



# Norethisterone acetate for the treatment of symptomatic bladder endometriosis



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**INTRODUCTION AND AIM OF THE STUDY:** Endometriosis of the urinary tract is a rare form of the disease, affecting approximately 1% of women with endometriosis. Bladder endometriosis is defined as endometriosis infiltrating the detrusor muscle. It may cause a wide range of symptoms including urinary frequency, dysuria, bladder pain and hematuria. These symptoms may either have increased severity during the menstrual cycle or have a non-cyclical presentation. Several studies demonstrated that the laparoscopic excision of bladder endometriotic nodules causes a significant improvement in symptoms that persists at long-term follow-up. Progestins, gonadotropin releasing hormone analogues and estrogen-progestin combinations may relieve urinary symptoms; however, few studies investigated the role of endocrine therapies in the treatment of symptoms caused by bladder endometriosis. Norethisterone acetate (NETA) is consolidated therapy for deep infiltrating endometriosis (1,2) but no previous study investigated the role of this drug in the medical therapy of bladder endometriosis. This study aimed to evaluate the efficacy of NETA in the treatment of symptoms caused by bladder endometriosis.

**MATERIAL AND METHODS:** This prospective study included women of reproductive age with bladder endometriosis. The inclusion criteria were: ultrasonographic diagnosis of bladder endometriosis; presence of pain and/or urinary symptoms. Exclusion criteria for the study were: use of hormonal therapies in the six months prior to inclusion in the study; unwillingness to tolerate menstrual changes; undiagnosed vaginal bleeding; immediate desire to conceive; pregnancy; psychiatric disturbances and history of drug or alcohol abuse. Study subjects received NETA (2.5 mg/day, Primolut-Nor; Schering, Milan, Italy). The intensity of urinary symptoms (suprapubic pain, dysuria, frequency, urgency) was measured using a 10 cm visual analogue scale (VAS). Study subjects had consultation at 3-, 6- and 12-month of treatment and then every year. The volume of the endometriotic nodule and the intensity of pain symptoms were evaluated before starting the treatment, after 3, 6 and 12 months of therapy and then every year. The volume of the bladder nodule was estimated by using virtual organ computer-aided analysis (VOCAL, GE Healthcare, Milwaukee, WI, USA). The primary objective of the study was to evaluate the changes in urinary symptoms between baseline and follow-up during treatment. The secondary endpoints of the study were to evaluate the changes in pain symptoms and in the volume of the bladder endometriotic nodules.

**RESULTS:** Thirty patients with a mean ( $\pm$ SD) age of 33.8 ( $\pm$  4.2 years) were included in the study. The median length of treatment was 23.5 months (range, 5-63 months). Fourteen patients (46.7%) completed the 12-month follow-up. The other 16 (53.3%) discontinued treatment because of ineffectiveness (n=10), weight gain (n=1) and irregular bleeding (three patients with spotting) and desire of pregnancy (n=2). Four out of the 14 patients who interrupted the treatment due to ineffectiveness or adverse events underwent surgery. Among those patients who completed the 12 months of treatment, a significant improvement was reported in the severity of all urinary symptoms ( $p < 0.05$  for all comparisons). There was also a significant improvement in non-menstrual pelvic pain and deep dyspareunia. Furthermore, the volume of the bladder endometriotic nodules significantly decreased at 12-month follow-up compared with baseline ( $p < 0.05$ ).

**INTERPRETATION OF RESULTS:** Results from this prospective pilot study show that about 50% of patients did not complete the 12-month follow-up because of treatment ineffectiveness or onset of adverse events. However, in patients who completed the 12-month follow-up, the treatment of bladder endometriosis with NETA was effective in improving the severity of endometriosis-related urinary symptoms, pain symptoms and in reducing the volume of the endometriotic nodule.

**CONCLUSIONS:** NETA should be considered a first-line option in the treatment of symptoms caused by bladder endometriosis. It may not only improve pain symptoms but also ameliorate urinary complains and decrease the volume of bladder nodules.

	Baseline	12-month follow-up	p
Sovrapubic pain	6.9 $\pm$ 1.4 (n=30)	3.6 $\pm$ 1.9 (n=21)	< 0.001
Frequency	5.8 $\pm$ 1.9 (n=20)	3.2 $\pm$ 1.4 (n=14)	< 0.001
Urgency	4.9 $\pm$ 1.7 (n=15)	3.3 $\pm$ 2.2 (n=10)	0.008
Dysuria	7.3 $\pm$ 1.2 (n=15)	2.5 $\pm$ 1.5 (n=10)	< 0.001
Hematuria	6.9 $\pm$ 1.1 (n=30)	3.1 $\pm$ 2.0 (n=21)	< 0.001

Data are presented as mean  $\pm$  standard deviation and number of patients

## REFERENCES:

1. Ferrero S, Remorgida V, Venturini PL. Current pharmacotherapy for endometriosis. *Expert Opin Pharmacother.* 2010;11:1123-34.
2. Vercellini P, Crosignani P, Somigliana E, Viganò P, Frattaruolo MP, Fedele L. 'Waiting for Godot': a commonsense approach to the medical treatment of endometriosis. *Hum Reprod.* 2011;26:3-13.