

## Treatment of Refractory Endometriosis-Related Pain with Vaginal Gestrinone in Pentravan Associated with Pinus Pinaster Extract and Resveratrol: A Preliminary Study

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### Abstract

**Introduction:** Sexual dysfunction is common in patients with endometriosis and in the majority of cases the cause of sexual dysfunction is pain. The aim of this study was to investigate the effect of a combination of vaginal gestrinone with oral pinus pinaster extract and resveratrol on the pain scores of patients with deep endometriosis refractory to previous hormone treatment.

**Methods:** Fifteen patients were treated with a combination of 5 mg of vaginal gestrinone in Pentravan<sup>®</sup> (Fagron, the Netherlands) three times a week and 100 mg of oral pinus pinaster extract (Fagron, the Netherlands) together with 30 mg of resveratrol (Fagron, the Netherlands) daily.

**Results:** Mean pain score was 9 prior to treatment, reducing significantly to 3 ( $p=0.03$ ) and 0.5 ( $p=0.004$ ) after 1 and 2 months of treatment, respectively. After six months, all patients were pain-free. Amenorrhea rates were 80% after the first month, reaching 100% during the remainder of the treatment. There were no statistically significant changes in blood chemistry except for SHBG levels, which decreased significantly.

**Conclusion:** This preliminary observational study showed that the combined treatment of vaginal gestrinone with natural antioxidants is very effective for the treatment of refractory pain in patients with deep endometriosis.

**Keywords:** Gestrinone; Pentravan<sup>®</sup>; Deep endometriosis; Dysmenorrhea; Pelvic pain

### Introduction

Sexual dysfunction is rather common in endometriosis, affecting almost 61% of patients. In 58% of these cases, the cause is the presence of pelvic pain, although in healthy women this is a rarely a cause of sexual dysfunction, being reported by only 1% of patients [1]. Pain improvement is therefore a crucial step in the management of sexual dysfunction in endometriosis patients and can be achieved through effective medical treatment.

Gestrinone (13- $\beta$ -ethyl-17 $\beta$  hydroxy 18,19 dinorpregnana-4,9,11 trien-one), a trienic steroid derivative of 19-nortestosterone, has been used to treat endometriosis. Because of its antiestrogenic, anti-progesterone and androgenic effects, gestrinone fulfills the expected pharmacological profile of a suitable drug for the treatment of endometriosis-related pain [2]. Furthermore it is effective when administered by several different routes of administration, including through the vaginal mucosa [2,3]. One advantage of using this route is the occurrence of a uterine first pass effect, which concentrates drugs in the pelvic region before reaching systemic circulation [4]. Furthermore, the vaginal route is associated with fewer side effects compared to the oral route [3].

Recently, the development of better permeation excipients such as Pentravan<sup>®</sup> prompted us to investigate the clinical efficacy of vaginal gestrinone in patients with deep endometriosis, severe dysmenorrhea and pelvic pain. Previous studies showed Pentravan<sup>®</sup> to be effective for the vaginal delivery of danazol to treat deep endometriosis-related pain [5,6]. In the present paper, the results of a preliminary pilot study using a combination of vaginal gestrinone in Pentravan<sup>®</sup>, administered simultaneously with oral pinus pinaster extract and resveratrol, are reported in a small group of patients with deep endometriosis and pelvic pain refractory to previous hormone therapy. The pinus pinaster extract and resveratrol were used because they had previously been shown to increase the efficacy of hormone treatment for the treatment

of endometriosis-related pain

### Aims

The aim of the present study was to investigate the effect of a combination of vaginal gestrinone with oral pinus pinaster extract and resveratrol on the pain scores of patients with deep endometriosis refractory to previous hormone treatment [7,8].

### Methods

Fifteen patients with deep endometriosis and severe pain refractory to previous hormone treatment were enrolled for this small pilot study to evaluate the efficacy of the combined treatment of vaginal gestrinone in Pentravan<sup>®</sup> with oral pinus pinaster extract and resveratrol. They were advised to use gestrinone in Pentravan<sup>®</sup> vaginally. Gestrinone is licensed by the Brazilian drug regulatory authority (ANVISA) for use as an oral medication for the treatment of endometriosis; however, the drug is also widely used off label in the form of subdermal implants for the same indication since the oral route is associated with a higher incidence of side effects [3].

The inclusion criteria for this study were a previous diagnosis of deep endometriosis made either by laparoscopy or transvaginal

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ultrasonography following bowel preparation, a pain score >7 and previous unsuccessful medical treatment. Previous treatment included hormonal treatment with continuous regimens of oral contraceptives (n=7), dienogest (n=4) or a combination of pinus pinaster extract and resveratrol (n=4).

All patients were counseled with respect to this treatment regimen and gave their informed consent to participate in the study. Global pain scores, applied to both dysmenorrhea and dyspareunia, were rated by the patient at baseline and 1, 2 and 6 months following treatment using a visual analogic scale in which 0 was indicative of no pain and 10 reflected the worst pain imaginable. The patients were treated with a combination of 5 mg of vaginal gestrinone in Pentravan® (Fagron, the Netherlands) three times a week with 100 mg of oral pinus pinaster extract (Fagron, the Netherlands) and 30 mg of resveratrol (Fagron, the Netherlands) daily. These medications were prepared by a licensed compounding pharmacy. The patients were instructed to insert the gestrinone/Pentravan® preparation into the vagina at bedtime using a disposable plastic applicator. Vaginal ultrasonography was performed to measure uterine volume and blood tests were carried out at baseline and after two months of treatment. This study was conducted at the *Instituto da Mulher*, Itaigara Memorial Day Hospital, Salvador, Brazil and was approved by the institute's internal review board. Statistical analysis was performed using Student's t-test for paired samples, with significance defined at p<0.05. The distribution of the data was normal, since the pre- and post-treatment pain scores were matched. The main outcome of the present study was the comparison of pain scores evaluated using a visual analogue scale before and following treatment.

## Results

The patients ranged in age from 22 to 47 years; with a mean age of 33 ± 7 years [mean ± Standard Deviation (SD) of the mean]. Twelve patients were nulliparous and, of the remaining three, two had had a cesarean section and one had had a normal delivery.

The mean global pain score of these endometriosis patients at baseline was 9, decreasing significantly to 3 (p=0.03) at the end of the first month of treatment and to 0.5 (p=0.004) after two months of treatment. After six months, all patients were pain free, even during sexual intercourse. Amenorrhea rates were 80% after the first month, with all patients achieving amenorrhea by the second month of treatment. Uterine volume decreased from 108 cm<sup>3</sup> to 88 cm<sup>3</sup> after the second month of treatment. There were no statistically significant changes in total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides or liver enzymes after 2 months of treatment. Mean SHBG levels decreased significantly from 55 nmol/l to 9 nmol/l (p=0.03) (Table 1).

Variable	Baseline (mean ± SD)	After two months of treatment (mean ± SD)	Statistical significance
Glucose (mg/dl)	81 ± 4	82 ± 4	NS
SHBG (nmol/l)	55 ± 32	9 ± 3	p = 0.03
Total cholesterol (mg/dl)	184 ± 27	177 ± 10	NS
HDL (mg/dl)	53 ± 15	37 ± 15	NS
LDL (mg/dl)	122 ± 18	125 ± 22	NS
AST (U/l)	25 ± 4	27 ± 5	NS
ALT (U/l)	17 ± 4	32 ± 20	NS

SD: Standard Deviation; NS: Not Significant; SHBG: Sex Hormone Binding Globulin; HDL: High-Density Lipoprotein cholesterol; LDL: Low-Density Lipoprotein cholesterol; ALT: Alanine Transaminase; AST: Aspartate Transaminase

**Table 1:** Effect of vaginal testosterone in Pentravan® with oral pinus pinaster extract and resveratrol on blood analysis.

Side effects such as leg pain, headache and acne were reported by four patients in the first two months of use; however, they were mild enough not to affect patients' compliance with the treatment.

## Discussion

This preliminary observational study showed that the combination of vaginal gestrinone in Pentravan®, administered together with oral pinus pinaster extract and resveratrol, represents an extremely effective treatment for pelvic pain in patients with deep endometriosis. Although a placebo effect cannot be ruled out, it should be noted that these patients had been unsuccessfully treated in the past with a variety of hormonal treatments alone or with the combination of the pinus pinaster extract and resveratrol alone.

Because of their previous failure to respond to active hormone treatment, it would not have been ethically acceptable to treat any of these patients with placebo.

The incidence of androgenic side effects with the vaginal route appears to be lower than with the oral route and this may be due to the lower blood levels of gestrinone achieved with this route of administration [2,3]. However, the reduction in systemic blood levels did not compromise the therapeutic efficacy of the drug because vaginal absorption leads to high concentrations of gestrinone in the pelvis, with lower systemic blood levels [4]. This could explain not only the effectiveness of gestrinone for the treatment of endometriosis-related pain, as reported, but also the high rates of amenorrhea.

The reduction in pain scores was probably also enhanced by the concomitant use of natural NF-Kappa.b inhibitors such as the anthocyanidins present in the pinus pinaster extract [7]. As previously published by our group, both pinus pinaster extracts and pycnogenol increase the pain-relieving effects of continuous oral contraceptives or vaginal danazol in patients with endometriosis [6,7]. Similar results have also been reported with the use of resveratrol [8]. These potent antioxidants probably reduced the oxidative stress in the endometriosis lesions, thus contributing to the successful pain-relieving effects of the treatment. However further studies comparing gestrinone either alone or in association with the pinus pinaster extract and resveratrol are necessary to confirm whether this association is more effective than the use of gestrinone alone. It would also be interesting to treat other forms of endometriosis with this combination, since one of the limitations of the present study was that it was confined to patients with deep endometriosis, although this form of endometriosis is particularly associated with severe pelvic pain [1]. However these initial findings suggest that the combination of hormone therapy with gestrinone and natural antioxidants was extremely effective for the treatment of pain in a select group of patients with deep endometriosis who had previously failed to respond to other medical treatments. These initial findings also show that the vaginal mucosa seems to represent an effective route for the administration of gestrinone in Pentravan® for the treatment of pain associated with deep endometriosis.

When used orally, gestrinone decreases SHBG levels, leading to an increase in free testosterone [9]. Similar effects were also found in the present study with the use of the vaginal route. The increase in free testosterone can be beneficial for the regression of endometriosis since androgen receptors are present in the lesions [10].

In conclusion, these preliminary results show the excellent pain-relieving effects of this combination treatment of vaginal gestrinone with natural antioxidants in patients who had failed to respond adequately to previous hormone therapy.

## Conflicts of Interest

Hugo Maia Jr. is a speaker for Fagron.

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