European Journal of Obstetrics and Gynecology 299 (2024) 213–218

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Full length article

The use of oral nomegestrol acetate/estradiol in rapid and random start preparation of endometrium before office hysteroscopic polypectomies: A multicenter, prospective, randomized controlled trial

Andrea Etrusco [a,b], Vittorio Agrifoglio [a,b], Vito Chiantera [b,c], Antonio D'Amato [d,*], Giuseppe Russo [e], Tullio Golia D'Augè [f], Andrea Giannini [g], Gaetano Riemma [h], Basilio Pecorino [i], Federico Ferrari [j], Antonio Simone Laganà [a,b], Marco Monti [f]

[a] Unit of Obstetrics and Gynecology, "Paolo Giaccone" Hospital, 90127 Palermo, Italy
[b] Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, 90133 Palermo, Italy
[c] Unit of Gynecologic Oncology, National Cancer Institute – IRCCS – Fondazione "G. Pascale", 80131 Naples, Italy
[d] Department of Interdisciplinary Medicine (DIM), Unit of Obstetrics and Gynecology, University of Bari "Aldo Moro", Policlinico of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy
[e] EPFL, 1015 Lausanne, Switzerland
[f] Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Policlinico Umberto I, 00161 Rome, Italy
[g] Unit of Gynecology, Sant'Andrea Hospital, Department of Surgical and Medical Sciences and Translational Medicine, Sapienza University of Rome, 00189 Rome, Italy
[h] Department of Woman, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", 80138 Naples, Italy
[i] Obstetrics and Gynecology Division, Umberto I Hospital, Kore University of Enna, 94100 Enna, Italy
[j] Department of Clinical and Experimental Sciences, University of Brescia, 25136 Brescia, Italy

ARTICLE INFO

Keywords:
Hysteroscopy
Preoperative treatment
Endometrial polyps
Combined oral contraceptives
Nomegestrol acetate
Estradiol

ABSTRACT

Objective: To evaluate the use of oral nomegestrol acetate/estradiol in random start rapid preparation of endometrium before office hysteroscopic polypectomy.
Study design: Multicenter, prospective, randomized controlled trial.
Setting: University hospitals.
Participants: 80 adult women undergoing office hysteroscopic polypectomy between January 2023 and March 2024 were randomized to intervention (n = 40) or control (n = 40). Exclusion criteria included the presence of endouterine pathology other than endometrial polyps solely.
Methods: Subjects in the intervention group were treated with oral nomegestrol acetate/estradiol 1.5 mg/2.5 mg/day started taking the drug from an indefinite time in the menstrual cycle (random start) for 14 days. Subjects in the control group did not receive any pharmaceutical treatment and underwent polypectomy between days 8 and 11 of the menstrual cycle.
Results: On the day of the procedure, the difference in pre- and post-office hysteroscopic polypectomy endometrial ultrasound thickness was statistically significant between the two groups, with endometrial thickness in both measurements being thinner for the intervention group ($p < 0.001$). In the nomegestrol acetate/estradiol-treated group, compared with the control, there was also a statistically significant difference in the physician's assessment of the quality of endometrial preparation ($p < 0.001$), the quality of visualization of the uterine cavity ($p < 0.001$), and satisfaction with the performance of the procedure ($p < 0.001$). Finally, all surgical outcomes analyzed were better in the treatment group.
Conclusion: Treatment with nomegestrol acetate/estradiol could provide rapid, satisfactory and low-cost preparation of the endometrium before office polypectomy, thus improving surgical performance and woman's compliance.
Trial registration: ClinicalTrials.gov NCT06316219.

* Corresponding author at: Department of Interdisciplinary Medicine (DIM), Unit of Obstetrics and Gynecology, University of Bari "Aldo Moro", Policlinico of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy.
E-mail address: antoniodamato19@libero.it (A. D'Amato).

https://doi.org/10.1016/j.ejogrb.2024.06.019
Received 24 April 2024; Received in revised form 2 June 2024; Accepted 9 June 2024
Available online 10 June 2024

Introduction

Over the years, there has been a change in the application of hysteroscopy. This technique that was initially conceived as a purely diagnostic procedure [1], due to its proven safeness and feasibility, is now commonly considered the gold standard to treat under direct visualization many endouterine pathologies in an office setting [2,3]. The technologies currently developed, such as miniaturization of the instruments and improvement of the optics has brought to safely perform several procedures in an office setting, causing only minimal or no women's discomfort [4]. This progresses allowed to achieve concrete benefits in terms of cost-effectiveness and enhanced productivity of physicians' as well as patient's time [5]. Although considered a safe procedure, hysteroscopy is not devoid of complications including uterine perforation, bleeding, severe pain, infection, cervical laceration, venous air embolisms, or fluid overload [6,7]. A thin endometrium makes all intrauterine maneuvers easier, ensures good visual control, reduces the operative time, increases ease of procedure, and decreases the risk of fluid intravasation [10]. Furthermore, thin endometrium is recommended to reduce intraoperative bleeding, operative difficulties, and duration of procedure. For this purpose, preoperative drug treatment may be advisable in infertile women [8]. Classically, before women undergo procedures such as hysteroscopic myomectomy, drugs like analogs of gonadotropin-releasing hormone (GnRha) have been used [9], these, given the cost and the not uncommon presence of side effects, are not suitable for endometrial preparation in women to be referred for all the hysteroscopic procedures such as office hysteroscopic polypectomies (OHP). As of today therefore, progestins or combined oral contraceptives (CoC) are preferred for this purpose [10,11]. However, to date, no conclusive data make it possible to determine which is the best preoperative treatment to use for endometrial preparation prior to hysteroscopic procedures. Another factor that for a long time limited endometrial preparation was the belief that a long time was needed to effectively shrink the endometrium and that such preparation could not be initiated at any time during the menstrual cycle. Although some experience on rapid progestin preparation has been reported to date, including the use of 5 mg nomegestrol acetate (NOMAC) in a progestin-only pill formula [12,13], these have never examined the possibility of employing a CoC and random start protocols (Fig. 1).

Considering this assumption, the aim of our study was to evaluate the use of oral combination nomegestrol acetate/estradiol (NOMAC/E2) in random start rapid preparation of endometrium before OHP.

Methods

A multicenter, prospective, randomized, parallel-group study (ClinicalTrials.gov NCT06316219) was conducted at the Unit of Gynecology and Obstetrics, Azienda Ospedaliera Universitaria Policlinico "Paolo Giaccone", Palermo, and the Unit of Gynecology and Obstetrics, Azienda Ospedaliera Universitaria Policlinico "Umberto I", Rome, between January 2023 and March 2024.

The study design is in accordance with the Declaration of Helsinki,

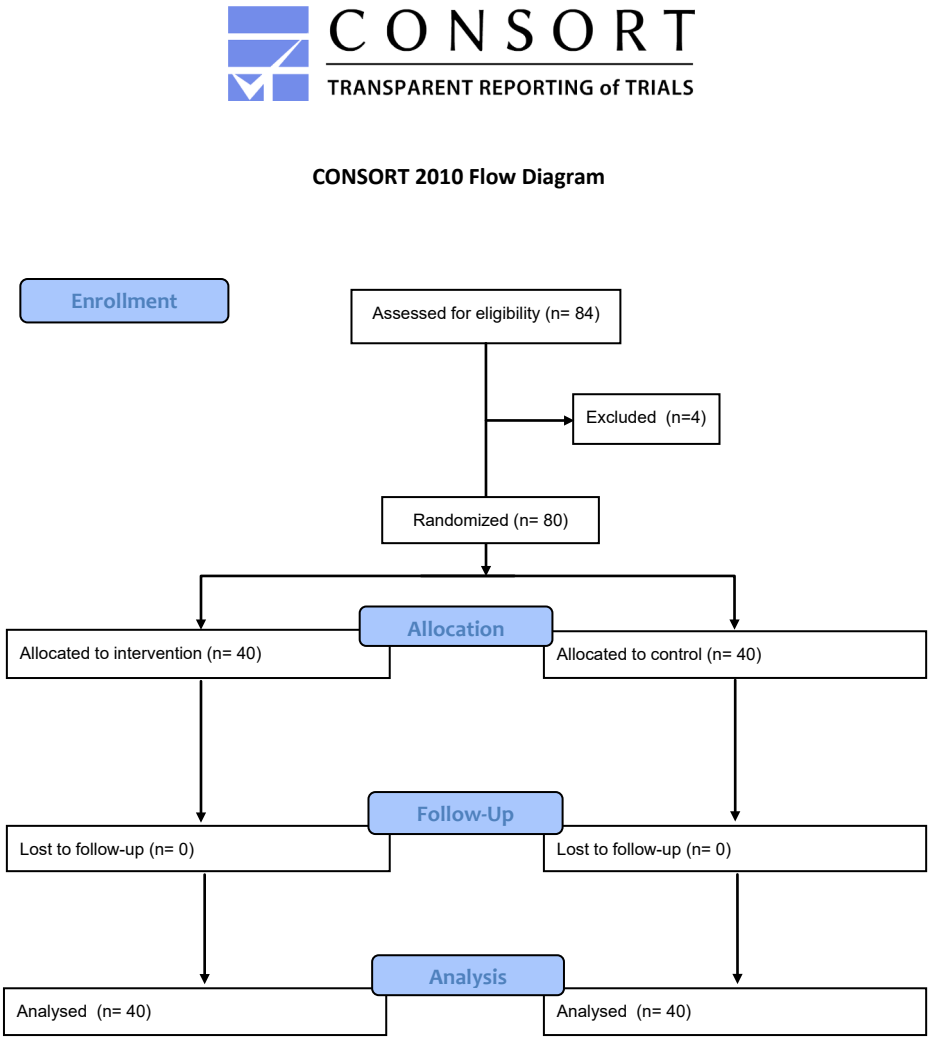

Fig. 1. CONSORT 2010 flow diagram.

complies with the guidelines of the Committee on Publication Ethics (https://publicationethics.org/) and has been approved by the Institutional Review Board of the lead university hospital (Azienda Ospedaliera Universitaria Policlinico "Paolo Giaccone", Palermo, Italy; Approval ID: 03/2023). All design, analysis, data interpretation, writing and revisions followed the CONSORT (CONsolidated Standards of Reporting Trials) [14] and SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) [15] statements, available through the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network (https://www.equator-network.org/).

Each woman who participated in this study was informed about the procedures to which they would undergo and signed a consent form for data collection for research purposes.

A cohort of 80 women was consecutively selected from a population with suspected endometrial polyp resulting from 2D/3D transvaginal ultrasound (TVS) screening for abnormal uterine bleeding (AUB). All TVS were performed during the proliferative phase of the menstrual cycle in order to obtain the most indicative images. An ultrasound measurement of endometrial thickness was performed for all women.

All women arrived at the TVS armed with the Pictorial Bleeding Assessment Chart (PBAC) correctly filled out with menstrual cycle data for the month prior to the visit.

Because the goal was to perform a single "*see and treat*" procedure in order to derive tangible cost-effectiveness benefits and improved woman satisfaction, women did not undergo a previous diagnostic hysteroscopy.

Only women with the ultrasound suspicious of endometrial polyps and who had no risk factors for taking a CoC were included in the present study. Women with (1) the presence of submucosal myomas; (2) the presence of congenital uterine malformations; (3) hormone therapy in the previous eight weeks (including the drug tested in this study); (4) adnexal or uterine diseases (including oncologic diseases) for which hysteroscopy is not the gold standard of management were excluded from enrollment.

After enrollment, women were randomly assigned in an unstratified ratio of 1:1 to two groups: the first one (intervention group) was treated with oral NOMAC/E2 2.5 mg/1.5 mg/day (Zoely, Teva B.V., Netherlands); the second one (control group) was given no pharmaceutical treatment and underwent to OHP between days 8 and 11 of the menstrual cycle. The treatment group started taking the drug from an indefinite time in the menstrual cycle (random start) for 14 days. A computer-generated randomization program was used, with random assignment to one of the two groups. Investigators were masked for treatment assignment. All women taking less than 80 % of the assigned dose of the study drug were considered noncompliant and excluded from the study. All women performed a pregnancy test (blood or urine) before the start of therapy and repeated it on the day of procedure.

Each woman had an outpatient admission, and during this any side effects (headache, bloating, nausea, heaviness of the lower limbs) reported during drug treatment were recorded.

No medication was administered either orally or vaginally to prepare the cervix before OHP. For all enrolled women, the hysteroscopic procedure was performed in the complete absence of anesthesia.

Immediately before and immediately after OHP, two new ultrasound measurements of endometrial thickness were performed.

Uterine cavity distension was induced by insufflation of saline at 50–80 mmHg using an ENDOMAT system (Karl Stortz, Tuttlingen, Germany). We used a hysteroscope consisting of a 2.9-mm Hopkins optic system with 30° oblique view, a 4.3-mm-diameter inner sheath sec. Bettocchi equipped with a channel for semi-rigid surgical instruments, and a 5-mm-diameter outer sheath sec. Bettocchi for the release of distention fluid (Karl Stortz, Tuttlingen, Germany). All procedures were performed by two single operators (A.E. and M.M.). During hysteroscopy, the physician, who was unaware of the treatment, classified the endometrium according to the criteria reported by Baggish et al. [16] into three types: (1) ''normal'' if consistent with a normotrophic endometrium; (2) ''hypotrophic with normotrophic areas'' if not completely atrophic; (3) ''atrophic'' if completely atrophic. All OHPs were performed using 5-Fr hysteroscopic micro-instruments (scissors and grasping forceps).

During the procedure, the quality of endometrial preparation, the quality of visualization of the uterine cavity, and the physician's satisfaction in performing the OHP was assessed by asking the physicians to score by scoring a 5-cm visual analog scale (VAS) from 0 (minimal) to 5 (optimal). Similarly, the woman was asked to rate the pain felt during and after the hysteroscopic procedure by assigning a score by scoring a 10-cm VAS from 0 (No pain) to 10 (unbearable).

In addition, the following data were recorded: the number and size of polyps removed; the duration of the office hysteroscopic procedure, from insertion to removal of the hysteroscope; the amount of distention medium used; the number of complete resections and whether multiple procedures were needed; the presence of intra- and postoperative complications; the presence of uterine bleeding during the procedure; the need to administer pain medication after the procedure; and the time to discharge (calculated in minutes from the end of the procedure).

During the menstrual cycle following the procedure, women were asked to complete the PBAC again to detect any differences between the two groups. Finally, a 6-month follow-up was conducted to assess any recurrence of endometrial polyps.

With an assumed rate of achievement of the primary endpoints (atrophying effect on endometrium and quality of endometrial preparation) of 90 % for NOMAC/E2, and a dropout rate of 0 %, a sample size of 90 units would achieve 80 % power to detect the treatment difference at a 5 % significance level. Statistical analysis was performed by an author (G.R.) using SPSS11 software (SPSS, Chicago, IL). In order to compare the data between the two groups, we used Student's *t*-test for parametric data and Mann-Whitney's *U* test for nonparametric data. The dichotomous variables were analyzed with the X^2 test and Fisher's exact test (when required). A p value <0.05 was considered statistically significant.

Results

We initially assessed 84 women for eligibility. However, 3 women in the treatment group did not take the drug correctly, and one patient in the control group did not perform the procedure at the centers involved in the study. Thus, we included 80 women in the intention-to-treat analysis. All participants had regular menstrual cycles. There were no significant differences between the two groups in terms of age (38.6 ± 8.6 vs 40.1 ± 7.8, p = 0.4), parity (p = 0.2), and BMI (29.1 ± 8.3 vs 28.4 ± 6.7, p = 0.7) (Table 1). None of the women treated with NOMAC/E2 reported any side effects during the days of taking the drug. There were also no statistically significant differences between the two groups in terms of endometrial thickness at the time of diagnosis (14.4 ± 4.2 vs 14.2 ± 5.5, $p = 0.8$) (Table 2). Women in the control group were treated on average at 9.1 ± 0.4 day of menstrual cycle, women in the NOMAC/

Table 1
Basic characteristics of included patients.

	Intervention group	Control group	*p*
Patients, n	40	40	
Age (years), mean ± SD	40.1 ± 7.8	38.6 ± 8.6	0.4
Body Mass Index, (kg/m^2), mean ± SD	28.4 ± 6.7	29.1 ± 8.3	0.7
Parity			0.2
Nulliparous, n (%)	12 (30)	19 (47.5)	
Multiparous, n (%)	28 (70)	21 (52.5)	

Data are presented as mean ± standard deviation (SD) or n (%).
Intervention group: random start nomegestrol acetate/estradiol (NOMAC/E) treatment.
Control group: no treatment.

Table 2
Characteristics of the endometrium.

	Intervention group	Control group	*p*
Patients, n	40	40	
Day of the menstrual cycle on which the procedure was performed, mean	–	9.1 ± 0.4	
Day of start of start nomegestrol acetate/estradiol intake, mean	7.6 ± 0.7	–	
Endometrial thickness			
Endometrial thickness at diagnosis (mm), mean ± SD	14.2 ± 5.5	14.4 ± 4.2	0.8
Endometrial thickness pre-surgery (mm), mean ± SD	8.3 ± 3.9	13.2 ± 4.5	<0.001
Endometrial thickness post-surgery (mm), mean ± SD	3.8 ± 1.3	6.8 ± 4.8	<0.001
Endometrial pattern (day of surgery)			<0.001
Atrophic, n (%)	34 (85.0)	1 (2.5)	
Hypotrophic with normotrophic areas, n (%)	6 (15.0)	2 (5)	
Normal, n (%)	0 (0.0)	37 (92.5)	

Data are presented as mean ± standard deviation (SD) or n (%).
Intervention group: random start nomegestrol acetate/estradiol (NOMAC/E) treatment.
Control group: no treatment.

E2 group after 14 days after the start of treatment at a random time of menstrual cycle; the recorded mean of the day of CoC initiation was on day 7.6 ± 0.7 of menstrual cycle. On the day of the procedure, the difference in pre- and post-OHP endometrial ultrasound thickness was statistically significant between the two groups, with endometrial thickness in both measurements being thinner for the NOMAC/E2-treated group (pre-OHP: 13.2 ± 4.5 vs 8.3 ± 3.9, $p < 0.001$; post-OHP: 6.8 ± 4.8 vs 3.8 ± 1.3, $p < 0.001$) (Table 2).

At the time of the procedure, in the control group, the endometrial patterns (Table 2) were: ''normal'' (non-responder women) in 37 cases (92.5 %); ''hypotrophic with thickened areas'' in 2 cases (5 %); and ''atrophic'' in 1 cases (2.5 %). In the NOMAC/E2-treated group, however, we reported the following endometrial patterns: ''normotrophic'' (nonresponder women) in 0 cases (0.0 %); ''hypotrophic with thickened areas'' in 6 cases (15 %); ''atrophic'' in 34 cases (85 %). In the NOMAC/E2-treated group, compared with the control, there were more women who showed ''hypotrophic with normotrophic areas'' or ''atrophic'' endometrial patterns ($p < 0.001$).

Table 3 lists the characteristics of polyps, surgical items, pre- and post-treatment PBAC, and the number of recurrences. The number of polyps removed was comparable between the two groups and there were statistically significant differences in the size of polyps removed (7.0 ± 3.4 vs 7.6 ± 3.9, $p = 0.4$ range was 3–22 cm for the intervention group and 2–14 cm for controls). We did not report any complication during and after the procedure. In the NOMAC/E2-treated group, there was a reduction in the duration of the procedure, and in the number of bleedings during OHP ($p = 0.001$).

There was also a statistically significant difference in the physician's assessment of the quality of endometrial preparation (3.6 ± 0.9 vs 4.6 ± 0.5, $p < 0.001$), the quality of visualization of the uterine cavity during the procedure (3.8 ± 0.4 vs 4.6 ± 0.4, $p < 0.001$), and satisfaction with the performance of the procedure (3.5 ± 0.7 vs 4.6 ± 0.5, $p < 0.001$).

NOMAC/E2-treated women also experienced less pain both during (6.8 ± 1.3 vs 5.6 ± 1.1, p < 0.001) and after the procedure (5.0 ± 1.7 vs 2.6 ± 1.3, $p < 0.001$), with less need to take analgesics ($p = 0.01$) and reduced time to discharge after the procedure ($p < 0.001$).

Pre-operative PBAC were evaluable ($p = 0.5$); on re-evaluation of post-OHP menstrual cycle PBAC, the NOMAC/E2-treated group had lower values (88.4 ± 32.1 vs 72.1 ± 21.9, $p < 0.001$).

Table 3
Analysis of endometrial polyps characteristics, intraoperative data and PBAC.

	Intervention group	Control group	*p*
Patients, n	40	40	
Polyps			
Multiple polyps, n (%)	5 (12.5)	7 (17.5)	0.7
Removed polyps, mean ± SD (range)	1.2 ± 0.4 (1–3)	1.3 ± 0.9 (1–3)	0.5
Size of the polyps (mm), mean ± SD (range)	7.0 ± 3.4 (3–22)	7.6 ± 3.9 (2–14)	0.4
Surgery items			
Operative time (min), mean ± SD	7.3 ± 3.1	10.3 ± 4.1	<0.001
Distension medium (mL), mean ± SD	720.0 ± 296.9	813.4 ± 356.4	0.2
Quality of endometrial preparation (VAS[a]), mean ± SD	4.6 ± 0.5	3.6 ± 0.9	<0.001
Surgeon satisfaction (VAS[a]), mean ± SD	4.6 ± 0.5	3.5 ± 0.7	<0.001
Quality of visualization of the uterine cavity during the procedure (VAS[a]), mean ± SD	4.6 ± 0.4	3.8 ± 0.4	<0.001
Complete resection, n (%)	40 (100)	39 (97.5)	1,00
Need for two surgeries, n (%)	0 (0.0)	1 (2.5)	1,00
Intra-operative complications, n (%)	0 (0.0)	0 (0.0)	–
Post-operative complications, n (%)	0 (0.0)	0 (0.0)	–
Patient pain during procedure (VAS[b]), mean ± SD	5.6 ± 1.1	6.8 ± 1.3	<0.001
Patient pain post-procedure (VAS[b]), mean ± SD	2.6 ± 1.3	5.0 ± 1.7	<0.001
Need to take pain medication after surgery, n (%)	0 (0.0)	7 (17.5)	0.01
Bleeding during surgery, n (%)	0 (0.0)	10 (20.6)	0.001
PBAC			
Pre-surgery, mean ± SD	152.5 ± 88.0	163.4 ± 44.6	0.5
Post-surgery, mean ± SD	72.1 ± 21.9	88.4 ± 32.1	<0.001
Time to discharge (min), mean ± SD	5.5 ± 1.9	8.9 ± 3.6	<0.001
Recurrence, n (%)	0 (0.0)	7 (17.5)	<0.001

Data are presented as mean ± standard deviation (SD) or n (%).
Intervention group: random start nomegestrol acetate/estradiol (NOMAC/E) treatment.
Control group: no treatment.
PBAC: Pictorial Bleeding Assessment Chart.
[a] VAS: Visual Analogue Scale from 0 (minimal) to 5 (optimal).
[b] VAS: Visual Analogue Scale from 0 (no pain) to 10 (unbearable).

Finally, after six months of follow-up, there were 7 (17.5 %) recurrences for the control group and none in the treatment group.

Discussion

The presence of a thin endometrium plays an important role in allowing the best operative conditions in hysteroscopic procedure, and, for this reason, diagnostic or operative procedures are scheduled in the early follicular phase, between the eighth and eleventh menstrual days, as the most favorable physiological condition associated with endometrial thickness reduction [17]. Difficulty in timing the procedure for the immediate postmenstrual phase and the unpredictable thickness of the unprepared endometrium have resulted in a focus on the use of endometrial thinning hormonal agents before the procedure [18], with the rationale being based on the ability to reduce endometrial growth and vascularization. Although several drugs have been used to achieve hypotrophy/atrophy of the endometrium before hysteroscopic procedure [19,20], there is currently no clear consensus on which drug

treatment is best. Administration of GnRHa is an effective method for endometrial preparation. Reliable thinning of the endometrial mucosa is obtained after 2 months of therapy. However, because of cost and potency, GnRH agonists may be considered overtreatment in cases of OHP [10].

In addition, few studies have been focused on rapid preparations to date [12,13], but there has been no question of whether there is a real need to initiate drug administration in the first few days of menstrual flow. The study by Florio et al. [13] had examined the use of NOMAC as a rapid preparation, but not in combination and not randomly. Consistent with our study, the authors had concluded that NOMAC may be useful in endometrial preparation prior to operative hysteroscopy. OHP, however, remains the most common procedure for a hysteroscopist, and the ability to complete it under the most appropriate conditions should be the physician's prerogative [21]. In addition, the introduction of increasingly cutting-edge technologies that are adapted to the outpatient setting allow an increasing number of hysteroscopic office procedures [2,3]. The adoption of rapid endometrial preparation with random start would also allow for more efficient management of the waiting list, preventing some procedures from being skipped due to the lack of synchronization between the availability of pre-established hospital space and the women's menstrual cycle. The use of 5 mg NOMAC for 14 days, starting from day 1 of menstrual cycle has showed to be a fast, satisfactory and low-cost preparation of the endometrium before the procedure [12], but has not been analyzed in a combined administration nor in a random start protocol.

In the present study, we explored the efficacy of the 2.5 mg NOMAC/1.5 mg E2 combination in the rapid preparation of the endometrium for office hysteroscopy. To the best of our knowledge, this is the first study to investigate the use of this combination of molecules for the purpose of atrophying the endometrium in a rapid setting with random start. The combination of nomegestrol acetate and 17-E2 (identical to endogenous estrogen) was introduced in a monophasic combined oral contraceptive approved by the European Medicines Agency in 2011 [22]. Nomegestrol acetate is a selective progestin structurally related to progesterone that exhibits strong antigonadotropic activity and moderate anti-androgenic properties and does not possess estrogenic, androgenic, glucocorticoid, or mineralocorticoid activity [23]. Together, nomegestrol acetate and 17-E2 provide effective inhibition of ovulation with acceptable cycle control and have minimal effects on markers of hemostasis and endocrine function [24]. We found that administration of NOMAC/E2 for 14 days, initiated at a random time in the menstrual cycle, was able to achieve a reduction in endometrial thickness, as demonstrated by ultrasonographic evaluation, and in agreement with visual inspection, a significant effect was demonstrated in achieving a highly favorable operative condition for office hysteroscopy compared with controls.

The treatment provided an effective endometrial suppression, resulting in the visualization of a thin, regular, pale endometrium, which allowed better exposure of the polyp to be removed. In addition, women after preparation showed intraoperatively the total absence of endometrial imbibition once OHP was initiated, as evidenced not only by higher grade of physician's satisfaction, but also and especially by an even smaller endometrial thickness at the ultrasound check compared with controls after the procedure. This could probably allow even more radical procedures, eliminating even the lowest part of the polypoid pedicle and reducing the number of recurrences [25]. For hysteroscopic removal of submucosal uterine myomas, multiple premedication regimens have been used that could best prepare the lesion for surgery [26,27]. Future studies should investigate whether the use of a rapid, random onset protocol can also be employed for hysteroscopic myomectomy of submucosal myomas.

Nevertheless, several elements should be considered for a proper data interpretation. First, the sample of enrolled patient is limited, so our findings need to be confirmed in larger cohorts; second, only the hysteroscopists who performed the procedures were different due to the multicenter nature of the study, so these variables could have affected the results; third, only the hysteroscopists, but not the patients, were masked to the treatment allocation: this may consider a potential bias for patient- reported outcomes (such as pain during and after the procedure and need to take pain medication after the procedure); we did not perform any cost-effect analysis, so this would be the ground for future investigations on the topic. Finally, although the NOMAC/E2 combination has been shown more favorable venous thromboembolism risk profile than other formulations [28], it should be clarified that CoCs are not appropriate for all patients since some women have risk factors for thromboembolic events in their medical history and therefore may not be candidates to take, even for a very short period, a CoC. Further studies should therefore examine the feasibility of this endometrial preparation regimen even with drugs such as progestin-only-pills that better suit the needs of patients with risk factors that prohibit the use of CoC.

Conclusions

Our data suggest that pre-operative treatment with NOMAC/E2 could provide rapid, adequate and low-cost preparation of the endometrium before office hysteroscopy, thus improving surgical performance and women compliance. However, our analysis is based on a small cohort, so we strongly urge further studies on larger cohorts with greater statistical power that can accurately define the possible use of NOMAC/E2 as a rapid endometrial preparation with random start before OHP.

Funding statement

The present research was not funded.

Data sharing statement

Data are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Andrea Etrusco: Writing – review & editing. **Vittorio Agrifoglio:** Visualization, Investigation. **Vito Chiantera:** Supervision. **Antonio D'Amato:** Data curation. **Giuseppe Russo:** Software. **Tullio Golia D'Augè:** Validation. **Andrea Giannini:** Writing – review & editing. **Gaetano Riemma:** Writing – review & editing. **Basilio Pecorino:** Methodology. **Federico Ferrari:** Formal analysis. **Antonio Simone Laganà:** Conceptualization. **Marco Monti:** Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Mazzon I, Etrusco A, Laganà AS, Chiantera V, Di Angelo AS, Tosto V, et al. Training in diagnostic hysteroscopy: the 'Arbor Vitae' method. Medicina (Kaunas) 2023;59(6):1019.
[2] Etrusco A, Buzzaccarini G, Laganà AS, Chiantera V, Vitale SG, Angioni S, et al. Use of diode laser in hysteroscopy for the management of intrauterine pathology: a systematic review. Diagnostics (Basel) 2024;14(3):327.
[3] Etrusco A, Laganà AS, Chiantera V, Gerli S, Carugno J, Sorrentino F, et al. Efficacy, safety, and feasibility of the treatment of intrauterine pathologies with the mini-resectoscope: a systematic review. Int J Gynaecol Obstet 2024.
[4] Zelivianskaia A, Robinson JK. Office hysteroscopy: setting up your practice for success. Obstet Gynecol Clin North Am 2022;49(2):315–27.
[5] Salazar CA, Isaacson KB. Office operative hysteroscopy: an update. J Minim Invasive Gynecol 2018 Feb;25(2):199–208.
[6] Bradley LD. Complications in hysteroscopy: prevention, treatment and legal risk. Curr Opin Obstet Gynecol 2002;14(4):409–15.

[7] Ciebiera M, Łoziński T, Wojtyła C, Rawski W, Jakiel G. Complications in modern hysteroscopic myomectomy. Ginekol Pol 2018;89(7):398–404.
[8] Rai VS, Gillmer MD, Gray W. Is endometrial pre-treatment of value in improving the outcome of transcervical resection of the endometrium? Hum Reprod 2000;15 (9):1989–92.
[9] Corrêa TD, Caetano IM, Saraiva PHT, Noviello MB, Santos Filho AS. Use of GnRH analogues in the reduction of submucous fibroid for surgical hysteroscopy: a systematic review and meta-analysis. Rev Bras Ginecol Obstet 2020;42(10): 649–58.
[10] Haimovich S, Mancebo G, Alameda F, Agramunt S, Hernández JL, Carreras R. Endometrial preparation with desogestrel before Essure hysteroscopic sterilization: preliminary study. J Minim Invasive Gynecol 2013;20(5):591–4.
[11] Cicinelli E, Pinto V, Quattromini P, Fucci MR, Lepera A, Mitola PC, et al. Endometrial preparation with estradiol plus dienogest (Qlaira) for office hysteroscopic polypectomy: randomized pilot study. J Minim Invasive Gynecol 2012;19(3):356–9.
[12] Cicinelli E, Pinto V, Tinelli R, Saliani N, De Leo V, Cianci A. Rapid endometrial preparation for hysteroscopic surgery with oral desogestrel plus vaginal raloxifene: a prospective, randomized pilot study. Fertil Steril 2007;88(3):698–701.
[13] Florio P, Imperatore A, Litta P, Franchini M, Calzolari S, Angioni S, et al. The use of nomegestrol acetate in rapid preparation of endometrium before operative hysteroscopy in pre-menopausal women. Steroids 2010;75(12):912–7.
[14] Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010;152(11):726–32.
[15] Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;8(346):e7586.
[16] Baggish MS, Valle RF, Barbot J. Diagnostic and operative hysteroscopy: a text and atlas. Year Book Medical Publishers; 1989. p. 334.
[17] Obstet Gynecol 2020 Mar;135(3):754–6.
[18] Tan YH, Lethaby A. Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. Cochrane Database Syst Rev 2013;11: CD010241.
[19] Laganà AS, Giacobbe V, Triolo O, Granese R, Ban Frangež H, Vrtačnik-Bokal E, et al. Dienogest as preoperative treatment of submucous myomas for hysteroscopic surgery: a prospective, randomized study. Gynecol Endocrinol 2016;32(5):408–11.
[20] Kamath MS, Kalampokas EE, Kalampokas TE. Use of GnRH analogues pre-operatively for hysteroscopic resection of submucous fibroids: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2014 Jun;177:11–8.
[21] Vitale SG, Haimovich S, Laganà AS, Alonso L, Di Spiezio SA, Carugno J, et al. Endometrial polyps. An evidence-based diagnosis and management guide. Eur J Obstet Gynecol Reprod Biol 2021 May;260:70–7.
[22] Westhoff C, Kaunitz AM, Korver T, Sommer W, Bahamondes L, Darney P, et al. Efficacy, safety, and tolerability of a monophasic oral contraceptive containing nomegestrol acetate and 17β-estradiol: a randomized controlled trial. Obstet Gynecol 2012 May;119(5):989–99.
[23] Zoely: a new combined oral contraceptive. Drug Ther Bull. 2014;52(8):90–3.
[24] Yang LPH, Plosker GL. Nomegestrol acetate/estradiol: in oral contraception. Drugs 2012;72(14):1917–28.
[25] Grow DR, Iromloo K. Oral contraceptives maintain a very thin endometrium before operative hysteroscopy. Fertil Steril 2006;85(1):204–7.
[26] Laganà AS, Vitale SG, Muscia V, Rossetti P, Buscema M, Triolo O, et al. Endometrial preparation with Dienogest before hysteroscopic surgery: a systematic review. Arch Gynecol Obstet 2017;295(3):661–7.
[27] Etrusco A, Laganà AS, Chiantera V, Vitagliano A, Cicinelli E, Mikuš M, et al. Feasibility and surgical outcomes of hysteroscopic myomectomy of FIGO type 3 Myoma: a systematic review. J Clin Med 2023;12(15):4953.
[28] Gaussem P, Alhenc-Gelas M, Thomas JL, Bachelot-Loza C, Remones V, Ali FD, et al. Haemostatic effects of a new combined oral contraceptive, nomegestrol acetate/ 17β-estradiol, compared with those of levonorgestrel/ethinyl estradiol. A double-blind, randomised study. Thromb Haemost 2011;105(3):560–7.