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ORIGINAL ARTICLE

Nomegestrol acetate versus combined oral contraceptive as rapid endometrial preparation for operative hysteroscopy: a prospective randomised pilot study

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Introduction

Hysteroscopy is now the established "gold standard" for the assessment and treatment of intrauterine pathology such as fibroids, polyps, synechiae, septa and endometrial resection and/or destruction, and is regarded as a safe, acceptable and well-tolerated procedure [1–5]. 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 [6–9]. For these reasons, the days immediately after menstruation are the best period for hysteroscopy. Scheduling surgery during the early follicular phase is not always possible, so several drugs have been proposed to reduce endometrial thickness, intra-operative bleeding, surgical difficulties and duration of surgery [6, 10, 11]. Even if preoperative treatment with gonadotropin-releasing hormone analogues (GnRH-a) or danazol for 2 or 3 months has been recommended to remove large intramural sub-mucous myomas or perform endometrial resection [9], they are not as often used for procedure preparation especially in case of minor hysteroscopy. GnRH-a result in a state of temporary menopause and are expensive, while danazol induces unfavourable side effects including weight gain, growth of hair, acne and general malaise [12]. Several studies have reported that gestrinone also is capable of reducing uterine volume, menorrhagia and endometrial thickness [13–15].

A limiting factor existing among the previous treatments is the long time required to reduce the endometrium. Recently, to speed up endometrial preparation, other original treatments have been proposed as oral progestins and vaginal raloxifen [16], nomegestrol acetate [17] and oral contraceptives [18], and they obtained good results in terms of preparation of the endometrium, cost and acceptability. Shortening the preparation time before surgery may improve patient compliance and work organization [19].

The aim of this prospective, randomised study was to compare the effectiveness of nomegestrol acetate versus combined oral contraceptive treatments as short preoperative endometrial preparation before hysteroscopic surgery.

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Materials and methods

Between February and July 2011, 42 pre-menopausal women were prospectively enrolled in the study. The inclusion criteria were: hysteroscopic diagnosis of endocavitary pathologies and regular menstrual cycle rhythms for the previous 6 months. Exclusion criteria were: age <18 and >45, hormonal therapies in the previous 12 weeks, previous uterine surgery, concomitant adnexal pathologies, endometriosis and cardiovascular, hepatic or renal impairment.

The study protocol was conformed to the ethical guidelines of the 1975 Helsinki Declaration, and the Institutional Review Board of the department approved it. Written informed consent was obtained from each female patient upon enrolment.

Before treatment (day 14 of the menstrual cycle), each woman received a trans-vaginal ultrasound (TVUS) evaluation to measure endometrial thickness, ovarian size and number of ovarian follicles. On day 1 of the menstrual cycle, patients were randomised to receive 3 weeks of therapy with 5 mg of nomegestrol acetate daily (group A, n=21) or 20 μg of ethinyl estradiol/75 mg gestodene daily (group B, n=21). Allocation to one of the two parallel treatment groups (21 in each) was performed using the SPSS v 17.0 randomisation program (SPSS Inc., Chicago, IL). Both surgeons were not aware of the therapy at the time of surgery.

Surgery was performed the day after the last assumption of hormonal medicament. Patients were hospitalized the same day of surgery. Preoperative exams as TVUS, ECG and routine blood test were performed in the early morning, and side effects experienced by the patients during treatment were recorded. The effectiveness of the therapy was intraoperatively evaluated by assessing the visibility of the uterine cavity, the endometrial features, the difficulty of the procedure and the success of surgery. Hormonal effects of the studied drugs are evaluated by assessing endometrial thickness and number and size of ovarian follicles.

Operative hysteroscopy was performed under general anaesthesia by two expert endoscopic surgeons (L.M. and L.M.), using a bipolar resectoscope. More specifically, after the tenaculum was placed and the cervix dilated to Hegar 8, the procedure used a 22-Fr continuous-flow resectoscope fitted with a cutting loop electrode at a power setting of 120-W cutting current. A sterile saline solution was used for uterine distension.

To evaluate the visibility, we assigned a score from 0 to 1 for each of the five following parameters: left ostium, right ostium, fundus, anterior wall and posterior wall. A score from 0 to 2 was classified as “bad visibility”, a score of 3 was classified as “moderate visibility” and a score from 4 to 5 was rated as “good visibility”.

The endometrial features assessed by direct vision during hysteroscopic procedure were classified according to Baggish and Barbott as: “atrophic” when the endometrium was thin, regular and pale; “normal” when the endometrial appearance was compatible with the proliferative phase; “normal with small hyperplastic areas” when only small focused areas of thickness were present and “hyperplastic” when a diffuse thick polypoid endometrium was found [6].

The difficulty of the procedure and the success of surgery were evaluated by the surgeon marking two separated 100-mm visual analogue scale from 0 (minimum) to 100 (maximum). One month after surgery, women underwent a diagnostic hysteroscopy to confirm the completeness of the treatment.

Statistical analysis was performed with SPSS 11 (SPSS, Chicago, IL). Data were expressed as mean±SD (range) or as number (percent) of cases. To compare data between the two groups, a Student's t test was used for parametric data and the Mann–Whitney test for non-parametric data. Dichotomous variables were analysed with the χ^2 test and the Fischer exact test, when appropriate. A P value of <0.05 was considered statistically significant.

Table 1 Patients' main characteristics

	Group A (n=21), NOMAC	Group B (n=21), EE/GSD	P value
Age (median, SD; years)	35±6	37±7	0.35
BMI (median, SD; kg/m^2)	22±2	21±3	0.22
Parity (median, range; number)	1 (0–2)	1 (0–2)	0.8

NOMAC 5 mg nomegestrol acetate, *EE/GSD* 20 μg ethinyl estradiol/75 mg gestodene, *BMI* body mass index

Results

Between February to July 2011, we identified 42 pre-menopausal women who were consecutively enrolled in

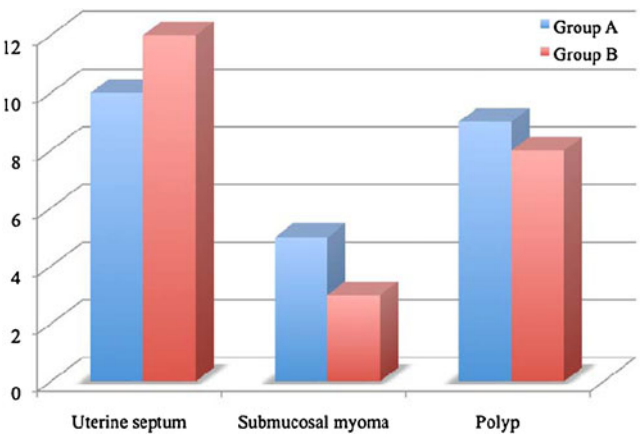

Fig. 1 Prevalence of endocavitary pathologies. NOMAC: 5 mg nomegestrol acetate; EE/EGST: 20 μg ethinyl estradiol/75 mg gestodene

Table 2 Endometrial and follicle pattern before and after treatment

	Group A, NOMAC	Group B, EE/GSD	*P* value (inter-group)
Endometrial thikness before treatment (median, SD; mm)	7.2±1.2	6.9±0.9	0.08
Endometrial thikness after treatment	4.6±2.0	3.9±0.2	0.001
P value (intra group)	.001	.0001	
Mean diameter of dominant follicle before treatment (median, SD; mm)	14.8±0.4	15.0±0.4	0.07
Mean diameter of dominant follicle after treatment (median, SD; mm)	9.5±1.0	6.4±0.9	0.0001
P value (intra group)	0.0001	0.0001	

NOMAC 5 mg nomegestrol acetate, *EE/GSD* 20 μg ethinyl estradiol/75 mg gestodene

the study. The two study groups were similar for age, parity and body mass index (BMI) (Table 1), as well as for prevalence of uterine endocavitary pathologies (Fig. 1). No differences were retrieved at enrolment between groups in terms of endometrial thickness (group A, 7.2±1.2 mm; group B, 6.9±0.9 mm; P=0.08) and mean follicular diameter (P=0.07) (Table 2).

The reduction in endometrial thickness in group B (EE/GSD) was statistically significantly greater than in group A (NOMAC) (P<0.001) as well as the ovarian dominant follicle mean diameter (P<0.0001) (Table 2).

An assessment of the endometrium during surgery showed that all patients responded to the treatment with a significant difference between groups. Surgeon satisfaction in terms of endometrial preparation was higher for women of group B compared with group A (83.4 % "good visibility" group B vs 57.5 % group A) (Table 3). At hysteroscopy, the endometrial mucosa appeared to be very thin, hypotrophic, regular and pale in all of the women of the two groups. However, we observed some cases of "hyperplastic endometrial features" in group A; the endometrial surface was high and irregular, with areas of stromal oedema and glandular development (Fig. 2).

Difficulty to perform hysteroscopic surgery was greater in group A, mean 5 (range 3–9), than with group B, mean 2 (range 0–6), P<0.001. No significant differences emerged in relation to time taken for cervical dilatation, operating time, postoperative complications and completeness of surgery.

Table 3 Visibility score

Visibility score	Group A (n=21), NOMAC	Group B (n=21), EE/GSD	*P* value
Bad visibility	3 (14 %)	0 (0 %)	0.06
Moderate visibility	6 (28 %)	3 (14 %)	0.08
Good visibility	12 (58 %)	18 (86 %)	0.002

NOMAC 5 μg nomegestrol acetate, *EE/GSD* 20μg ethinyl estradiol/75 mg gestodene

Discussion

The success of hysteroscopic surgery is related to good and constant visibility during the procedure, bearing in mind that the surgical field is extremely limited and very often narrowed by endometrial thickness and by the endouterine pathology itself [20]. With a prepared endometrium, the uterine cavity became easier to explore, and endocavitary pathologies are easy to detect and treat. A preoperative pharmacological treatment for endometrial mucosa thinning is recommended to achieve the best conditions of visibility [21, 22]. The efficacy of GnRH agonists and danazol administration for thinning the endometrium before hysteroscopic surgery has been reported by several investigators [9, 12]. However, they are expensive drugs with many side effects, and they require a long time to thin the endometrium.

Oral contraceptives and progestogens have been also proposed as a rapid treatment before hysteroscopic surgery, but only few randomised data are available to assess their effectiveness as endometrial thinning agents [15–18].

Shortening the preparation time before surgery may increase patients' compliance and improve work organization. The results of this study demonstrate that a short treatment

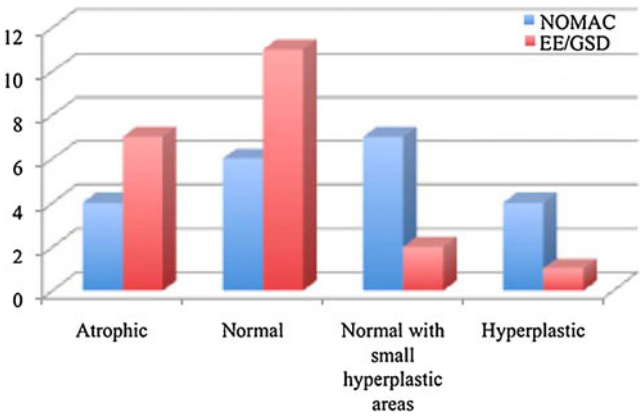

Fig. 2 Endometrial features during hysterosocopy. *NOMAC* 5 mg nomegestrol acetate, *EE/EGST* 20 μg ethinyl estradiol/75 mg gestodene

with both 5 mg of nomegestrol acetate and 20 μg of ethinyl estradiol/75 mg gestodene before operative hysteroscopy provides a very fast and effective endometrial suppression.

According to TVUS evaluation, the endometrial features under direct hysteroscopic exploration of the cavity demonstrated that endometrial preparation was better in group B than in group A. Indeed, all group B women had very thin, pale and regular endometrium. In contrast, in group A in some cases, the endometrial surface was high and irregular, with areas of stromal oedema and glandular development probably related to the progestin-induced decidualization. Accordingly, surgeon satisfaction was significantly greater for group B. Side effects, owing to the short period over which the two drugs were administered, were infrequent in both treatments, without significant differences between the two groups. Limitations of this trial were the limited number of cases and the presupposition that no variation occurs in endometrial features in the natural menstrual cycle; nevertheless, it is unlikely that the natural variations could significantly affect the study results.

Conclusions

In conclusion, our data suggest that both treatments, used for a brief period, are good ways to prepare the endometrium before hysteroscopic surgery. Satisfactory endometrial preparation can be obtained with only 3 weeks of treatment, and this improves acceptability and scheduling for hysteroscopic treatment. However, the endometrial preparation with 5 mg nomegestrol acetate appears to be less comfortable for the surgeon in terms of visibility of the uterine cavity than 20 μg ethinyl estradiol/75 mg gestodene endometrial preparation. No differences in completeness of surgery, operative time and intraoperative complications were noticed.

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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