Rapid endometrial preparation for hysteroscopic surgery with oral desogestrel plus vaginal raloxifene: a prospective, randomized pilot study

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Objective: To evaluate the effects after 10 days of an original treatment combining oral progestins with vaginal raloxifene to maximize the antiproliferative effect on the endometrium.
Design: Prospective, randomized, clinical pilot study.
Setting: Academic research environment.
Patient(s): Ninety women with endometrial polyps.
Intervention(s): On day 1 of the subsequent menstrual cycle, patients were randomized to receive oral desogestrel (n = 30) for 10 days combined with a tablet of raloxifene (60 mg) per vaginam (group A); oral desogestrel at 60 mg/day (n = 30; group B); or oral danazol at 200 mg, three times a day (n = 30; group C).
Main Outcome Measure(s): Ultrasound measurement of endometrial thickness on day 11 of both the pretreatment and treatment cycles, surgeon satisfaction (0 to 10, visual analogue scale), and side effects.
Result(s): At the second evaluation, the mean percentage reduction in endometrial thickness in group A was statistically significantly greater than in the other groups. Surgeon satisfaction in terms of endometrial thinning was also greater with group A.
Conclusion(s): Oral desogestrel plus vaginal raloxifene provides a fast, low-cost, and satisfactory preparation of the endometrium for operative hysteroscopy. (Fertil Steril® 2007;88:698–701. ©2007 by American Society for Reproductive Medicine.)

Key Words: Hysteroscopy, endometrial preparation, raloxifene, danazol, desogestrel, resectoscopy

Resectoscopy is considered the gold standard for the treatment of pathologic endouterine conditions such as fibroids, polyps, synechiae, septa, and endometrial resection and/or destruction (1). In fertile women, hysteroscopic procedures are best performed when the endometrium is thin because the operating time is lessened and fluid absorption decreases, making surgery easier (2–5). For these reasons, the days immediately after menstruation are the best period for hysteroscopic surgery; however, scheduling surgery during the early follicular phase is not always possible, so several drugs have been proposed for thinning the endometrium.

Gonadotropin-releasing hormone analogues (GnRH-a) are the best-studied method, and they have proved very effective for endometrial preparation. A reliable thinning of the endometrial mucosa is obtained after 2 months of treatment (6, 7). However, because of the cost and potency, GnRH-a is actually an "overtreatment" for cases requiring minor hysteroscopic surgery, such as removal of small endocavitary fibroids, endometrial polyps, or uterine septa.

Thanks to its androgenic characteristics and capacity for reducing circulating estradiol and progesterone levels, danazol at a daily dosage of 600 mg orally for 6 weeks produces reliable endometrial atrophy. Compared with GnRH-a, danazol may require less time to prepare the endometrium, and it also is less expensive. However, the antiestrogenic activity and androgenic propensity of danazol could induce unfavorable side effects. More recently, gestrinone, a trienic steroid with antiestrogen and antiprogestin activities, has been shown to reduce uterine volume, menorrhagia, and endometrial thickness (8, 9).

Oral contraceptives have been also proposed as a simple and inexpensive treatment for obtaining a thin endometrium. Grow and Iromloo (10) have reported that oral contraceptives, when begun in the early follicular phase, maintain a reliably thin endometrium of 4.1 ± 1.6 mm, as measured by ultrasound in 100 women on the 18th day of the pill pack. However, the potential thrombotic risk of oral contraception in cases of surgery may limits its usefulness for this kind of pretreatment.

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Because all of the present treatments for endometrial preparation require 1 to 2 months to be effective, shortening the preparation time before surgery may improve patient acceptability and work organization. To speed up endometrial suppression, we proposed an original treatment combining oral progestins with vaginal raloxifene, a compound with selective antiestrogenic action, as a preoperative endometrial preparation for operative hysteroscopy. The rationale for this treatment was based on the hypothesis that effectiveness in endometrial thinning could be maximized by combining the ovarian suppression and antiproliferative effect of an oral progestin with the direct antiestrogenic effect on the endometrium of raloxifene, a selective estrogen receptor modulator administered by the vaginal route. Vaginal administration should have the advantage of allowing the compound to be selectively distributed to the uterus thanks to the so-called first uterine pass effect, or preferential vagina-to-uterus distribution (11, 12).

The aim of this prospective, randomized study was to evaluate the effectiveness of this original combined treatment in shortening the time for endometrial preparation compared with traditional treatments. To this end, we compared the changes in endometrial thickness after 10-days' administration of oral danazol, oral desogestrel, and oral desogestrel plus vaginal raloxifene in women who were undergoing hysteroscopic surgery.

MATERIALS AND METHODS

From March 2006 to July 2006, the study enrolled 145 premenopausal women (mean age: 29.6 ± 10.7 years; range: 19 to 41 years) who had reported regular menstrual cycle rhythms for the previous 6 months and in whom diagnostic hysteroscopy was indicated due to echographic diagnosis of endometrial polyp. The study was approved by the institutional review board, and all of the patients gave their informed consent.

The women were asked to visit our department on day 11 of their menstrual cycle. Before the hysteroscopy, the women underwent a transvaginal ultrasonographic evaluation of their uterine cavity. Echographies were carried out using a 5-MHz transvaginal transducer, and all were performed by a physician experienced with ultrasonography (V.P.). Endometrial thickness was measured as the maximal distance between the two myometrial interfaces in a longitudinal scan, ensuring avoidance of the polyp in the measurement; in all of the women, the presence of a dominant follicle was also assessed.

Diagnostic hysteroscopies were performed by the vaginoscopic approach using a lens-based 2.7-mm outer-diameter (OD) mini-telescope, equipped with a 3.5-mm outer-diameter single-flow diagnostic sheath. A simple drop from a saline bag suspended 1-m above the patient was used to distend the uterine cavity.

The first step in exploration of the uterine cavity consisted of a panoramic view of the cavity; next was the examination of both cornua, tubal ostia, and anterior and posterior walls. All of the hysteroscopies were performed by two of the authors (E.C. and N.S.) in an outpatient setting without any kind of anesthesia.

The study excluded all cases where the presence of large or multiple polyps, myomas, adhesions, septa, or uterine position prevented a reliable endometrial thickness measurement or where no dominant follicle was detected. The study selected a total of 90 premenopausal women (mean age: 32.6 ± 5.6 years; range: 20 to 40 years) with a single endometrial polyp (maximal size at ultrasound, range: 1 to 2.5 cm) confirmed by diagnostic mini-hysteroscopy.

A computer-generated randomization sequence determined which women received one of three different treatments for 9 days starting on day 1 of the subsequent menstrual cycle. Group A received 75 μg/day of oral desogestrel (Cerazette, Organon, Rome, Italy) plus a 60-mg (oral) tablet of raloxifene hydrochloride (Optruma; Eli Lilly, Florence, Italy) that was administered each day by vaginal route at bedtime. Group B received 75 μg/day of oral desogestrel (Cerazette; Organon, Rome, Italy). Group C received oral danazol (Danatrol; Sanofi, Rome, Italy) at 200 mg, three times a day.

The transvaginal ultrasonography was repeated on the day of surgery; the endometrial thickness was measured (on day 11 of the cycle) by the same investigator (V.P.), who was blinded to the treatment performed.

In all cases, a polypectomy was performed using a monopolar resectoscope under local anesthesia. More specifically, after the tenaculum was placed and the cervix dilated to Hegar 10, the procedure used a 26-F continuous-flow resectoscope fitted with a cutting loop electrode at a power setting of 120-W cutting current. A sterile 1.5% mannitol-sorbitol solution was used for uterine distension.

At the time of surgery, the surgeon's satisfaction (E.C.) with the endometrial preparation was evaluated. The surgeon, who was unaware of the treatment, was asked to score the degree of satisfaction with the preparation by marking a 10-cm visual analogue scale from 0 (minimal) to 10 (optimal).

Before discharge, women were asked to report any side effects experienced during the treatment; they were sent home within 2 hours after surgery.

The data, reported as mean ± standard deviation, were compared using unpaired and paired Student's *t* tests. $P<.05$ was considered statistically significant.

RESULTS

The results of endometrial thickness measurements on day 11 of the cycle before treatment and after 10 days of endometrial preparation are reported in Table 1.

The three groups were found to be homogeneous as regards endometrial thickness in the follicular phase, and the values were in the normal range. In all groups, the endometrial thickness after 10 days of treatment was statistically significantly lower than the pretreatment values ($P<.001$). The

mean endometrial thickness after treatment was statistically significantly smaller in group A compared with both B and C ($P<.001$); the endometrial thickness in group C was also statistically significantly smaller than in group B ($P<.03$).

However, when considering the mean percentage reduction in endometrial thickness, the women of group A had a statistically significantly greater reduction than seen in the other groups (−44.9% vs. −13.8% and −19.2% for groups A, B, and C, respectively; $P<.001$). The difference between groups B and C did not reach statistical significance.

Surgeon satisfaction in terms of endometrial preparation was also statistically significantly higher for women of group A compared with the other groups (7.3 ± 1.1, 4.2 ± 1.0, and 4.0 ± 0.8 for groups A, B, and C respectively; $P<.001$). At hysteroscopy, the endometrial surface in all of the women of group A appeared hypotrophic, regular, and pale, with no evidence of glands. In group B, the endometrial surface was irregular with areas of stromal edema and sporadic evidence of glands; in group C, the appearance of the mucosa was similar to that of group B, except for glands that were never visible.

No side effects were reported by the women of group A. In group B, four (13.3%) women reported spotting; in the danazol group (group C), headache, nausea, and bloating were reported by two (6.7%), three (10%), and one (3.3%) of the women, respectively.

TABLE 1

Endometrial thickness in 90 cycling women as assessed at transvaginal ultrasounds on day 11 of the pretreatment cycle and on the same day of subsequent cycle after 10 days treatment with oral desogestrel plus vaginal raloxifene clorhidrate (group A), oral desogestrel (group B), and oral danazol (group C).

	Endometrial thickness (mm)	
Group	Pretreatment cycle	Treatment cycle
A	6.3 ± 1.2	3.0 ± 0.9[a,b]
B	6.9 ± 0.7	5.9 ± 0.7[a]
C	6.8 ± 0.7	5.4 ± 0.9[a,c]

Note: Data are mean ± standard deviation. Group A: Oral desogestrel (Cerazette; Organon, Rome, Italy) administered at 75 μg daily plus raloxifene clorhidrate (Optruma; Eli Lilly, Florence, Italy) at 60 mg daily by vaginal route. Group B: Oral desogestrel (Cerazette, Organon, Rome, Italy) administered at 75 μg daily. Group C: Oral danazol (Danatrol; Sanofi, Rome, Italy) administered at 200 mg t.i.d.

[a] Difference between pretreatment and posttreatment values, $P<.001$.

[b] Difference between posttreatment values in group A versus both group B and group C ($P<.001$).

[c] Difference between posttreatment values in group C and group B ($P<.02$).

Cicinelli. Desogestrel and vaginal raloxifene for hysteroscopy. Fertil Steril 2007.

DISCUSSION

Operative hysteroscopy is best performed with a thin endometrium. With a prepared endometrium, the uterine cavity is wider and easier to explore; intracavity abnormalities (e.g., polyps and myomas) are easy to detect and frequently are smaller compared with previous evaluation. This implies that removal may be easier, operating time shorter, and the volume of distention media needed for the procedure lower; therefore, the procedure may be safer and more acceptable to patients.

The results of this study demonstrate, for the first time in the literature, that the combination of oral desogestrel and vaginal raloxifene provides a very fast and effective endometrial suppression. This original protocol was more effective than both the oral progestin alone and the oral danazol treatments, providing a very thin endometrium (<3 mm thickness) after just 10 days of administration. In our experience, the reduction in time needed to obtain a satisfactory endometrial preparation improves both patient acceptability and working organization, as it facilitates scheduling and avoids the need to postpone surgery for a long period of time.

We can speculate that the effectiveness of the proposed combined treatment relies on the combined action of the two compounds. Oral desogestrel provides an antigonadotropic effect, ovarian suppression, and an antiestrogenic effect on the endometrium. Raloxifene is a selective estrogen receptor modulator that exerts an antiestrogenic effect on the endometrium (13).

Vaginal administration allows steroids like progesterone and danazol to reach high concentrations in the endometrium (11, 12, 14); for instance, the endometrial concentration of progesterone after vaginal administration is 14 times higher that that measured after IM administration of the same dose of progesterone (11). To our knowledge, there have been no data in the literature pertaining to vaginal administration of raloxifene; because vaginal administration delivers drugs preferentially to the uterus, raloxifene might also concentrate in the endometrium and provide a strong antiproliferative effect if administered by this route. This may explain the significantly different effects that we found between groups A and B, the women treated with oral desogestrel in combination with vaginal raloxifene versus those treated with desogestrel alone.

In accordance to echographic measurements, the direct hysteroscopic exploration of the cavity also demonstrated that endometrial preparation was better in group A than in the other groups. Indeed, all group A women had very thin, pale, and regular endometria. In contrast, in group B the endometrial thickness was irregular, with areas of stromal edema and partial glandular development, probably related

to the progestin-induced decidualization. In women of group C, the irregularity of the endometrial surface could be explained as the incomplete effect of danazol, which requires longer treatment to induce hypotrophy. Accordingly, surgeon satisfaction was significantly greater for group A women than in other groups.

A limitation of this study was our assumption that no natural variation in endometrial thickness occurs when different cycles are compared for the same cycle day. Unfortunately, comparisons across cycles would have required at least one month of delay before surgery could be scheduled. Moreover, to the best of our knowledge, no paper in literature has investigated the intercycle endometrial thickness variations in natural cycles. Although it cannot be excluded that some variations could occur in the endometrial thickness at the same days of different cycles, it is unlikely that the natural variations could significantly affect the study results. Indeed, women enrolled in the study were normally cycling for at least 6 months; in all cases, the second measurement was lower than the first one, and the percentage reduction in endometrial thickness in women receiving the combined treatment (group A) was more than three times greater than observed in women treated with only desogestrel (group B) and two times greater than those treated with danazol (group C).

To demonstrate that a synergistic effect would exist in group A, a raloxifene-only arm would be useful; however, the study design did not consider raloxifene-only treatment because the rationale of the study was to improve the effectiveness of oral contraceptives as pretreatment for hysteroscopic surgery, not to evaluate vaginal raloxifene as an alternative treatment. Moreover, vaginal raloxifene alone does not block ovulation, so it was not considered as the sole treatment. Based on results of the study, we are planning to investigate the effects of vaginal raloxifene alone.

The combined treatment was well tolerated by all of the women, and no side effects were reported. About 10% of the women treated with desogestrel complained of bleeding; we can speculate that the hypotrophic effect of raloxifene can explain the lack of endometrial bleeding.

Finally, the proposed treatment has an additional advantage of lower cost, as it is much cheaper than treatment with GnRH-a.

In conclusion, oral desogestrel plus vaginal raloxifene provides a fast, low-cost, and satisfactory preparation of the endometrium for operative hysteroscopy. Satisfactory endometrial preparation can be obtained with only 10 days of treatment, and this improves acceptability and scheduling for hysteroscopic treatment.

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