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CLINICAL ARTICLE

Vaginal danazol for women with rectovaginal endometriosis and pain symptoms persisting after insertion of a levonorgestrel-releasing intrauterine device

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ABSTRACT

Objective: To evaluate the effectiveness of treatment with vaginal danazol in improving the pain symptoms caused by rectovaginal endometriosis that persist after insertion of a levonorgestrel-releasing intrauterine device (LNG-IUD). *Methods:* This pilot observational study included 15 women with rectovaginal endometriosis and pain symptoms persisting after LNG-IUD insertion. Vaginal danazol (100 mg per day) was self-administered for 6 months. The intensity of pain symptoms and the volume of rectovaginal endometriotic nodules were evaluated. *Results:* Twelve women were satisfied or very satisfied with the treatment. After treatment with vaginal danazol for 3 months, there was a significant decrease in the intensity of pain symptoms compared with their intensity before the administration of danazol. The intensity of pain symptoms decreased further at 6-month follow-up. The volume of the rectovaginal nodules decreased after treatment with vaginal danazol for 6 months (1.7 ± 0.8 cm^3) compared with the baseline volume (2.3 ± 0.9 cm^3; $P<0.001$). Adverse effects of the treatment were minimal and well tolerated. *Conclusion:* Although a placebo effect cannot be excluded, the results indicate that vaginal danazol decreases the severity of endometriosis-related pain symptoms after LNG-IUD insertion.

1. Introduction

The insertion of a levonorgestrel-releasing intrauterine device (LNG-IUD) significantly improves the pain associated with endometriosis [1–6]; in addition, this procedure decreases serum CA-125 levels [7], American Society for Reproductive Medicine (ASRM) stage of endometriosis [2], and the risk of recurrence of dysmenorrhea after surgery [8,9]. However, after 6 months of therapy, between 25% and 32% of patients wish to have the device removed because of the persistence of pain symptoms [2,3]. It is not known whether the addition of other hormonal therapies to an LNG-IUD is beneficial in treating endometriosis-related pain symptoms.

Treatment with danazol reduces the intensity of symptoms caused by endometriosis, but its long-term use is limited by the occurrence of androgenic adverse effects [10,11]. In contrast, vaginally administered danazol improves pain symptoms caused by endometriosis with minimal adverse effects [12,13]. The daily administration of vaginal danazol does not affect the pituitary–ovarian axis [14] and does not inhibit ovulation [15].

The aim of this pilot observational study was to assess whether administration of vaginal danazol improved pain symptoms caused by rectovaginal endometriosis and that persisted after LNG-IUD insertion.

2. Materials and methods

Study participants had received a previous diagnosis of rectovaginal endometriosis during laparoscopies performed in other hospitals; however, the nodules were not excised or were incompletely excised. Pain symptoms persisted or recurred after surgery. The diagnosis of rectovaginal endometriosis was made by vaginal and rectal examinations and was confirmed by rectal water contrast transvaginal ultrasonography [16,17]. The local Institutional Review Board approved the study protocol. All participants provided written informed consent.

Enrollment in the current study was offered to women who had experienced persistence of pain symptoms after the insertion of an LNG-IUD (Mirena; Schering, Berlin, Germany) and for this reason had requested that the device was removed. Patients dissatisfied with the LNG-IUD because of adverse effects of treatment were not invited to participate in the study.

Exclusion criteria for the administration of danazol were von Willebrand disease or coagulopathies (known or suspected); personal and/or family history of deep vein thrombosis, active thrombophlebitis, thromboembolic disorders, or cerebrovascular accidents; myocardial infarction or ischemic heart disease; hypertension; liver disease; any endocrine disorders other than controlled thyroid disease; or a smoking habit of at least 20 cigarettes per day.

A daily dose of 100 mg of vaginal danazol (Danatrol, Sanofi Synthelabo, Milan, Italy) was self-administered for 6 months. Compliance with therapy was investigated by giving the patients a diary to record the administration of vaginal danazol. Patients were allowed to

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take nonsteroidal anti-inflammatory drugs when needed (naproxen sodium, 550 mg tablet); however, they were asked to record in the diary the number of tablets used each month during treatment.

Pain symptoms were assessed before vaginal danazol was administered and then after 3 months and 6 months of treatment. The severity of dysmenorrhea, deep dyspareunia, nonmenstrual pelvic pain, and dyschezia was determined by using a 10-cm visual analog scale. In addition, patients were asked to complete a questionnaire that investigated the presence and severity of dysmenorrhea, deep dyspareunia, and nonmenstrual pelvic pain graded from 0 (absence of pain) to 3 (severe pain) points on a multidimensional categorical rating scale modified from the scale devised by Biberoglu and Behrman [18] and previously described by other authors [8].

The volume of the rectovaginal endometriotic nodules was determined by virtual organ computer-aided analysis (VOCAL, GE Healthcare, Milwaukee, USA) before starting the treatment with vaginal danazol and after treatment with danazol for 6 months.

The paired *t* test and the Wilcoxon signed rank test were used to compare the intensity of pain symptoms before and after treatment with vaginal danazol. A *P* value of <0.05 was considered statistically significant.

3. Results

Out of 19 women who fitted the criteria for inclusion in the study, 15 (78.9%) agreed to participate. The mean (±standard deviation; SD) age of the study population was 37.9±3.6 years; the mean (±SD) body mass index (BMI, calculated as the weight in kilograms divided by the square of the height in meters) was 22.7±2.2 kg/m^2. Eight women (53.3%) had previous pregnancies. Before using vaginal danazol, the patients had used the LNG-IUD for 8.4 (±2.5) months. At the time of starting the administration of vaginal danazol, 2 women were amenorrheic. Thirteen of the women were sexually active. No patient had displacement of the LNG-IUD during the study period. One woman did not complete the 6-month treatment with vaginal danazol, and she underwent surgery at the fifth month of therapy because of the persistence of pain symptoms. The remaining 14 women (93.3%) completed the 6-month treatment with vaginal danazol. At the completion of treatment, 8 women were satisfied, 4 women were very satisfied, and 2 women were dissatisfied with the treatment. Therefore, 80% (12/15) of the patients were satisfied with the treatment.

After treatment with vaginal danazol for 3 months, there was a significant decrease in the intensity of dysmenorrhea ($P<0.001$), nonmenstrual pelvic pain ($P<0.001$), deep dyspareunia ($P=0.005$), and dyschezia ($P=0.009$) when compared with the intensity of these symptoms before the administration of danazol. Similarly, after treatment with vaginal danazol for 6 months, the intensity of dysmenorrhea ($P<0.001$), nonmenstrual pelvic pain ($P=0.001$), deep dyspareunia ($P=0.002$), and dyschezia ($P=0.001$) was significantly lower than before the administration of danazol (Table 1). The intensity of pain symptoms continued to decrease during the administration of danazol; after treatment with danazol for 6 months, the intensity of dysmenorrhea ($P=0.002$), nonmenstrual pelvic pain ($P=0.007$), deep dyspareunia ($P=0.011$), and dyschezia ($P=0.002$) was significantly lower than after treatment with danazol for 3 months (Fig. 1).

The multidimensional categorical rating scale scores for dysmenorrhea were significantly lower after treatment with vaginal danazol for 3 months ($n=13$; $P=0.002$) and 6 months ($n=11$; $P=0.004$) than when the LNG-IUD alone was used. The score for dysmenorrhea continued to decrease during the administration of danazol, but the difference between treatment for 3 months and for 6 months did not reach statistical significance ($P=0.078$). For the 11 women who completed the treatment and were menstruating at the last follow-up, the median decrease in the multidimensional categorical rating scale scores for dysmenorrhea between treatment with LNG-IUD alone and treatment with danazol for 6 months was 2 points (range, 0–3). The scores for nonmenstrual pelvic pain were significantly lower after treatment with vaginal danazol for 3 months ($n=12$; $P=0.002$) and 6 months ($n=12$; $P<0.001$) than when the LNG-IUD alone was used. The scores for nonmenstrual pelvic pain were significantly lower after treatment with vaginal danazol for 6 months than after treatment with vaginal danazol for 3 months ($P=0.016$). In the 12 women who completed the treatment and who had nonmenstrual pelvic pain,

Table 1
Intensity of pain symptoms during the study.

	Dysmenorrhea	Nonmenstrual pelvic pain	Deep dyspareunia	Dyschezia
Intensity of symptoms on the 10-cm VAS scale				
LNG-IUD alone [a]	6.0±3.1 (13)	5.3±1.2 (12)	6.2±3.0 (12)	3.5±3.0 (11)
After 3 months of treatment with danazol [a]	4.2±2.7 (13) ($P<0.001$ compared with LNG-IUD alone)	3.0±1.2 (12) ($P<0.001$ compared with LNG-IUD alone)	4.9±3.3 (12) ($P=0.005$ compared with LNG-IUD alone)	2.5±2.1 (11) ($P=0.009$ compared with LNG-IUD alone)
After 6 months of treatment with danazol [a]	2.2±2.2 (11) ($P<0.001$ compared with LNG-IUD alone; $P=0.002$ compared with 3-month treatment)	1.9±1.6 (12) ($P=0.001$ compared with LNG-IUD alone; $P=0.007$ compared with 3-month treatment)	3.3± 3.1 (11) ($P=0.002$ compared with LNG-IUD alone; $P=0.011$ compared with 3-month treatment)	1.7 ±1.8 (11) ($P=0.001$ compared with LNG-IUD alone; $P=0.002$ compared with 3-month treatment)
Multidimensional categorical rating scale				
LNG-IUD alone [b]	3 (0–3) (13)	3 (2–3) (12)	3 (0–3) (12)	NA
After 3 months of treatment with danazol [b]	1 (0–2) (13) ($P=0.002$ compared with LNG-IUD alone)	1 (0–3) (12) ($P=0.002$ compared with LNG-IUD alone)	2 (0–3) (12) ($P=0.016$ compared with LNG-IUD alone)	NA
After 6 months of treatment with danazol [b]	0 (0–2) (11) ($P=0.004$ compared with LNG-IUD alone; $P=0.078$ compared with 3-month treatment)	1 (0–2) (12) ($P<0.001$ compared with LNG-IUD alone; $P=0.016$ compared with 3-month treatment)	1 (0–3) (11) ($P=0.008$ compared with LNG-IUD alone; $P=0.250$ compared with 3-month treatment)	NA

Abbreviations: LNG-IUD, levonorgestrel-releasing intrauterine device; NA: not available; VAS, visual analog scale.
[a] Data are presented as mean±SD (number of patients).
[b] Data are presented as median (range) (number of patients).