The use of nomegestrol acetate in rapid preparation of endometrium before operative hysteroscopy in pre-menopausal women

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ABSTRACT

The presence of a thin endometrium has an important role in allowing the best conditions for hysteroscopic surgery. Here, we explored the efficacy of a 14-day administration of nomegestrol acetate, a progestogen with high progestogen potency effects, in rapid endometrial preparation to operative hysteroscopy.

A total of 86 fertile women selected for operative hysteroscopy received for 14 days either 5 mg day−1 of nomegestrol acetate (n = 43; group A) or 4 mg day−1 of folic acid (n = 43; group B), starting on day 1 of the subsequent menstrual cycle. Before treatments on days 12–14 of the menstrual cycle, all patients underwent endometrial thickness measurement; ultrasonography of the ovaries to measure the appearance of a dominant follicle; diagnostic hysteroscopy with endometrial biopsy; plasma estradiol (E2), progesterone (P), luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels measurements. On the day of surgery, patients repeated endometrial and ovarian ultrasonography and, E2, P, LH and FSH measurement.

At enrolment, endometrial thickness, mean follicular diameter and E2, P, LH and FSH concentrations did not differ between groups. At the time of operative hysteroscopy (i.e., after 14 days' treatment) group A, but not group B, showed significant (all P < 0.001) reduction of endometrial thickness, mean diameter of dominant follicle, E2, P and LH concentrations. Endometrial preparation was judged more effective in group A than B, since the endometrial mucosa in all of the women of group A appeared to be very thin, hypotrophic, regular and pale. In conclusion, administration of nomegestrol acetate was effective in reducing endometrial thickness, also acting on the hypothalamus–pituitary–ovarian axis, thus allowing highly favourable operative hysteroscopic conditions.

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1. Introduction

Blind sampling with dilatation and curettage of the uterine cavity was, until recently, a routine procedure in gynaecology. With the advent of advanced optics, safer distension techniques and adequately trained surgeons, hysteroscopy is now the established ‘gold standard’ for the assessment and management of intrauterine pathology, and is regarded as a safe, acceptable and well-tolerated procedure [1–4]. Its therapeutic indications extend to resection of submucous myomas, fibroid and polyps, division of intrauterine septum and intrauterine synchieae, endometrial resection and ablation, directed biopsy and removal of a lost intrauterine device.

Hysteroscopic surgery has changed the surgical landscape, reducing procedural and postoperative morbidity, with clear benefits for patients [1].

In fertile women, preoperative pharmacologic treatment has been recommended to reduce endometrial thickness, intraoperative bleeding, surgical difficulties and duration of surgery [5–7]. Among the several drugs proposed in the past years, gonadotrophin releasing hormone (GnRH) analogues have been suggested for removal of large intramural submucous myomas or endometrial resection [8], due to their effect in thinning the endometrium. However, they are not as often used for procedure preparation, especially in cases of ‘minor’ hysteroscopy surgery, because they result in a state of temporary menopause and, not last, due to the cost [9]. Further, danazol, a medication usually used for endometriosis treatment, at a daily dosage of 400 mg orally for 6 weeks, is able to induce endometrial atrophy, reducing
consequently the thickness of the endometrium as well as its vascularisation. However, despite it being less expensive than GnRH analogues, its anti-oestrogenic activity and androgenic propensity could induce unfavourable side effects including weight gain, growth of hair, acne and general malaise [9].

Another limiting factor among existing treatments for endometrial preparation is the long time required to efficiently reduce the endometrium; other than that, they could be costly and be accompanied by clinical drawbacks. The search for a new treatment able to overcome most of the previously encountered disadvantages is mandatory to improve patient acceptability of the hysteroscopic procedure and work organisation for medical staff.

Nomegestrol acetate, a progestogen designed to have no androgenic or oestrogenic actions and high progestogen potency effects, shares several pharmacological properties that can be considered useful in the pre-surgery endometrial preparation [10,11]. Indeed, studies have shown that nomegestrol acetate has little effect on carbohydrate, lipid or hepatic metabolism, and it is able to reduce endometrial thickness, uterine volume and menorrhagia without significant side effects [10–14].

In the present study, we evaluated whether preoperative oral administration of nomegestrol acetate in women with endometrial polyps is able to reduce endometrial thickness and difficulties in hysteroscopic surgery.

2. Materials and methods

Between March 2007 and November 2008, we identified 110 pre-menopausal women, who had reported regular menstrual cycle rhythms for the previous 6 months, and in whom sonohysterosalpingoscopy (saline-infusion sonohysterography, SIS) and diagnostic hysteroscopy with endometrial biopsy, performed on days 12–14 of the menstrual cycle, indicated the presence of endometrial polyps (Table 1). The following exclusion criteria were applied: presence of fibroids; hormonal therapies in the previous 8 weeks; uterine and/or concomitant adnexal pathologies; cardiovascular, hepatic or renal impairment; and any medical condition that would have increased the surgical risk [3]. The study also excluded all cases where the presence of adhesions, septa or uterine position prevented a reliable endometrial thickness measurement, or where no dominant follicle was detected. Therefore, 24 women were excluded for the following reasons: fibroids (n = 7); concurrent hormonal therapies (n = 3); uterine and/or concomitant adnexal pathologies (n = 2); cardiovascular (n = 3) or hepatic (n = 1) impairment; adhesions (n = 3); septa (n = 2) or uterine position (n = 1); and the absence of dominant follicle (n = 1). The data from the remaining 86 were considered for the study. The Institutional Review Board approved the study, and all patients received detailed information about the study and the surgical procedure, to which they gave their consent.

2.1. Study protocol

The women became eligible for treatment sequentially, and as such they were randomly assigned to receive for 14 days, starting on day 1 of the subsequent menstrual cycle, 5 mg day−1 per 14 days of nomegestrol acetate (Lutenyl, Theramex, Italy) administered each day by oral route at bedtime (group A) or 4 mg day−1 per 14 days of commercially available folic acid (Folanemin, Theramex, Italy) by oral route at the same time (group B), using the sequential treatment assignment with balancing for prognostic factors [15]. The procedure ensures treatment groups of equal size (n = 43 for both nomegestrol acetate and folic acid treatments) as well as the balance across the treatments of the effects of prognostic factors [15]. The person responsible for patient selection and drug dispensing was blind to whether the next patient would receive nomegestrol acetate or folic acid. A flowchart of the study is presented in Fig. 1.

At enrolment (on days 12–14 of the menstrual cycle), all patients underwent SIS evaluation of their uterine cavity with endometrial thickness measurement; ultrasonography of the ovaries to measure the appearance of a dominant follicle; diagnostic hysteroscopy with endometrial biopsy; blood sampling for measurements of plasma estradiol (E2), progesterone (P) luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels. On the day of surgery, patients repeated ultrasound exam to measure endometrial thickness and ovarian features and blood sampling for measurements of plasma E2, P, LH and FSH levels.

2.2. Hormone measurements

Hormone (FSH, LH, E2 and P) measurements were performed with commercially available kits (Diagnostic Systems Laboratories), with intra- and inter-assay coefficients of variation determined by the manufacturer with routine quality control material <10%.

2.3. Saline-infusion sonohysterogram (SIS)

Patients were placed in the dorsal lithotomic position, a standard bivalve speculum was inserted and, the uterine cervix was cleansed with an antiseptic solution (povidone–iodine). A paediatric Foley catheter was inserted into the uterine cavity through the cervical os until it reached the fundus and the balloon of the catheter was inflated with 2 ml of normal saline solution. The speculum was then withdrawn and a transvaginal ultrasound (5 MHz) probe introduced. Up to 20 ml of sterile saline solution was infused into the uterine cavity; 5–10 ml usually proved to be sufficient to distend the cavity, and the distended cavity was observed directly by sonography. The same volume solution (20 ml) was then gradually flushed into the uterine cavity via the opening connected to the inner lumen allowing visualisation of endometrial diseases. Afterwards, gentle suction via the same opening was applied to recover the fluid. The location and size of any uterine abnormalities were noted. The anterior and posterior endometrial thicknesses were measured as the maximal distance between the two myometrial interfaces in a longitudinal scan, ensuring avoidance of the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Anthropometric and clinical findings related to women belonging to group A (nomegestrol acetate) and group B (placebo). Data are presented as mean ± SD. BMI: body mass index.</th>
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<tbody>
<tr>
<td></td>
<td>Group A (n = 43)</td>
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<tr>
<td>Age</td>
<td>29.3 ± 6.7</td>
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<tr>
<td>BMI</td>
<td>22.5 ± 1.4</td>
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<td>Parity</td>
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<td>Endometrial polyps diameter (mm)</td>
<td>1.8 ± 0.5</td>
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<td>Endometrial thickness (mm)</td>
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<td>After treatment</td>
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<td>Ovarian follicle diameter (mm)</td>
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<td>After treatment</td>
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<td>Hormone concentrations at enrolment</td>
<td></td>
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<tr>
<td>LH (IU l−1)</td>
<td>5.23 ± 0.33</td>
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<tr>
<td>FSH (IU l−1)</td>
<td>4.7 ± 0.6</td>
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<td>E2 (pg ml−1)</td>
<td>507 ± 14.7</td>
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<tr>
<td>P (ng ml−1)</td>
<td>7.5 ± 1.7</td>
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<tr>
<td>Hormone concentrations after treatment</td>
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<tr>
<td>LH (IU l−1)</td>
<td>3.43 ± 0.11b</td>
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<tr>
<td>FSH (IU l−1)</td>
<td>6.1 ± 0.3a</td>
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<tr>
<td>E2 (pg ml−1)</td>
<td>21.1 ± 5.1</td>
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<tr>
<td>P (ng ml−1)</td>
<td>1.9 ± 0.3b</td>
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a,c,e,g,i,k: P > 0.000 vs value at enrolment.
b,d,f,h,j,l: P > 0.05 vs value at enrolment.
Fig. 1. Flow diagram of the clinical trial.

Fig. 2. Changes of circulating levels of E2, P, LH, and FSH before and after 14 days treatment of nomegestrol acetate (group A, gray bars) or placebo (folic acid, group B, open bars).
2.4. Diagnostic hysterectomy

Office hysterectomy was performed using the vaginoscopy approach, with office hysterectomy using Telescope 2.9 mm (HOP-KINS II Forward-Oblique Telescope 30°; Karl Storz, Tuttlingen, Germany) and continuous flow sheath. The uterine cavity was distended with physiological solution and irrigated using an electronic irrigation pump (Hysteromat; Karl Storz®, Karl Storz, Tuttlingen, Germany). Examination was performed as an office procedure, without anaesthesia or cervical dilatation. During diagnostic hysteroscopy, all patients underwent endometrial biopsy for histological classification of endometrial tissue and to exclude any possible malignancy [16].

2.5. Operative hysterectomy

Patients were hospitalised the same day of surgery that was performed in the morning, 10–12 h after the last assumption of nomegestrol or placebo. Electrocardiogram and routine blood tests were performed on the day of surgery, and side effects experienced by patients during treatment were recorded.

Operative hysteroscopy was performed in the inpatient day surgery under general anaesthesia by members who had comparable levels of experience and who were blind to the preoperative treatment allocated. After the cervical canal was dilated to a Hegar dilator of size 10 or 11 mm, a rigid monopolar resectoscope with a 10-mm outer sheath diameter and 30° forward-oblique lens fitted with a cutting loop electrode at a power setting of 100 W cutting current was used (Karl Storz GmbH, Tuttlingen, Germany). The uterine cavity was distended with 1.5% glycine solution at an insufflation pressure of 80–100 mm Hg, with careful monitoring of fluid balance. The first step in the 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.

At the time of surgery, endometrial appearance was assessed by direct vision and was classified, according to criteria reported by Baggish and Barbot [17], as ‘normal’ if compatible with a normotrophic endometrium; ‘hypotrophic with normotrophic areas’ if not completely atrophic; and ‘atrophic’ if completely atrophic. An endometrial sample was taken from each patient by resection of both cornua, tubal ostia and anterior and posterior walls.

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2.6. Outcomes measure

We compared outcome measures between days 12 and 14 of the untreated cycle and at the same time in the treated cycle. Outcome measures were changes before and after treatments of: (i) endometrial thickness and ovarian follicle dimensions; (ii) circulating concentrations of pituitary (LH and FSH) and ovarian (E2 and P) hormones; and (iii) endometrial appearance both at diagnostic and operative hysteroscopy. Details regarding the time required for each cervical dilatation and the duration of surgical procedure (from the insertion to the removal of the resectoscope); surgical associated side effects (postoperative complications occurring during from the termination of surgery to discharge 4–5 h after surgery); and side effects experienced by patients during treatment were also recorded. Intra-operative bleeding was defined, as ‘light’ when bleeding did not interfere with surgery, ‘moderate’ when bleeding required the coagulation of vessels and ‘severe’ when haemorrhage required immediate suspension of hysteroscopy. Measurements of inflow, outflow and amount of distension liquid absorbed by the patient were taken meticulously.

At the time of surgery, the surgeon’s satisfaction with the endometrial preparation was evaluated by asking the surgeons who were unaware of the treatment to score the degree of satisfaction with the preparation by making a 10-cm visual analogue scale from 0 (minimal) to 10 (optimal). An unbiased and independent person not involved in the procedures of the study itself documented and scored differences between the two treatments.

2.7. Statistical analysis

All data were analysed with Prism software (GraphPad Software Inc., San Diego, CA, USA), and were expressed as mean ± SD (range) or as number (%) of cases. The Kolmogorov–Smirnov test was used to evaluate whether values had a Gaussian distribution, in order to choose between parametric and non-parametric statistical tests. To compare data between the two groups, Student’s t-test was used for parametric data and the Mann–Whitney test for non-parametric data. Dichotomous variables were analysed with the χ² test and the Fisher’s exact test, when appropriate. P < 0.05 was considered statistically significant.

3. Results

The two study groups were similar for age, parity and body mass index (BMI), as well as for incidence and volume of uterine cavity pathologies (P > 0.05) (Table 1). Nevertheless, no differences were retrieved at enrolment between groups in terms of endometrial thickness (group A: 6.4 ± 1.0 mm; group B: 6.0 ± 1.2 mm; P = 0.1); mean follicular diameter (group A: 15.2 ± 0.9 mm; group B: 14.8 ± 1.2 mm; P = 0.08) and; concentrations of E2 (group A: 98.7 ± 14.7 pg ml⁻¹; group B: 101.3 ± 16.6 pg ml⁻¹; P = 0.44). P (group A: 7.5 ± 1.7 ng ml⁻¹; group B: 8.2 ± 2.3 ng ml⁻¹; P = 0.11); LH (group A: 5.23 ± 0.33 IU l⁻¹; group B: 5.12 ± 0.21 IU l⁻¹; P = 0.07); and FSH (group A: 4.7 ± 0.6 IU l⁻¹; group B: 4.8 ± 0.4 IU l⁻¹; P = 0.37) (Table 1; Fig. 2).

On the contrary, significant changes were observed after 14 days of treatment with nomegestrol acetate (group A) or placebo (folic acid, group B), since mean endometrial thickness after treatment was significantly (P < 0.001) smaller in group A (3.9 ± 0.2 mm) than in group B (6.2 ± 0.6 mm), as well as the mean diameter of the dominant follicle (group A: 9.0 ± 0.8 mm; group B: 15.0 ± 1.4 mm; P < 0.0001). Moreover, whilst no difference was retrieved in endometrial thickness and follicle diameter in group B before and after placebo assumption, in women belonging to group A, there was a significant (both P < 0.001) reduction of both parameters from enrolment to the time of operative hysteroscopy (i.e., after 14 days treatment with nomegestrol acetate) (Table 1; Fig. 1).

With respect to hormones, the concentrations of E2 (21.1 ± 5.1 pg ml⁻¹; P = 1.9 ± 0.3 ng ml⁻¹) and LH (3.43 ± 0.11 IU l⁻¹) were significantly (P = 0.000) lower in group A than in group B (E2: 101.4 ± 15.2 pg ml⁻¹; P: 7.9 ± 0.4 ng ml⁻¹; LH: 5.22 ± 0.31 IU l⁻¹), whilst FSH levels were significantly (P = 0.000) higher (6.1 ± 0.31 IU l⁻¹) in group A than group B 4.8 ± 0.6 IU l⁻¹ (Table 1; Fig. 1). Again, in group B, no difference was retrieved in hormone levels before and after treatment, whilst women belonging to group A had significant (all P = 0.001) variations of all hormonal values after 14 days of nomegestrol acetate assumption (Table 1; Fig. 2). Women had elevated levels of serum P in the control cycle on days 12–14, which were suppressed with the nomegestrol acetate in the treatment cycle on days 12–14 (Table 1; Fig. 2).

Table 2 refers to data collected at hysteroscopy. At enrolment, there was good correlation among histological examination, anamnestic data regarding the last menstrual cycle and, visual
shown compared with placebo. The effectiveness of the proposed favourable operative condition for hysteroscopic surgery was with visual inspection, a significant effect in achieving a highly ness, as shown by ultrasonographic evaluation and, in accordance for 14 days was able to obtain a reduction of endometrial thick-
hysteroscopy. We found that administration of nomegestrol acetate in rapid endometrial preparation to operative the case of danazol, activities[9].

4. Discussion

The presence of a thin endometrium has an important role in allowing the best operative conditions in hysteroscopic surgery and, for this reason, diagnostic or operative procedures are scheduled in the immediate post-menstrual phase, as the most favourable physiological condition associated with reduced endometrial thickness. Due to the difficulties often encountered in reliably arranging surgery for this time, various hormonal agents have been used to reduce endometrial thickness [9]. The rationale of their use is based on the ability to reduce endometrial growth and vascularity, thus causing endometrial atrophy, due to their anti-oestrogenic, as in the case of GnRH analogues, or androgenic, as in the case of danazol, activities [9].

In the present study, we explored the efficacy of nomegestrol acetate in rapid endometrial preparation to operative hysteroscopy. We found that administration of nomegestrol acetate for 14 days was able to obtain a reduction of endometrial thickness, as shown by ultrasonographic evaluation and, in accordance with visual inspection, a significant effect in achieving a highly favourable operative condition for hysteroscopic surgery was shown compared with placebo. The effectiveness of the proposed treatment would rely on the fact that nomegestrol acetate is a progesterational molecule that binds almost exclusively to the progestosterone receptor and does not interfere with the other steroid receptors, thus avoiding androgenic, oestrogenic or glucocorticoid side effects [10–14]. Indeed, nomegestrol acetate is one of the progstins possessing methyl groups in the 19 position, which confers upon it no oestrogenic activity [18,19], bind properties for oestrogens receptor [20,21]. Nevertheless, nomegestrol acetate is also able to block the enzymes involved in oestradiol biosynthesis (sul- phatase, 17-hydroxysteroid dehydrogenase) [22,23] and, simultaneously, to reduce the cellular level of oestrogens receptor (ER) mRNA by decreasing the transcription of the ER gene [19,20,22–25].

The present findings and our data related to nomegestrol acetate ability in lowering endometrial thickness together would suggest that the activity of nomegestrol acetate is mainly directed on the endometrial target. However, in the present study, we found that the administration of nomegestrol acetate was also associated with changes in the activity of the hypothalamus–pituitary–ovarian axis, since its administration was associated with the reduction of LH, E2 and P concentrations, and inhibition of folliculogenesis. These data confirm previous findings on the antiovulatory ability of nomegestrol acetate that would act at the pituitary level where the progesterone receptor is expressed only in gonadotroph cells [26]. The anti-gonadotropic activity of nomegestrol acetate, together with its anti-oestrogenic effect locally on the endometrium, can help us in explaining the concordance between visual appearance at hysteroscopy and biochemical (changes in hormones related to ovulation) and biophysical (ultrasonographic data related to changes in endometrial thickness) measures. Indeed, we found that the endometrial mucosa of women treated by nomegestrol acetate appeared to be very thin, hypotrophic, regular and pale. This finding is not surprising, since it was already reported that the endometrium of women in whom nomegestrol acetate inhibited ovulation had features similar to those depicted by the present study. The presence of a thin endometrium may also explain the low prevalence of bleeding in patients treated by nomegestrol acetate undergoing hysteroscopy preparation. Thus, the appreciable reduction of endometrial vascularity obtained using nomegestrol acetate may also contribute to lowering the risk of operative liquid absorption and, consequently, lower risk of electrolytic alterations. The possibility of existing inter-patient variation of pre-treatment endometrial thickness altering the comparison of treatment effects, thus representing a limitation of the study, was overcome by the visual appraisal obtained at diagnostic hysteroscopy and the meticulous measurement of endometrial thickness performed during SIS in the pre-treatment period the month before surgery. Although it cannot be excluded that some variations could occur in the endometrial thickness in the same patient at the same days of different cycles, it is unlikely that the natural variations could significantly affect the study results.

In conclusion, our data suggest that pre-surgical treatment with nomegestrol acetate could provide a fast, satisfactory and low-cost preparation of the endometrium before surgery, thus improving surgical performance and patients’ compliance. The mechanisms by which nomegestrol acetate induces this effect may be related to a suppressive effect on follicular development and anovulation through an inhibitory regulation of GnRH, participating in the control of gonadotropin release also at the pituitary level, as well as suppressing of endometrial growth as seen by transvaginal sonography, which accounts for the reduction in endometrial thickness and bleeding at hysteroscopy.

References


