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Full length article

# Efficacy and acceptability of long-term norethindrone acetate for the treatment of rectovaginal endometriosis

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ABSTRACT

*Objective:* To study the efficacy of long-term treatment with norethindrone acetate (NETA) in patients with rectovaginal endometriosis.
*Study design:* This retrospective cohort study included 103 women with pain symptoms caused by rectovaginal endometriosis. Patients received NETA alone (2.5 mg/day up to 5 mg/day) for 5 years. Primary outcome was the degree of satisfaction with treatment after 5 years of progestin therapy. Secondary outcomes were the assessment of any variation in pain symptoms and the volumetric assessment of the disease by magnetic resonance imaging (MRI).
*Results:* Sixty-one women completed the 5-year follow-up (61/103, 59.2%) with 16 women withdrawing because of adverse effects (38.1%). Overall, 68.8% (42/61) of the women who completed the study were satisfied or very satisfied of this long term NETA treatment. This represents a 40.8% (42/103) of the patients enrolled. Intensity of chronic pelvic pain and deep dyspareunia significantly decreased during treatment ($p < 0.001$ versus baseline at 1 and 5 year). Dyschezia improved after 1-year respect to baseline ($p = 0.008$) but remained stable between first and second year ($p = 0.409$). At the end of 5 years treatment, a radiological partial response was observed in 33 patients (55.9%, n 33/59); a stable disease in 19 patients (32.2%, n 19/59). Seven women (7/59, 11.9%) displayed a volumetric increase of rectovaginal endometriosis under NETA treatment.
*Conclusion:* Five-year therapy with NETA is safe and well tolerated by women with rectovaginal endometriosis. Due to its low cost and good pharmacological profile, it represents a good candidate for long-term treatment in this setting.

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## Introduction

Endometriosis is an estrogen-dependent chronic inflammatory disease [1]. The optimal treatments for endometriosis have not been completely standardized yet and for this reason several women undergo medical and/or surgical treatment during their life to treat the disease. Current medical regimens (hormonal treatments) act improving disease symptoms through the suppression of estrogens circulation [2]; however, due to the lack of response or compliance to long-term hormonal treatment, many women opt during their life for the surgical removal of the disease [3].

Laparoscopic surgical excision of pelvic endometriotic nodules might represent a definitive treatment in some patients [4], however this "radical" surgery is technically demanding and deep endometriotic lesions may not be completely excised by inexperienced surgeons. Furthermore, even in experienced hands, it may cause long and short term complications [5] which may not be easily accepted by young women undergoing surgery for a benign disease [6,7].

For those women, who do not accept primary or secondary surgical treatment or just want to postpone this option, a medical therapy (hormonal therapy), possibly for long-term periods, is necessary [8]. Thus, it becomes a key objective ensuring that

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hormonal therapies are being accepted for long periods of time, with a good pain control and with few side effects.

Hormonal therapies (particularly progestins and estro-progestins combinations) have been repeatedly demonstrated to be safe, well tolerated and effective in the treatment of women with symptomatic endometriosis but, unfortunately, very few studies have investigated the effects of long-term treatment in women with endometriosis-related pelvic pain (>12 months) [9]. Furthermore, it is common clinical experience that patients with extensive deep endometriosis (such as intestinal and bladder nodules) have used hormonal therapies for years to control pain and/or for contraception; however, the impact of these therapies on the progression of unoperated deep nodules remain to be elucidated. Limited data showed that, in some patients, deep endometriosis can progress despite the use of hormonal therapies [10,11].

Norethindrone acetate (NETA) has been used widely in women with rectovaginal endometriosis up to 12 months follow-up, demonstrating a good pain control, with tolerable clinical (weight gain, reduce libido) and haematological (lipid profile alteration) side effects and it appears a good candidate for long-term single drug management in this setting [12–19].

This retrospective study aimed to assess the efficacy and the volumetric control of five years therapy with NETA alone in treating pain symptoms of women with rectovaginal endometriotic nodules that did not infiltrate the rectum.

## Materials and methods

This study was based on a retrospective analysis of a database that was prospectively collected between October 2004 and August 2016. The local Ethic Committee approved the study protocol. All women signed an informed written consent to record their data for scientific purposes.

The study included patients who had a diagnosis of rectovaginal endometriosis between October 2004 and July 2011 and suffered pain symptoms requiring hormonal treatment.

The diagnosis of rectovaginal endometriosis was suspected on the basis of vaginal and rectal examination and it was confirmed by magnetic resonance imaging (MRI). Infiltration of the muscularis mucosae of the rectum was also excluded by at least one of the following techniques: rectal water-contrast transvaginal ultrasonography [20,21] or multidetector computerized tomography enema [22]. All these techniques were previously shown to be accurate in the diagnosis of rectosigmoid endometriosis.

We included in the study patients who, at the time of starting the treatment with NETA, had persistence of pain symptoms of

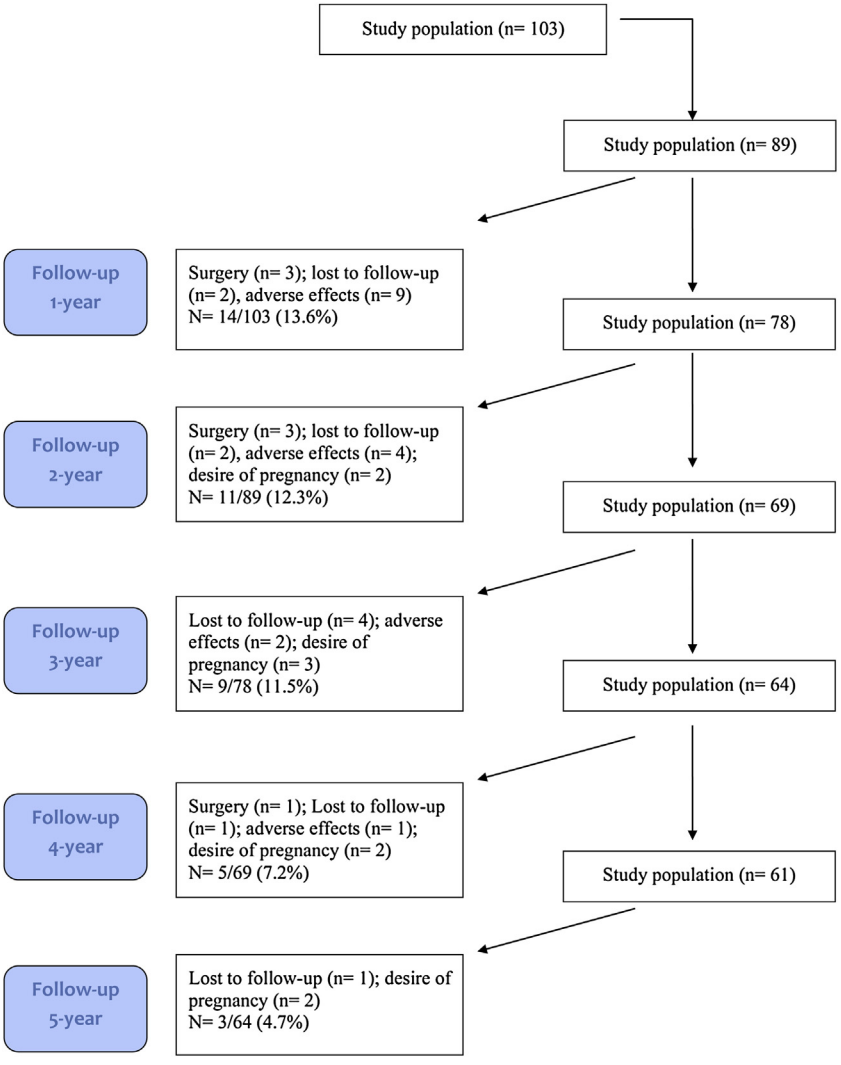


**Fig. 1.** Flow chart showing women's progress through the study.

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