Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study

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Objective: To assess the proportion of patients satisfied with their treatment before and after a systematic change from norethindrone acetate to dienogest as the first-line progestin for symptomatic endometriosis.
Design: Before and after study.
Setting: Academic department.
Patient(s): The last 90 new consecutive endometriosis patients in whom norethindrone acetate was used, and the first 90 new consecutive endometriosis patients in whom dienogest was used.
Intervention(s): Norethindrone acetate at the oral dose of 2.5 mg once a day until June 6, 2013, then dienogest at the oral dose of 2 mg once a day thereafter.
Main Outcome Measure(s): Degree of satisfaction with treatment after 6 months of progestin therapy and assessment of any variations in pain symptoms, psychological status, sexual function, or health-related quality of life associated with the introduction of dienogest.
Result(s): The proportion of satisfied plus very satisfied women after 6 months of treatment was 71% in the "before" period (norethindrone acetate) and 72% in the "after" period (dienogest). The implementation of dienogest was not associated with statistically significant ameliorations in overall pain relief, psychological status, sexual functioning, or health-related quality of life. Treatment was well tolerated by 58% of norethindrone acetate users compared with 80% of dienogest users. After dienogest implementation, the absolute risk reduction in the occurrence of any side effect was 13.9% (95% confidence interval, 0.8%–28.6%).
Conclusion(s): Considering the large difference in the cost of the two drugs, dienogest should be suggested selectively in women who do not tolerate norethindrone acetate. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Before and after study, dienogest, endometriosis, norethisterone acetate, pelvic pain

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According to major international guidelines, progestins, with or without estrogens, should be considered as the first-line medical therapy for symptomatic endometriosis (1–4). Because hormone therapies may be needed for long periods of time, compounds with a particularly favorable safety/efficacy/tolerability/cost profiles should be chosen (5, 6).

Dienogest, a semisynthetic 19-nortestosterone derivative progestin, has been evaluated, registered, and recently marketed also as a medical treatment for endometriosis. According to the available evidence, dienogest is highly effective in relieving pain symptoms in women with endometriosis and is very well tolerated (7, 8). Therefore, this drug has been considered an advance in the management of the disease (9). Dienogest has been compared in randomized controlled trials with either a placebo using a

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superiority design (10) or a gonadotropin-releasing hormone (GnRH) agonist using a noninferiority design (11). The choice of these study designs and comparators may satisfy registration purposes (12, 13), but they do not allow definition of the precise role of dienogest in the current therapeutic armamentarium. In fact, it is already well known that all available hormone treatments for endometriosis perform better than placebo (5, 13), and no international guideline recommends a GnRH agonist as the first-line, standard medical treatment for symptomatic endometriosis (1–4). The outcome of interest to patients and clinicians appears to be whether dienogest is superior to currently used progestins. However, according to a recent systematic literature review, dienogest has never been compared with other progestins in the treatment of endometriosis (14).

Norethindrone acetate, a 19-nortestosterone derivative progestin, has been repeatedly evaluated in women with endometriosis (15–20) and has been routinely used in our referral center for several years (21–23). Norethindrone acetate is approved by the U.S. Food and Drug Administration and the Italian Ministry of Health for the treatment of endometriosis. Given this background, we decided to assess whether replacement of norethindrone acetate with dienogest as the progestin of choice for the treatment of endometriosis is associated with measurable benefits for the patients with symptomatic disease. We adopted a before and after study design. Therefore, our study was not focused on the *efficacy* of the two progestins (i.e., which works better under ideal and highly controlled conditions, such as in a randomized controlled trial) but rather on their *effectiveness* (which of the two drugs works better in real life—that is, under nonideal circumstances).

The main objective of our study was to assess the proportion of patients satisfied with their treatment before and after a change at a system level from norethindrone acetate to dienogest as the first-line progestin prescribed for symptomatic endometriosis. Our secondary objective was the evaluation of variations in pain symptoms, psychological status, sexual function, and health-related quality of life associated with the implementation of dienogest.

MATERIALS AND METHODS

Design

Our report was prepared according to the Strengthening the Reporting of Observational studies in Epidemiology guidelines for reporting observational studies (24). A before and after study design (25) was adopted with the objective of assessing the effectiveness of norethindrone acetate and dienogest. Dienogest was marketed in Italy on June 6, 2013. Until that date, the first-choice progestin prescribed in our outpatient endometriosis clinic was norethindrone acetate. After June 6, the first-choice progestin prescribed was dienogest. Presently, norethindrone acetate is reimbursed by the Italian National Health System, but dienogest is not. Our current indications to treatment of endometriosis with a progestin are moderate or severe pain symptoms associated with deep endometriosis (rectovaginal, bladder, and bowel lesions), and nonresponse or intolerance or contraindications to oral contraceptives used continuously, independent of the lesions' types, in women who prefer medical therapy rather than surgery.

The investigation was performed in an academic department, and the institutional review board approved the study (Comitato Etico Milano Area B, determination 604). Patients referred to our unit for endometriosis treatment routinely sign an informed consent for the use of their clinical data for research purposes. The possibility of undergoing subsequent visits to assess the impact of various medical therapies is stated in this form as well.

Patients

We considered 18- to 40-year-old women who were not seeking conception and who had a surgical diagnosis of endometriosis in the previous 24 months or a current nonsurgical diagnosis of endometriosis (26). Nonsurgical diagnoses were based on ultrasonographic criteria in patients with ovarian endometriomas (27); on visual inspection of the posterior fornix and biopsy of vaginal lesions in women with rectovaginal endometriosis (21, 22); on ultrasonographic criteria (28), cystoscopic findings, and biopsy of vesical lesions in women with bladder detrusor endometriosis; on physical signs at rectovaginal examination and ultrasonographic criteria (29) in those with deep lesions infiltrating the Douglas pouch and parametria; and on ultrasonographic criteria (30), double contrast barium enema, and rectosigmoidoscopy/colonoscopy findings in women with full-thickness bowel lesions. Magnetic resonance imaging was performed in selected circumstances. Patients were excluded in case of obstructive uropathy or symptomatic bowel stenosis; evidence of complex adnexal cysts or an ovarian endometrioma with a diameter greater than 4 cm at vaginal ultrasonography; the typical contraindications to progestins; an allergy to components of the study medications; a diagnosis of concomitant pelvic inflammatory disease; and pelvic varices or genital malformations identified at previous surgery.

After June 6, 2013, all the patients being evaluated for the first time were informed that a new medical treatment for endometriosis was available (dienogest) and that, based on published evidence, it was highly effective and particularly well tolerated. They were also informed that another progestin for endometriosis (norethisterone acetate) had been used in our center for several years, but that no direct comparisons had been conducted, so it was not possible to define which progestin was more favorable in terms of pain symptoms relief, although dienogest was possibly associated with fewer side effects with respect to norethindrone acetate. The two medications did not appear to differ with regard to safety profiles, but their cost did: dienogest was more expensive than norethindrone acetate. Women were also informed that progestins induce only temporary pain relief and are not expected to definitively cure endometriosis, so prolonged periods of treatment might be necessary.

Treatments

Norethindrone acetate was prescribed at the oral dose of 2.5 mg once a day. Dienogest was prescribed at the oral