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ORIGINAL RESEARCH ARTICLE

Long-term vaginal danazol treatment in fertile age women with adenomyosis

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ABSTRACT

Background: The aim of the study was to evaluate the clinical efficacy of long-term vaginal danazol treatment in fertile age women with adenomyosis on pain symptoms and abnormal uterine bleeding (AUB).

Methods: A retrospective study on 66 young women with dysmenorrhea and/or dyspareunia, AUB and 2D-ultrasound diagnosis of adenomyosis was conducted at University Hospital of Siena (Italy). Women included were treated with a daily low-dose vaginal danazol (200 mg) for 6 months, followed by 2 different schedules: group A) continuous treatment for further 18 months (n = 30); group B) cyclic intermittent treatment with 3 months' therapy followed by 3 months' interval for further 18 months (n = 36). A visual analog scale (VAS) for pain symptoms, a pictorial blood-loss assessment chart (PBAC) for uterine bleeding, 2D-ultrasound signs of adenomyosis and quality-of-life measures were assessed at baseline and after both vaginal progestin regimens.

Results: The pain symptoms, PBAC score and uterine volume were significantly reduced ($p<0.0001$) after 6 months, and the reduction persisted in both group of patients until the end. Mental and physical index score values increased ($p<0.0001$) in both groups at the end of treatment, with significantly higher mental index scores in intermittent than in continuous treatment ($p<0.0001$), associated with some drop-out (10%).

Conclusions: A long-term treatment with vaginal danazol is effective to control pain and AUB in women with adenomyosis. The 6 months' treatment followed by a cyclic 3 months' treatment for further 18 months has the best compliance in symptomatic patients with adenomyosis.

Keywords: Abnormal uterine bleeding, Adenomyosis, Dysmenorrhea, Endometriosis, Pelvic pain, Vaginal danazol

Introduction

Adenomyosis is a uterine disorder characterized by pelvic pain symptoms, abnormal uterine bleeding (AUB) and infertility. Dysmenorrhea and dyspareunia are the most common presenting symptoms; however, the clinical presentation of adenomyosis is often mixed and occasionally it may be even asymptomatic (1). Adenomyosis is considered a common disturbance in women over 40 years of age (2); however, using the current ultrasound technologies, adenomyosis is detected in 30% of young women (3) and is described as a cause of infertility and negative assisted reproductive technologies (ART) outcome (4). The non-invasive diagnosis of adenomyosis is now possible with magnetic resonance imaging (MRI) and transvaginal sonography (TVS) – as an alternative to hysterectomy – for symptomatic patients who require preservation of fertility (5-7).

Clinical studies focusing on medical treatment for adenomyosis are rare (8). However, several nonhormonal (i.e., non-steroidal anti-inflammatory drugs) and hormonal treatments (i.e., progestins, oral contraceptives, GnRH agonists) are currently off-labelled used to control pain symptoms and AUB in adenomyosis (1, 9, 10). The rationale for medical treatment is based on pathogenetic mechanisms shared with endometriosis, such as sex-hormones aberrations, impaired apoptosis and increased inflammation (11). An antiproliferative effect of progestins suggests their use for treating adenomyosis. The intrauterine device releasing levonorgestrel (Lng-IUD) has been used for AUB, resulting extremely effective in resolving also pain associated with adenomyosis (12, 13). In addition, Lng-IUD reduces uterine volume, uterine artery blood flow and bleeding in adenomyosis (14).

Among progestins, danazol acts through a direct interaction with endometrial receptors for androgen/progesterone, reducing menstrual bleeding and blood loss (15). Danazol has a low tolerability for oral administration because of its systemic side effects; however, vaginal danazol has been underlined as an effective treatment for painful symptoms in endometriosis (16, 17) and AUB (18, 19); it has a direct effect on uterus acting locally with few side effects (20).

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The present study aimed to evaluate the efficacy in terms of pain and bleeding of long-term vaginal danazol treatment in fertile age women with adenomyosis and the impact on their quality of life.

Methods

An observational retrospective study was conducted on a group of women with symptomatic adenomyosis referred to the Gynecologic Unit of University Hospital of Siena from January 1, 2010, through October 31, 2015, undergoing to long-term vaginal danazol treatment. The study was approved by the local Ethical Committee. The following inclusion criteria were applied: presence of pain symptoms (dysmenorrhea and dyspareunia), AUB, 2D-ultrasonographic diagnosis of adenomyosis (two or more ultrasound features associated with adenomyosis were found). Dysmenorrhea or dyspareunia were evaluated by a visual analog scale (VAS), and those included in the study had a score consistent with moderate (5-8) or severe pain (>7). Menstrual bleeding was assessed by using of the pictorial blood-loss assessment chart (PBAC), menorrhagia was defined as a PBAC >100 during one menstrual period, which corresponds to a blood loss of more than 80 mL (21). Exclusion criteria were: history of endometriosis or actual presence of endometriotic lesions at the transvaginal ultrasound assessment, endometrial hyperplasia, endometrial polyps and/or uterine myomas, the common contraindications to progestin use; a diagnosis of concomitant pelvic inflammatory disease, desire of pregnancy at the beginning and during therapy. A group of 66 fertile age women (age range between 25 and 39 years) undergoing long-term vaginal danazol (24 months) was selected and their medical records were reviewed.

All ultrasonographic examinations were performed by the same examiner (LL) during the secretive phase of the menstrual cycle and uterine or/and endometrial abnormalities were excluded. The presence of TVS features associated with adenomyosis were determined as: (i) heterogeneous myometrium like an irregular myometrial echotexture with decreased or increased echogenicity; (ii) hypoechoic striation in the myometrium (parallel shadowing) as a pattern of thin acoustic shadowing not arising from echogenic foci and/or leiomyoma; (iii) myometrial anechoic lacunae or cysts as a round anechoic area within the myometrium; (iv) asymmetrical myometrial thickening of the uterine walls defined as thicker posterior or anterior uterine wall unrelated to leiomyoma; (v) presence of straight vessels, into the hypertrophic myometrium at the Power Doppler examination, seen as diffusely spread small vessels which do not follow the normal course of the arcuate and radial arteries inside the myometrium (6). Evaluation was suggestive for diffuse adenomyosis when at least two of the recognized 2D-TVS features of the disease were observed.

All patients were treated for 6 months with danazol (200 mg/day by vaginal route) and then a group was continued for a further 18 months (group A) (n = 30) and another continued with 3 months off therapy followed by 3 months' therapy (group B) (n = 36). All selected patients started danazol treatment on the 1-3 day of the menses and, since danazol is not contraceptive, they were advised to use barrier contraceptive methods. Symptom-related pain intensity using VAS score and PBAC score were assessed before treatment, after 6, 12 and 24 months. Transvaginal ultrasound assessment was performed at first evaluation, after 6 months and at the end of period of observation. All other possible adverse effects (i.e., spotting, amenorrhea, hirsutism, vaginal discomfort, change in cervical secretion, mood changes) were monitored at each observation. Quality of life was measured using the SF-12 questionnaire at baseline and at the end of treatment. This tool is a well-known 12-item generic quality-of-life measure that assesses physical and mental functioning over the previous 4 weeks. Scores range from 0 to 100 for each dimension, with 100 indicating optimal quality of life (22, 23).

Analysis of data was performed using the GraphPad Prism version 5.00 for Windows (GraphPad Software, Inc, San Diego, California) and MedCalc® Package (Version 12.4.0.0). Data analyzed by descriptive statistics are presented as means and standard deviations (means ± SD). Statistically significant differences were evaluated using one-way ANOVA. SF-12 questionnaire score was computed, and statistical significance of changes from baselines was evaluated by paired *t*-test. The statistical significance was achieved when $p<0.05$.

Results

The clinical characteristics of all patients are shown in Table I. No statistically significant difference was found in age, BMI and parity. Group A and Group B patients had a similar mean VAS score for dysmenorrhea and dyspareunia at first evaluation. Indeed, no difference was observed concerning PBAC score and uterine volume between the two groups (Tab. I).

A statistically significant reduction of VAS score for dysmenorrhea (Fig. 1), dyspareunia (Fig. 2) and PBAC score (Fig. 3) was observed for both continuous (Tab. II) and intermittent protocol (Tab. III) after 6, 12 and 24 months of danazol treatment ($p<0.0001$). Concerning ultrasound features of adenomyosis, both protocols of vaginal danazol treatment significantly reduced uterine volume ($p<0.0001$) (Fig. 4; Tabs. II and III), while the others ultrasound signs remains unchanged.

The main scores for mental and physical component of the SF-12 are shown in Tables I-III. All items of mental and physical

TABLE I - Baseline characteristics of group A and group B

	Group A (n = 30)	Group B (n = 36)	p value
Age (y)	31.8 ± 4.3	32.8 ± 4.1	NS
BMI (kg/m^2)	21.7 ± 3.8	21.6 ± 3.0	NS
Nulliparity (n) (%)	24 (80)	29 (80.5)	NS
Pain symptoms (VAS)			
Dysmenorrhea	8.1 ± 1.1	8.1 ± 1.2	NS
Dyspareunia	6.1 ± 1.1	5.8 ± 1.0	NS
PBAC	134.3 ± 19	132.3 ± 19.3	NS
Uterine volume (cc)	300.7 ± 97.2	311.3 ± 90.6	NS
SF-12 mental index	39.9 ± 4.5	39.1 ± 5.0	NS
SF-12 physical index	42.3 ± 4.3	42.1 ± 4.0	NS

BMI = body mass index; VAS = visual analog scale; PBAC = pictorial blood-loss assessment chart; NS = not significant.

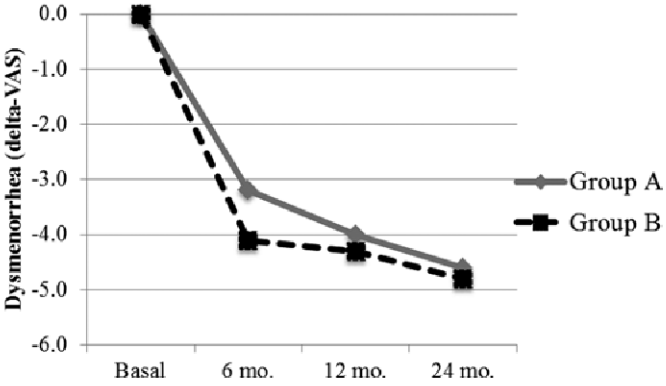

Fig. 1 - Group A and group B delta-VAS values of dysmenorrhea (difference between VAS at 6, 12 and 24 months' follow up and the baseline VAS for dysmenorrhea). VAS = visual analog scale.

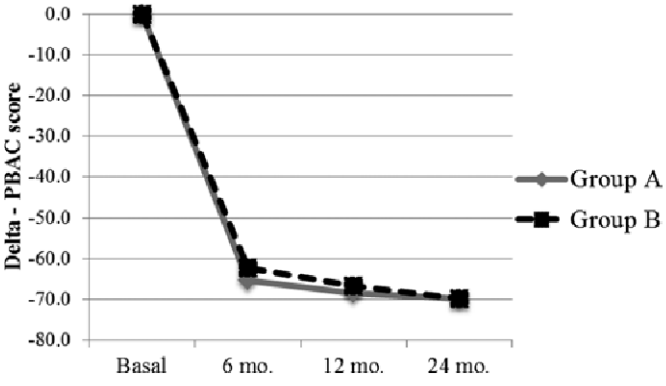

Fig. 3 - Group A and group B delta-PBAC scores (difference between PBAC score at 6, 12 and 24 months' follow-up and the baseline PBAC score). PBAC = pictorial blood-loss assessment chart.

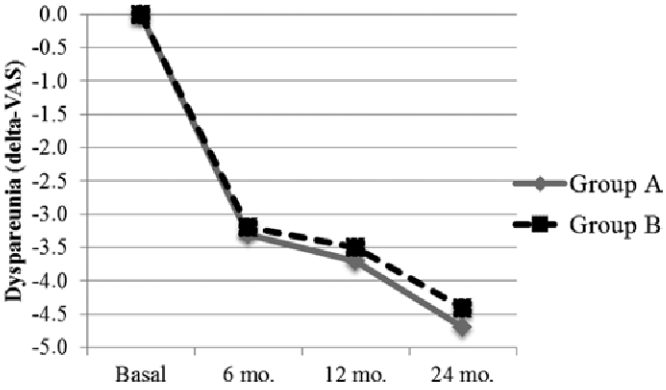

Fig. 2 - Group A and group B delta-VAS values of dyspareunia (difference between VAS at 6, 12 and 24 months' follow up and the baseline VAS for dyspareunia). VAS = visual analog scale.

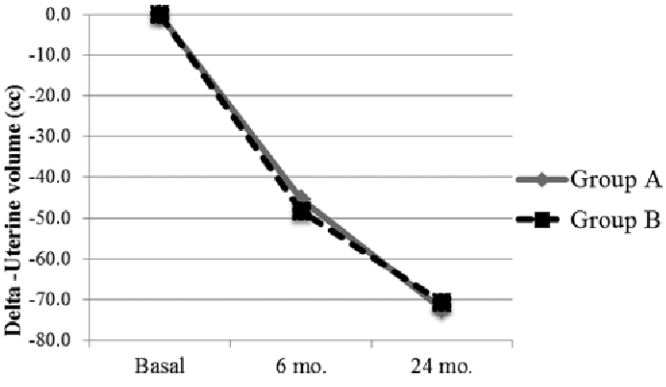

Fig. 4 - Group A and group B delta-uterine volume (cc) (difference between uterine volume at 6 and 24 months' follow-up and the baseline uterine volume).

TABLE II - Pain symptoms, bleeding and uterine volume in group A (6 months' danazol treatment followed by continuous treatment for a further 18 months)

	Before	6 months	12 months	24 months	p value
Dysmenorrhea (VAS)	8.1 ± 1.1	4.9 ± 1.1	4.1 ± 1.2	3.5 ± 1.0	<0.0001
Dyspareunia (VAS)	6.1 ± 1.1	2.8 ± 1.1	2.4 ± 1.1	1.4 ± 1.1	<0.0001
PBAC	134.3 ± 19.0	69.0 ± 11.7	65.8 ± 11.1	64.5 ± 10.9	<0.0001
Uterine volume (cc)	300.7 ± 97.2	255.3 ± 83.5	NA	228.4 ± 86.9	<0.0001
SF-12 mental index	39.9 ± 4.5	NA	NA	47.2 ± 4.9	0.0001
SF-12 physical index	42.3 ± 4.3	NA	NA	55.0 ± 3.5	0.0001

VAS = visual analog scale; PBAC = pictorial blood-loss assessment chart; NA = not applicable.

index significantly improved from baseline to 24 months' follow up, with significantly higher scores in both protocols (p = 0.0001). Comparing mental index of Group A versus Group B, a significantly higher score was observed in intermittent than in continuous treatment (47.2 ± 4.9 vs. 52.3 ± 5.9) (p = 0.0005).

The treatment did not affect the menstrual cycle length; some local vaginal adverse effects (5%) or abnormal bleeding/spotting (3%) were referred.

In Group A, 3/30 (10%) patients interrupted the treatment during the follow-up.

TABLE III - Pain symptoms, bleeding and uterine volume in group B (6 months' danazol treatment followed by a cyclic 3-months treatment for a further 18 months)

	Before	6 months	12 months	24 months	p value
Dysmenorrhea (VAS)	8.1 ± 1.2	4.0 ± 8.3	3.8 ± 1.0	3.3 ± 0.8	<0.0001
Dyspareunia (VAS)	5.8 ± 1.0	2.6 ± 1.1	2.3 ± 1.1	1.4 ± 1.0	<0.0001
PBAC	132.3 ± 19.3	70.0 ± 11.6	65.7 ± 12.0	62.4 ± 11.8	<0.0001
Uterine volume (cc)	311.3 ± 90.6	262.9 ± 81.3	NA	240.7 ± 84.3	<0.0001
SF-12 mental index	39.1 ± 5.0	NA	NA	52.2 ± 5.9	0.0001
SF-12 physical index	42.1 ± 4.0	NA	NA	54.8 ± 3.8	0.0001

VAS = visual analog scale; PBAC = pictorial blood-loss assessment chart; NA = not applicable.

Discussion

The present study showed that the use of vaginal danazol is highly effective in the long-treatment of pain symptoms and AUB related to adenomyosis and the effect is obtained both with a continuous or intermittent schedule, with a better compliance when danazol was cyclically administered.

Dysmenorrhea and dyspareunia significantly decreased after 6 months of treatment with an improved quality of life. This effect is related to reduced inflammation induced by progestin activity, since danazol has anti-inflammatory effect in vitro and in vivo effects decreasing the production of prostaglandins and cytokines; indeed, danazol significantly inhibits lymphocyte proliferation, reduces monocyte-enhanced endometrial proliferation in peripheral blood and increases peritoneal macrophage cytotoxicity (24-26).

The demonstration that the use of vaginal danazol does not affect the menstrual cycle and has poor side effects supports the hypothesis that when administered vaginally this dose of danazol has less androgenic/progestin effect and more direct effect on uterus. This is due to the negligible systemic absorption leading to undetectable serum levels, as previously demonstrated. Thus, the low dose of danazol does not affect the pituitary ovarian axis and does not modify the endometrial thickness induced by estrogens and progesterone (20, 27). When administrated orally at the dose of 600-800 mg/day, danazol affects the hypothalamic-pituitary-gonadal (HPO) axis, mood and behavioral changes and endometrial changes (28, 29). The present data on the efficacy, safety and high compliance of vaginal administration danazol agree with previous reports referring vaginal or intrauterine administration and support a limited systemic absorption (17-20, 27).

The issue of tolerability is of major importance when evaluating the overall benefits of long-term treatments for chronic conditions such as symptomatic adenomyosis. Indeed, pain relief; reduced AUB and regular menstrual cycle are relevant issues for the patients. The possibility that the effect is long lasting explains the better compliance of the intermittent vaginal treatment: patients prefer to have the 3-month cyclic protocol in comparison to the continuous administration since the vaginal administration may have some disadvantages, related to the possible vaginal discomfort.

The concomitant presence of adenomyosis is described in 49% of patients with deep infiltrating endometriosis undergoing to surgery, causing the postsurgical recurrence of pain and AUB (30). Thus, the vaginal danazol treatment may also be useful for recurrent pain symptoms in endometriosis (17, 31), even for persisting pain in cases of rectovaginal endometriosis treated with LNG-IUD (32, 33).

In conclusion, the 6-month vaginal danazol treatment followed by intermittent 3-month/cycle treatments for a further 18 months may be considered a valid choice to keep the adenomyosis-related pain and AUB under control.

Disclosures

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Conflict of interest: None of the authors has financial interest related to this study to disclose.

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