (0.8)	1–10	
Vision quality			
Group A	2.8 (1.1)	1–8	<.05
Group B	4.46 (0.6)	1–9	
Patient satisfaction (VAS)			
Group A	3.1 (0.9)	1–9	<.05
Group B	3.9 (1.1)	1–10	

Before = early proliferative phase (cycle day 5–7) of a spontaneous cycle (group A); After = after 9–11 days of Qlaira intake (group B); VAS = visual analog scale.

Results

All procedures were successfully performed, and no adverse effects or complications were reported. Results of endometrial thickness measurements before and after polypectomy, and surgeon and patient satisfaction rates are given in Table 1. The 2 groups of women were homogeneous insofar as age, parity, and polyp size (Table 2). Power analysis showed a value of 0.99 for all parameters measured.

Mean (SD) endometrial thickness was significantly less in women in group B than in women in group A: 5.1 (0.8) mm and 4.7 (0.7) mm, respectively, before the procedure, and 6.9 (0.8) mm and 4.6 (0.7) mm after the procedure ($p < .05$). Moreover, when considering mean variation between preoperative and postoperative endometrial thickness, the value in group B was significantly lower than that in group A.

Table 2

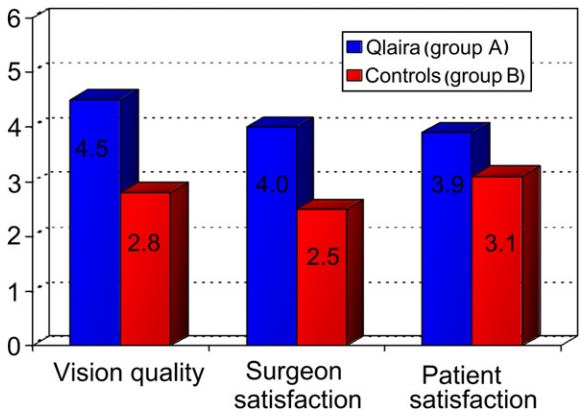
Patient characteristics

	Group A (n = 37)		Group B (n = 37)		
Variable	Mean (SD)	95% CI	Mean (SD)	95% CI	p Value
Age, yr	29.1 (6.2)	19–41	28.7 (5.3)	18–40	.09
BMI	28 (6.0)	19–37	29 (5.0)	17–39	.06

BMI = body mass index; CI = confidence interval.

Fig. 1

Quality of visualization during polypectomy, and surgeon and patient satisfaction rates in the treatment group vs the control group.



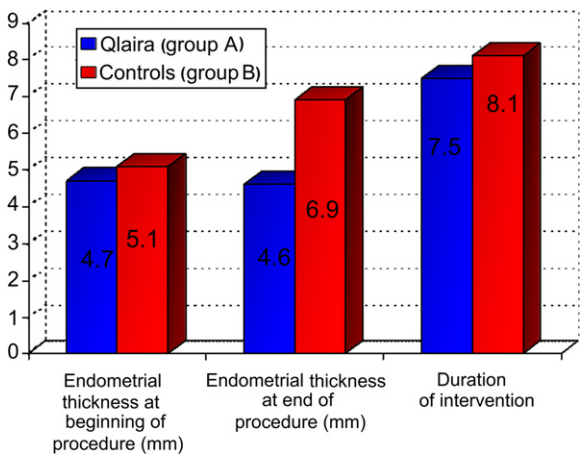
The duration of the intervention was significantly shorter in group B than in group A ($p < .05$). Similarly, surgeon satisfaction insofar as endometrial preparation and quality of visualization of the uterine cavity was significantly higher in group B than in group A ($p < .05$) (Fig. 1).

At hysteroscopy in 16 patients in group A (43.2%), the endometrium demonstrated normal proliferative features [11] and was flat and pink, whereas in 20 patients (55.5%), the endometrial surface was irregular with dyshomogeneous thickness, stromal edema, and altered vascularity. In contrast, in all but 3 of 33 women in group B (91.7%), the endometrial surface appeared hypotrophic, regular, and pale, and the endometrium remained thin during the procedure.

Surgeon satisfaction rate insofar as quality of visualization during polypectomy was significantly greater in group B than in group A. In addition, patient satisfaction rate was greater in women in group B than in group A (Fig. 2).

Fig. 2

Endometrial thickness at the beginning and the end of the procedure, and duration of the intervention were significantly less in the treatment group than in the control group ($p < .05$).



Discussion

Office operative hysteroscopy is facilitated by endometrial preparation [5]. Indeed, with a thin endometrium, the uterine cavity is wider and more easily explored, intracavity abnormalities (e.g., polyps and myomas) are easily detectable and frequently smaller compared with previous evaluation. This implies that removal may be easier, operating time shorter, and volume of distention medium needed for the procedure lower. Therefore, the procedure may be safer and better accepted by patients.

The results of the present study demonstrate that administration of Qlaira for 10 days provides rapid and effective endometrial suppression. The short time needed to obtain satisfactory endometrial preparation improves both patient acceptability and working organization because it facilitates scheduling and averts the need to postpone surgery for a prolonged period.

Administration of oral contraceptives is not an original technique for endometrial preparation [10]. Administration for 10 days of a combined contraceptive pill containing 30 μg ethinylestradiol and 150 μg desogestrel provided effective endometrial thinning [10]. Of note, we obtained a satisfactory and rapid endometrial preparation using an estrogenic exposition that is markedly lower than that of ethinylestradiol. This, in turn, may represent an advantage in terms of lower endometrial proliferation, higher compliance, and lower risks. Moreover, administration of progestin-like dienogest, with a strong endometrial antiproliferative effect, may contribute to explain the effectiveness of our treatment. Accordingly, in a recent study, dienogest directly inhibited proliferation of human endometrial epithelial cells, with suppression of cyclin D1 gene expression [11,12].

We withdrew the first pills (2 containing only E2 and 5 containing 2 mg E2 combined with 2 mg dienogest), and started therapy with the light yellow tablets (2 mg E2 and 3 mg dienogest) to maximize the combined effects of treatment.

In accordance with echographic measurements, direct hysteroscopic exploration of the cavity demonstrated that endometrial preparation was better in group B than in group A. In approximately 92% of women in group B, the endometrium was thin, pale, and regular. In contrast, in approximately 55% of women in group A, the endometrial appearance was variable and unpredictable. Surgeon satisfaction was significantly greater in group B.

In conclusion, Qlaira provides fast, inexpensive, and satisfactory preparation of the endometrium for operative hysteroscopy. Satisfactory endometrial preparation can be obtained with only 10 days of therapy, and this improves acceptability and scheduling of hysteroscopic treatment.

References

1. Gimpelson RJ, Whalen TR. Hysteroscopy as gold standard for evaluation of abnormal uterine bleeding. *Am J Obstet Gynecol*. 1995;173: 1637–1638.
2. Rai VS, Gillmer MDG, Gray W. Is endometrial pre-treatment of value in improving the outcome of transcervical resection of the endometrium? *Hum Reprod*. 2000;15:1989–1992.
3. Parazzini F, Vercellini P, De Giorgi O, et al. Efficacy of preoperative medical treatment in facilitating hysteroscopic endometrial resection, myomectomy and metroplasty: literature review. *Hum Reprod*. 1998; 13:2592–2597.
4. Vercellini P, Perino A, Consonni R, et al. Treatment with a gonadotrophin releasing hormone agonist before endometrial resection: a multicentre, randomised controlled trial. *BJOG*. 1996;103:562–568.
5. Sowter MC, Lethaby A, Singla AA. Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2002;(3):CD001124.
6. Donnez J, Vilos G, Gannon MJ, et al. Goserelin acetate (Zoladex) plus endometrial ablation for dysfunctional uterine bleeding: a large randomized, double-blind study. *Fertil Steril*. 1997;68:29–36.
7. Fedele L, Bianchi S, Gruft L, Bigatti G, Busacca M. Danazol versus a gonadotropin-releasing hormone agonist as preoperative preparation for hysteroscopic metroplasty. *Fertil Steril*. 1996;65:186–188.
8. Marchini M, Fedele L, Bianchi S, et al. Endometrial patterns during therapy with gestrinone for endometriosis: structural and ultrastructural study. *Hum Pathol*. 1992;23:51–56.
9. Florio P, Imperatore A, Litta P, et al. The use of nomegestrol acetate in rapid preparation of endometrium before operative hysteroscopy in premenopausal women. *Steroids*. 2010;75:912–917.
10. Grow DR, Iromloo K. Oral contraceptives maintain a very thin endometrium before operative hysteroscopy. *Fertil Steril*. 2006;85:204–207.
11. Dotto JE, Lema B, Dotto JE Jr, Hamou J. Classification of microhysteroscopic images and their correlation with histologic diagnoses. *J Am Assoc Gynecol Laparosc*. 2003;10:233–246.
12. Shimizu Y, Takeuchi T, Mita S, et al. Dienogest, a synthetic progestin, inhibits the proliferation of immortalized human endometrial epithelial cells with suppression of cyclin D1 gene expression. *Mol Hum Reprod*. 2009;15:693–701.