Efficacy of vaginal danazol treatment in women with recurrent deeply infiltrating endometriosis

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Objective: To describe a safe long-term medical treatment for deeply infiltrating endometriosis, a critical condition characterized by multiple painful symptoms and a high recurrence rate after surgical treatment.
Design: Prospective study.
Setting: University of Siena.
Patient(s): Twenty-one women with deeply infiltrating endometriosis.
Intervention(s): In a nonrandomized prospective study a low dose of vaginal danazol (200 mg/d) was self-administered for 12 months. After a previous laparoscopic surgery, these patients had reported recurrent severe dyspareunia, dysmenorrhea, and pelvic pain (in five cases also painful defecation).
Main Outcome Measure(s): Before and every 3 months during the treatment a visual analogue pain scale was used. Transvaginal and transrectal ultrasound examinations were performed before and after 6 and 12 months of treatment. Adverse effects were registered, and serum concentration of cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, glycemia, protein S, protein C, antithrombin III, and homocysteine was evaluated before and after 12 months.
Result(s): Dysmenorrhea, dyspareunia, and pelvic pain significantly decreased within 3 months and disappeared after 6 months of treatment, with a persistent effect during the 12 months of treatment. A relief of painful defecation was also shown. Ultrasound examination showed a reduction of the nodularity in the rectovaginal septum within 6 months. The medical treatment did not affect metabolic or thrombophilic parameters; few local vaginal adverse effects were reported.
Conclusion(s): Vaginal danazol resulted in effective medical treatment for the various painful symptoms in women with recurrent deeply infiltrating endometriosis, and because of the lack of significant adverse effects it may be proposed as an alternative to repeated surgery. (Fertil Steril® 2007;88:789–94. ©2007 by American Society for Reproductive Medicine.)

Key Words: Danazol, endometriosis, dysmenorrhea, dyspareunia, pelvic pain

Deeply infiltrating endometriosis is a particular form of endometriosis that penetrates >5 mm under the peritoneal surface, typically associated with marked proliferation of smooth muscle cells and fibrosis and strongly associated with pelvic pain (1). In particular, the deeply infiltrating endometriosis lesions are classified according to the invaded organs: [1] bladder, with an infiltration of the muscularis propria; [2] uterosacral ligaments, when the uterosacral ligaments are infiltrated; [3] vagina, when the deeply infiltrating endometriosis invades the anterior rectovaginal pouch, the posterior vaginal fornix, and the retroperitoneal area in between (rectovaginal septum); and [4] intestine, with an infiltration of the muscularis propria (2). Diagnosis of deeply infiltrating endometriosis is made by clinical signs, by transvaginal/transrectal ultrasound examination, and by biopsy during surgery (3).

Received June 28, 2006; revised December 21, 2006; accepted December 28, 2006.
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Dysmenorrhea, dyspareunia, and chronic pelvic pain are the most frequent symptoms in women with deeply infiltrating endometriosis. In several cases pain is mechanical and is provoked by the mobilization of the organ affected by the deeply infiltrating endometriosis lesions. Dyspareunia and dysmenorrhea are associated with involvement of the uterosacral ligaments, pelvic pain, and painful defecation during menses with involvement of the rectovaginal septum, and/or of bowel and functional urinary tract signs when the bladder and/or ureter are involved (4).

Deeply infiltrating endometriosis is a critical condition that is improved by surgical treatments; both laparoscopic and laparotomic consecutive operations are associated with pain relief even though associated with the risk of major complications. However, the recurrence rate is very high in these patients, and they want to postpone reoperation or do not accept the risk of additional morbidity or the results of surgery (hysterectomy, bilateral oophorectomy, deafferentation of nerves). The development of new drugs and alternative routes of administration is the object of several research efforts, as well as the attempts to prolong the beneficial effects of these agents (5).

In particular, vaginal or intrauterine methods of drug release represent an appealing option. A danazol-loaded vaginal ring has been tested with encouraging results in patients with deeply infiltrating endometriosis (6), and pain relief has been reported after use of a danazol-loaded intrauterine device in women with endometriosis (7). In addition, reduced side effects and proved safety suggest that the levonorgestrel-releasing intrauterine device may play an important role in long-term treatment of pain associated with endometriosis of the rectovaginal septum in patients with no immediate desire for pregnancy (8). We prospectively assessed the efficacy of a vaginal danazol treatment in painful symptoms in women with recurrent deeply infiltrating endometriosis.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of the Academic Health Center of Siena, and informed consent was obtained from each participant. Included in the study were women (N = 21) (median age 32.6 years; age range, 28–37 years) regularly menstruating, not wanting pregnancy, with a diagnosis of deeply infiltrating endometriosis involving the uterosacral ligaments and the rectovaginal septum. The baseline clinical characteristics of the women enrolled in the study are shown in Table 1 (9). The diagnosis had been made by biopsy during conservative laparoscopic surgery. The patients had been treated after surgery with various drugs (estrogenic-progestogenic, GnRH analogues, progestins) for different period of times. They were referred to our center because of pain recurrence (in all women dysmenorrhea, dyspareunia, and chronic pelvic pain were registered; five women also reported painful defecation). An involvement of the rectovaginal septum was confirmed by vaginal and rectal examination and by transvaginal and transrectal ultrasonographic evaluation (MyLab70; Esaote SpA, Genoa, Italy). The size of the endometriotic lesions was calculated by using the formula for the volume of an ovoid (D1 × D2 × D3 × 0.5222).

Exclusion criteria were obstructive uropathy or bowel stenosis; evidence of complex adnexal cysts or an ovarian endometrioma of diameter ≥3 cm at vaginal ultrasonography; therapies for endometriosis other than nonsteroidal anti-inflammatory drugs in the 3 months before study entry; the usual contraindications to estrogens and progestogens; a diagnosis of concomitant pelvic inflammatory disease; or known gastrointestinal, urologic, and orthopedic diseases.

Each patient was asked to complete a questionnaire on the presence and severity of dysmenorrhea, nonmenstrual pelvic pain, and deep dyspareunia, graded by using a 0- to 3-point multidimensional categorical rating scale modified from that devised by Biberoglu and Behrman (10). This scale defines dysmenorrhea according to loss of work efficiency and need for bed rest, nonmenstrual pain according to various degrees of discomfort and use of analgesics, and deep dyspareunia according to limitation of sexual activity. With respect to the original scheme, ratings of "pelvic tenderness" and "induration" were excluded to avoid the physician subjectivity inherent in an open-label trial (Table 2) (10).

TABLE 1

Distribution of study patients according to age, parity, body mass index, and endometriosis stage at previous surgery.

Variable	No. of patients	%
Age (y)		
<30	9	43
>30	12	57
Parity		
0	17	81
≥1	4	19
Body mass index[a]		
<21	3	14
21–22	9	43
23–24	7	33
>25	2	10
Disease stage[b]		
I	0	0
II	0	0
III	13	62
IV	8	38

[a] Body mass index = Weight (kg)/Height (m^2).
[b] According to the revised American Fertility Society classification (9).

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Vaginal danazol (200 mg/d) was self-administered for 12 months. Dysmenorrhea, dyspareunia, and chronic pelvic pain intensity were assessed before and every 3 months on the first day of the menses for 12 months, with use of an interview comprising a 10-point visual analogue pain scale (11). A score of 6 or greater was considered indicative of moderate or severe pain, whereas a score of 4 or less indicated mild or negligible pain. When enrolled all patients eligible for the study had a score consistent with moderate or severe pain. Transvaginal and transrectal ultrasound evaluation was done before and after 12 months of treatment. Serum concentrations of cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, glycemia, protein S, protein C, antithrombin III, and homocysteine were evaluated before and after 6 and 12 months. Menstrual cycle duration was monitored, and patients were required to follow natural contraceptive methods. All other possible adverse effects were monitored at each observation.

Statistical analysis included ANOVA for repeated measures by post hoc test with significance as a two-tailed $P<.05$.

RESULTS

The entire group of patients completed the 12-month study and remained regularly menstruating throughout the entire period of observation. Dysmenorrhea, dyspareunia, and pelvic pain significantly decreased after 3 months of treatment ($P<.01$), with a persistent effect until 12 months

TABLE 2

Verbal rating scale to score pain symptoms associated with rectovaginal endometriosis.

Symptom	Description	Degree	Score
Dysmenorrhea[a]	No discomfort	Absent	0
	Some loss of work efficiency	Mild	1
	In bed part of 1 day, occasional loss of work	Moderate	2
	In bed for one or more days, incapacitation	Severe	3
Pelvic pain[a]	No discomfort	Absent	0
	Occasional pelvic discomfort	Mild	1
	Noticeable discomfort for most of the cycle	Moderate	2
	Pain persisting during the cycle or requiring strong analgesics	Severe	3
Dyspareunia[a]	No discomfort	Absent	0
	Tolerated discomfort	Mild	1
	Intercourse painful to the point of interruption	Moderate	2
	Intercourse avoided because of pain	Severe	3

[a] Modified from Biberoglu and Behrman (10).

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($P<.01$) (Table 3 and Fig. 1). In the five cases of painful defecation the treatment was effective in reducing the symptoms.

Transvaginal and transrectal ultrasonography showed a decrease of the mean ± SD volume of rectovaginal plaques from a baseline value of 3.1 ± 1.2 mL to 1.9 ± 1.2 mL within 6 months ($P<.01$) (Fig. 2). A reduced volume (1.2 ± 0.8 mL) was confirmed at the end of the treatment ($P<.05$) (Fig. 3).

No significant change of serum metabolic and thrombophilic parameters measured was registered after 12 months of treatment (Table 4). A vaginal irritation during the first month of treatment in four cases was the major side effect but did not cause treatment withdrawal.

DISCUSSION

Our results showed that the use of low-dose vaginal danazol is highly effective in the treatment of the painful symptoms associated with recurrent deeply infiltrating endometriosis, reduces the size of endometriotic lesions, and has no systemic side effects.

TABLE 3

Grading of pain symptoms based on the verbal rating scale in patients with rectovaginal endometriosis before and after 12 months of medical therapy.

Symptoms	Baseline	3 Months	6 Months	9 Months	12 Months
Dysmenorrhea					
Absent	0	8	11	15	19
Mild	0	5	5	4	2
Moderate	8	6	3	2	0
Severe	13	2	2	0	0
Pelvic pain					
Absent	0	2	12	17	21
Mild	5	8	5	4	0
Moderate	16	11	4	0	0
Severe	0	0	0	0	0
Dyspareunia					
Absent	2	4	9	14	19
Mild	3	9	6	4	2
Moderate	11	5	3	2	0
Severe	5	3	3	1	0

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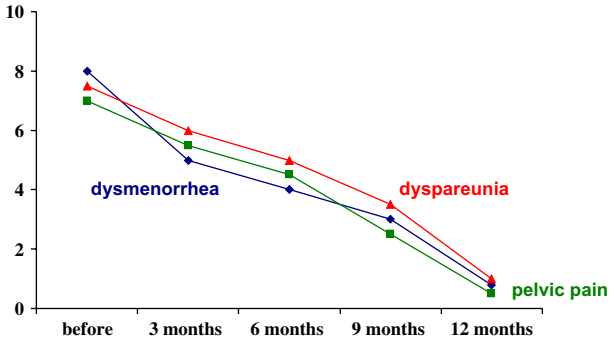
FIGURE 1

Variant of intensity of pain symptoms as assessed on a visual analogue scale during the study period.



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The subjective assessment of pain intensity by a visual analogue pain scale provided an adequate assessment of dysmenorrhea, dyspareunia, and pelvic pain, associated with

FIGURE 2

A transvaginal scan of a woman affected by deep infiltrating endometriosis (expression of a rectovaginal septum localization of endometriosis) before (**A**) and after 12 months of therapy (**B**).

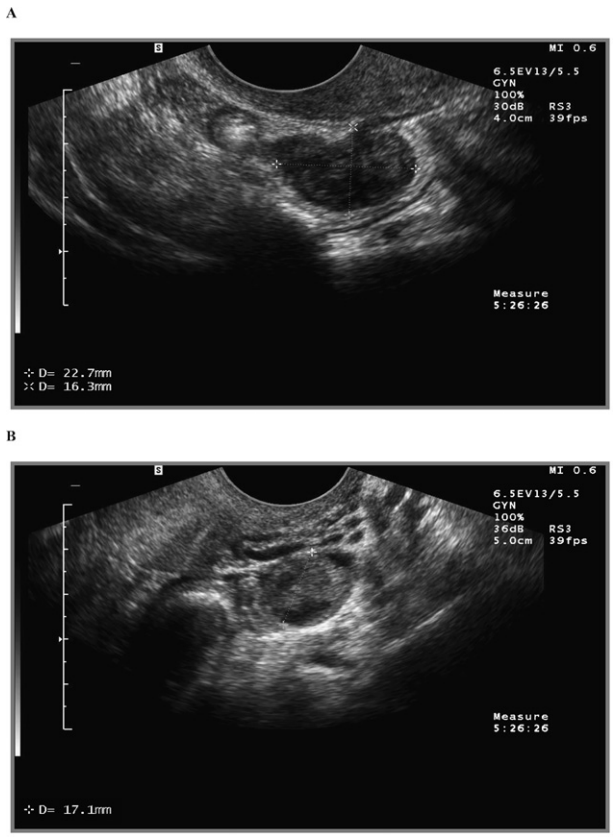

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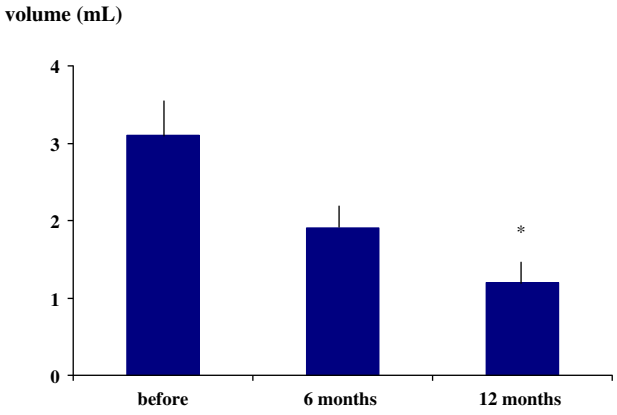
FIGURE 3

Mean ± SD volume of rectovaginal plaques from a baseline value to the end of the treatment ($P < .05$).



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an improved quality of life in these patients with deeply infiltrating endometriosis (11). The painful activity of endometriotic lesions is related to the vascularity of the lesions, to the inflammation, or to the adhesions (12–14). Indeed, similar to tumor metastasis, endometriotic implants require neovascularization to establish, grow, and invade. The effect on organic symptoms may be due not only to the volumetric reduction of rectovaginal plaques but also most probably to reduced intralesional and perilesional inflammation and to reduced production of prostaglandins and cytokines, which stimulate pain fibers. Major cytokines, growth factors, steroid hormones, and eicosanoids are responsible for angiogenesis and inflammation in endometriosis, and angiogenic factors are increased in the peritoneal fluid of patients with endometriosis, in the peritoneal endometric implants, and in ovarian endometriomas (15).

Other treatments are also effective in pain control in women with deeply infiltrating endometriosis. In fact, the intrauterine device releasing levonorgestrel decreases pelvic pain symptoms caused by peritoneal and rectovaginal endometriosis and reduces the risk of recurrence of dysmenorrhea after conservative surgery, associated with local drug concentrations greater than plasma levels and limited adverse effects (16).

Some oral progestogens (danazol, levonorgestrel, medroxyprogesterone acetate) may be effective in the control of pain symptoms in women with pelvic endometriosis also because of their anti-inflammatory in vitro and in vivo effects, but with adverse effects (17). Recently, low-dose norethindrone acetate treatment resulted in an effective, tolerable, and inexpensive medical alternative to repeated surgery for treating symptomatic rectovaginal endometriotic lesions in patients who did not seek conception (18).

The present ultrasound data confirmed the role of transvaginal and transrectal sonography as a first-line imaging

TABLE 4

Serum metabolic and coagulative parameters measured before and after 12 months of treatment in all patients (N = 21).

Parameters (normal range)	Baseline	12 Months
Total cholesterol (130–220 mg/dL)	162 ± 21	172 ± 23
Triglycerides (40–190 mg/dL)	110 ± 15	130 ± 18
Glycemia (60–110 mg/dL)	70 ± 8	76 ± 10
Total bilirubin (0.2–1.0 mg/dL)	0.5 ± 0.2	0.6 ± 0.1
Aspartate aminotransferase (5–40 UI/L)	8 ± 2	12 ± 6
Alanine aminotransferase (5–40 UI/L)	6 ± 1	9 ± 6
Protein S total (70%–140%)	80 ± 18	96 ± 10
Protein C (70%–140%)	75 ± 11	90 ± 9
Antithrombin III (80%–120%)	88 ± 7	94 ± 6
Homocysteine (<13 μm/L)	4 ± 2	5 ± 3

Note: Values are expressed as mean ± SD. All parameters, not significant ($P>.05$).

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technique for suspected deeply infiltrating endometriosis. Sonovaginography is a reliable method for the assessment of the rectovaginal septum and for the vaginal involvement associated with other sites of deeply infiltrating endometriosis (19). Transvaginal ultrasound is able to detect the rectovaginal septum because it is apposed to the peritoneum of the pouch of Douglas, which is directly in contact with the top of the rectovaginal septum (20). Nevertheless, the addition of transrectal sonography is a good option for identifying rectovaginal and uterosacral involvement (21).

Our study showed that the use of vaginal danazol does not affect the menstrual cycle and has few side effects. This is probably due to the negligible systemic absorption leading to undetectable serum levels, as previously demonstrated (6). The low dose of danazol does not affect the pituitary ovarian axis and does not modify the endometrial thickness induced by estrogens and progesterone. Oral danazol at high doses affects endometrium (22, 23). The evidence on unaffected serum concentrations of metabolic or thrombophilic parameters supports a safe treatment in contrast with the classical danazol treatment, which is associated with an increase of protein S, protein C, and antithrombin (24, 25). The present data on the safety and high compliance of vaginal administration of danazol agree with previous reports referring to vaginal or uterine administration and support a limited systemic absorption (6, 7). Conservative surgical treatment also obtains persistent improvement of the painful symptoms associated with endometriosis in large numbers of the patients. Presacral neurectomy markedly reduces the midline component of menstrual pain, but it is not effective in deep dyspareunia (26). The limits of conservative surgery are the frequent recurrences, also in the presence of classical medical treatments. Therefore, it is critical to have medical therapy to obtain meaningful improvement of the painful symptoms associated with limited side effects and good compliance, and our present data suggest that vaginal danazol administration may be one of the new alternatives to repeated surgery in the medical treatment of recurrent deeply infiltrating endometriosis. The issue of tolerability is of major importance when evaluating the overall benefits of long-term treatments for chronic conditions such as symptomatic endometriosis. It may be misleading to focus only on pain relief because drugs may well alleviate pain but also be associated with important disadvantages. The present study showed the efficacy of vaginal danazol in women with symptomatic deeply infiltrating endometriosis who want to avoid further surgery.

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