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Research Article

Clinical Experience with Vaginal Gestrinone in Pentravan® in the Treatment of Endometriosis Pain

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Abstract

An open clinical trial was conducted with 47 patients with endometriosis and pain, previously treated unsuccessfully with progestin alone or continuous oral contraceptives. The patients were treated with vaginal gestrinone in Pentravan® (5mg/ml) (Fagron, the Netherlands) together with oral pinus pinaster extract and resveratrol daily. Pain scores were evaluated at baseline and 1, 2, 3 and 6 months after beginning treatment. Vaginal ultrasonography was performed after 2 months. In twenty patients, both aromatase and VEGF expression were investigated by immunohistochemistry in the endometrium prior to and 3 months after the initiation of treatment. Blood was drawn at baseline and after 2 months of treatment. Mean pain score before treatment was 9, reducing significantly to 0.4 (p=0.0001) in the second month of treatment. After three months all patients were pain-free. Amenorrhea rates were 80% in the second month, reaching 100% for the remainder of the treatment. Uterine and ovarian cyst volume decreased during treatment. There were no statistically significant changes in total cholesterol, baseline FSH or LH. HDL-cholesterol, triglycerides, total testosterone and estradiol levels decreased significantly. Hemoglobin levels increased significantly from 12 to 13 grams (p=0.008). Liver enzymes remained unchanged. SHBG levels decreased significantly during treatment. Both VEGF and aromatase expression in the endometrium decreased significantly after 3 months of treatment. These preliminary results show that the association of vaginal gestrinone with oral resveratrol and pinus pinaster extract is an effective treatment for endometriosis-related pain, inducing amenorrhea in patients in whom previous treatment with progestin alone or oral contraceptives had failed.

Keywords: Gestrinone; progesterone resistance; testosterone; endometriosis; NF-Kappa.b

Introduction

Endometriosis is an inflammatory pathology in which estrogens are produced in both the eutopic endometrium and in the lesions. The synthesis of estrogens is the result of epigenetic changes leading to activation of the aromatase gene, thus stimulating local estrogen production, which will sustain and enhance the inflammatory milieu in both the eutopic endometrium and in the endometriotic lesions. These molecular changes lead to an overproduction of local prostaglandins and the ensuing excessive inflammation will result in the suppression of progesterone receptors, thus leading to progesterone resistance and treatment failure [1]. Progesterone receptor deficiency associated with the enhanced local estrogen production will lead to an imbalance between the effects of estrogen and progesterone, which will decrease the normal luteal-phase progesterone dominance and replace it with estrogen supremacy [2]. If endometriosis is viewed as a hyper-estrogenic, progesterone-resistant pathology affecting not only the endometrium but also the peritoneal milieu, this may suggest that novel therapeutic approaches are needed to overcome this obstacle. This will benefit patients in whom standard medical treatments, either with a continuous regimen of oral contraceptives or with progestins, have failed, without the need to rely on the use GNRH analogs to induce a hypoestrogenic menopausal-like state [3]. In endometriosis, the abnormal elevated expression of the estrogen receptor beta (ER-β) causes an imbalance in the ERβ-to-ERα ratio in stromal cells, which further suppresses progesterone receptor synthesis. Excessive estrogenic action thus results in an increase in cyclooxygenase-2 expression, greater progesterone resistance and inflammation [4]. One promising approach to overcome this problem would be to use hormones that counteract this estrogenic dominance and the ensuing excessive inflammation by activating the androgen receptor instead of the progesterone receptor. Testosterone is a steroid hormone that exerts anti inflammatory effects by blocking the activation and translocation of NF-Kappa.b transcription factor to cell nuclei, thus halting the inflammatory cascade [5]. Since this transcription factor is constitutively activated in endometriosis, its inhibition by testosterone will halt inflammation and decrease pain [6]. Testosterone receptors are expressed in the endometrial stroma [7], thus rendering this tissue responsive to androgenic hormones. This provides a plausible biological explanation for the use of androgenic hormones in the treatment of endometriosis. One drug that appears promising is gestrinone, which has been used for the treatment of endometriosis and myomas for more than three decades [8]. It is highly effective when administered by the oral route; however, its androgenic side effects precluded its wider acceptance. Nonoral routes for the administration of gestrinone have been developed in Brazil, particularly in the form of sub dermal implants [8]. Despite the lower incidence of androgenic side effects

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with the implants compared to the oral administration, sub dermal implants have the disadvantage that their insertion and removal involve invasive procedures and doses cannot easily be adjusted by the patient once the implants are inserted [8,9]. The development of simple, non-invasive and self-administered, non oral routes through which to deliver gestrinone may offer certain advantages over the use of implants for the treatment of endometriosis and myomas. One promising route for the administration of hormones is the vaginal mucosa. Previous studies in the 1980s showed that the insertion of a 2.5 mg pill containing gestrinone into the vagina two or three times a week effectively managed pain in endometriosis patients and induced amenorrhea in almost 50% of patients, with fewer side effects when compared to either the oral or sub dermal routes [9]. These initial results identified the vaginal mucosa as a promising route for the delivery of gestrinone for the treatment of pelvic pathologies because of the first uterine pass effect. This mechanism is a very effective means of concentrating hormones and other pharmacologically active agents in the pelvic region before they are distributed into the systemic circulation. This is accomplished through an active transport mechanism which acts locally and is greatly helped by the close proximity of the vaginal vein and artery. This creates a concentration gradient in the pelvic organs that enables vaginally administered hormones to reach high tissue levels despite rather low systemic blood levels [10]. Recently, the development of better permeation excipients such as Pentravan®, which proved effective for the vaginal delivery of danazol to treat deep endometriosis-related pain, prompted us to investigate its use with gestrinone in association with a combination of natural polyphenols endowed with antioxidant and anti inflammatory properties, not only for pelvic pain but also for menorrhagia [11]. One such compound consists of a complex mixture of flavonoids extracted from the bark of a pine tree (pinus pinaster), which blocks NF-Kappa.b activity after its binding to DNA responsive elements. The effects of pinus pinaster extract may be further potentiated with the concomitant use of resveratrol to inhibit aromatase activity in endometriosis patients, since this enzyme plays a pivotal role in the progression of endometriosis [12-16]. The present paper evaluates the effect of a combination of vaginal gestrinone in Pentravan® with oral pinus pinaster extract and resveratrol on pain scores and uterine bleeding in patients with endometriosis in whom previous treatments with dienogest or continuous oral contraceptives had failed. The concomitant presence of other pathologies such as myomas or adenomyosis was not a contraindication to the use of gestrinone by these patients with endometriosis and the effect of this treatment on these pathologies was also investigated.

Materials and Methods

The present report refers to an open clinical trial to evaluate a series of 47 patients with deep endometriosis or ovarian endometriotic cysts diagnosed either by vaginal sonography or laparoscopy and that had proved refractory to previous hormonal treatment. Associated pathologies consisted of adenomyosis (n=6) and myomas (n=16). The main presenting symptoms were persistent pain associated or not with menorrhagia. Twenty patients in this group were also seeking treatment for infertility and were scheduled to undergo in vitro fertilization (IVF). All patients had been previously treated by either a continuous regimen of oral contraceptives containing gestodene or drospirenone or by dienogest alone; however, they were still reporting pain associated with irregular bleeding. Prior to initiating treatment with vaginal gestrinone, all the patients were evaluated clinically. Global pain scores, applied to both dysmenorrhea and dyspareunia, were rated by the patient at baseline and 1, 2, 3 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 pinus pinaster extract (100mg) and resveratrol (30 mg) were prepared and placed in the same capsule at a local compounding pharmacy supervised by the same pharmacist (WSDS). All the resveratrol, pinus pinaster extract and gestrinone used in this study were obtained from the same supplier (Fagron, the Netherlands), and all were submitted to a quality control analysis conducted at Fagron's plant in Anapolis, Goias, Brazil to ensure the purity of the preparation. 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 sub dermal implants for the same indication, since the oral route of administration is associated with a higher incidence of side effects [9]. The patients were instructed to insert the gestrinone/Pentravan® preparation into the vagina at bedtime using a disposable plastic applicator. The resveratrol and pinus pinaster extract were given together in the same capsule (Vcaps®, Fagron, the Netherlands) to be taken orally at bedtime every day. Vaginal ultrasonography and blood tests were performed after the second month of treatment in all cases to measure uterine and endometriotic cyst volumes and to determine the effect of treatment on hormone levels and blood chemistry. This study was conducted at the Instituto da Mulher, Itaigara Memorial Hospital. All the patients were counseled with respect to this treatment regimen and gave their informed consent to participate in the study. A placebo group was not used since these patients had been submitted to previous treatments with oral contraceptives and progestins and had failed to respond effectively in terms of pain control management and improvement in their quality of life. Twenty-seven of these patients were scheduled to have laparoscopic surgery when they were referred to this institute for a second opinion. Twenty patients who had had a failed IVF procedure were referred to this hospital for hysteroscopy to evaluate the uterine cavity and to investigate the presence of aromatase expression in the endometrium. These patients reported pain and were counseled to use this treatment for at least three months before undergoing a second hysteroscopy and a subsequent IVF procedure. All the hysteroscopic procedures were carried out by the same two surgeons (HM and CH) with the use of a par cervical block and light intravenous sedation with protocol. When evaluation of the uterine cavity was complete, the hysteroscope was removed and a 4 mm Karman curette attached to a 10 ml disposable plastic syringe was introduced and the endometrium was aspirated. The samples were immediately fixed in 4% formalin and sent to pathology. Routine histology using hematoxylin & eosin (HE) staining was performed on all samples. Both the routine pathology and Immunohistochemical Evaluation of the endometrium were performed by the same pathologist (NP). The indication for hysteroscopy was to evaluate the uterine cavity and determine the presence of aromatase expression

Table 1: Effect of vaginal gestrinone in Pentravan® with oral pinus pinaster extract + resveratrol on pain scores in endometriosis patients.

Evaluation Moment	VAS Pain Score (mean ± SD)	p-value	n
Baseline	9 ± 1		47
1st month	3 ± 2	p<0.0001	47
2nd month	0.4 ± 1.2	p<0.0001	47
3rd month	0		47
6th month	0		27

by immunohistochemistry in the endometrium before and after gestrinone treatment, since these patients were scheduled to undergo an IVF procedure at the end of treatment (n=20). The incidence of positive aromatase and VEGF expression in the endometrium of gestrinone users was evaluated before and after treatment. The presence of these proteins in the endometrium was determined by immunohistochemistry following antigen retrieval. Both aromatase and VEGF expression were investigated using a commercially available monoclonal antibody supplied by Serotech, Raleigh, NC, USA. Antigen retrieval was performed using Tris-EDTA buffer at pH 8.0. The reaction was revealed using the DAKO Envision Flex detection system + Linker followed by DAB + substrate chromogen mix (DAKO). The presence of aromatase and VEGF expression was rated either as positive if there was any detectable staining reaction in the endometrium or negative when no reaction was observed. Statistical analysis was performed using the chi-square test to detect differences in the percentages of endometria positive for VEGF and aromatase expression. Student's t-test was used to detect differences in mean pain scores or blood chemistry before and after treatment with gestrinone. Significance was established at $p<0.05$.

Results

Dysmenorrhea was assessed using a visual analog pain scale at 1, 2 and 6 months after initiation of treatment. Prior to treatment, the mean pain score was 9. Vaginal gestrinone in Pentravan® significantly decreased the intensity of pain and induced amenorrhea. This response was rapid and already observed in the first month of treatment when the mean pain score decreased to 3. After the second month of treatment, almost 85% of the patients were pain free and the mean pain score fell to 0.4. Occasional flare ups of pain occurred in association with breakthrough bleeding; however, after the third month, all 47 patients enrolled in this clinical observation reported being free from pain, including dyschezia and dyspareunia. Twenty-seven completed the six months of treatment and remained pain free until the end of the study period. These results are summarized in (Table 1). Amenorrhea was reported by 90% of the patients after the second month of gestrinone use and after three months all patients reported being in amenorrhea. The cessation of menstrual bleeding was accompanied by a reduction in uterine volume, not only in patients with endometriosis/adenomyosis but also in the case of myomas. In the patients with myomas, uterine volume decreased significantly ($p=0.01$) from 217 cm^3 to 132 cm^3 at the end of the second month of treatment. In patients with adenomyosis/endometriosis, uterine volume reduced significantly from 146 cm^3 to 115 cm^3 ($p=0.04$). There was also a significant reduction in the volume of ovarian endometriotic cysts from 44 cm^3 to 24 cm^3 ($p=0.009$) after treatment. Vaginal gestrinone did not significantly decrease baseline blood levels of either FSH or LH after 2 months of treatment, although ovulation was suppressed in all patients using 5 mg of gestrinone vaginally three times a week. Blood levels of estradiol and total testosterone, on the other hand, decreased significantly. However, the decrease in total testosterone had no negative effect on libido, since there was a relative increase in free testosterone resulting from the considerable decrease in SHBG levels induced by the vaginal administration of gestrinone. Mean SHBG levels decreased significantly from 86 nmol/l to 12 nmol/L in the first two months of treatment ($p<0.0001$). Other metabolic parameters were also affected by this treatment. A significant decrease in triglycerides, HDL cholesterol and glucose was observed after 2 months of treatment. Total cholesterol levels and LDL, on the other hand, were not significantly affected. Because of the high rates of amenorrhea, there was a significant increase in hemoglobin levels, which was already apparent in the second month of treatment. Liver enzymes were not adversely affected by

Table 2: Effect of vaginal gestrinone in Pentravan® with oral pinus pinaster extract + resveratrol on metabolic and hormonal parameters.

Variable	Baseline (mean ± SD)	After two months of treatment (mean ± SD)	Statistical significance
Glucose (mg/dl)	86 ± 8	80± 7	p=0.01
SHBG (nmol/1)	86 ± 50	12± 6	p = 0.001
Total cholesterol (mg/dl)	180 ± 38	172±54	NS
HDL (mg/dl)	51 ± 12	30± 10	p<0.001
LDL (mg/dl)	128 ± 43	136 ± 60	NS
AST (U/l)	23 ±10	35± 44	NS
ALT (UI/l)	24± 14	42 ± 54	NS
LH (mIU/ml)	5 ± 3	5 ± 4	NS
FSH (mIU/ml)	7± 4	5 ± 2	NS
Estradiol (pg/ml)	92 ± 80	31 ± 20	p = 0.008
Total testosterone (ng/dl)	24 ± 14	18 ± 9	p = 0.007
Triglycerides (mg/dl)	99 ± 53	66± 24	p =0.0001
Hemoglobin (g/dl)	11.2 ± 1.5	12.5 ± 1	p = 0.007

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. FSH: follicle stimulating hormone LH: luteinizing hormone.

the treatment in the majority of the patients, except for three cases (3/47) in which there was an increase in alanine transaminase (ALT) and in aspartate transaminase (AST) levels after 2 months of treatment; however, levels returned to normal after discontinuation of treatment. In addition, in one case treatment was discontinued in the third month because the patient was planning to have an IVF procedure. These results are summarized in (Table 2).

The effect of gestrinone on aromatase and VEGF expression

Aromatase expression was detected in the eutopic endometrium of 17/20 endometriosis patients (85%) with a previous history of failed IVF attempts. The staining reaction was localized in the endometrial stroma and it was detected in both the proliferative and luteal phases of the menstrual cycle. Vaginal gestrinone, administered in association with oral pinus pinaster extract and resveratrol, caused a significant decrease in the percentage of endometria testing positive for aromatase expression in these endometriosis patients when compared to pretreatment values. After 3 months of treatment, only 3/20 (15%) of the endometrial samples showed any staining reaction in the stroma. VEGF reaction was detected in the endometrial stroma in 18/20 (90%) of endometriosis patients not in use of hormone therapy but in only 3/20 (15%) of the endometria of patients using gestrinone with pinus pinaster and resveratrol. Hysteroscopy performed after three months of gestrinone treatment revealed a thin endometrium with a decreased vascular network density, giving the mucosa a pale appearance. Histology showed an inactive endometrium with a compact stroma and atrophic glands. Decidual reaction was not observed in the stroma of any of the endometrial samples.

Discussion

Vaginal gestrinone in Pentravan®, when used in association with oral pinus pinaster and resveratrol, proved to be a very effective treatment for both pelvic pain and menorrhagia. The resolution of symptoms was accompanied by an actual decrease in both uterine and endometriotic cyst volume. The association of vaginal gestrinone with oral pinus pinaster extract + resveratrol also decreased aromatase and VEGF expression in the endometrium of patients with endometriosis. The suppression of aromatase and VEGF activity may be one of the mechanisms involved in the pain and menorrhagia ameliorating effects of this association and is likely a consequence of the decrease in inflammation, since the transcription of the VEGF gene is dependent on NF-Kappa.b activation [17]. The anti-estrogenic action of gestrinone, associated with its ability to reduce estradiol production by the ovary, may further inhibit endometrial proliferation and suppress bleeding, thus contributing to the high rates of amenorrhea. The androgenic effects of gestrinone are exerted not only through its direct interaction with the testosterone receptor but also by the increase in free testosterone resulting from the substantial decrease in SHBG levels. The anti-estrogenic effects of gestrinone, on the other hand, are not exerted by blocking the estrogen receptors but, rather, are the consequence of an antagonistic action resulting from of these androgenic effects [8,9]. Gestrinone also exerts anti-proliferative effects on the endometrium, which explains the pathology findings showing the presence of a basal endometrium with inactive glands and no signs of stromal decidualization. The absence of any decidual reaction in the endometria of gestrinone-treated patients is a consequence of the potent anti-progesterone effect of this hormone, since gestrinone does not function as a progestin but, rather, as an androgen. Coutinho et al. showed that the incidence of androgenic side effects was lower when gestrinone tablets were inserted in the vagina compared to other routes of administration [8,9]. This was due to the 10-fold lower blood levels of gestrinone achieved with this route without compromising the efficacy of the treatment. These findings are explained by the first uterine pass effect, which increases the concentration of gestrinone in the uterus despite lower systemic levels by direct local transport from the vaginal veins to the arteries [10]. Although this occurred when progesterone was used vaginally, it still remains to be proved in the case of vaginal gestrinone in Pentravan® as used in the present study, since the endometrial and tissue levels of this hormone were not determined. However, the excellent clinical results achieved in term of pain control and amenorrhea are better explained as a consequence of the effectiveness of the uterine first pass effect to concentrate gestrinone in the pelvic region before being diluted into the systemic circulation. Nevertheless, until data on blood and tissue levels of gestrinone are obtained, this explanation has to be considered speculative despite its plausibility from a biological point of view. Notwithstanding, the anti inflammatory effects of the association of gestrinone with pinus pinaster extract and resveratrol may also have contributed greatly towards enhancing the pain-relieving effects of gestrinone in these patients in whom previous treatment had failed [14,15]. Since resveratrol is also able to suppress aromatase expression, this provides an addictive effect to gestrinone in suppressing this enzyme in the endometrium [18]. However, until proper double-blind clinical trials are conducted, these results have to be considered preliminary. Although a placebo effect cannot be totally ruled out, these patients had an excellent response to this treatment in terms of pain control and amenorrhea when previous treatment using progestins and oral contraceptives had failed. Furthermore, the response was consistent in all cases and persisted throughout treatment. These initial results also suggest that the activation of the androgen receptor using hormones such as gestrinone may represent an effective alternative treatment for endometriosis when progestin therapy fails. The reduction in SHBG levels observed with the use of vaginal gestrinone together with resveratrol and pinus pinaster extract resulted in an increase in free testosterone levels, which will further enhance the anti inflammatory effects of treatment, since testosterone itself is able to decrease inflammation and relieve pain by inhibiting the NF-Kappa.b pathway [5]. Testosterone is an inhibitor of NF-Kappa.b activation, and this explains its analgesic effects and the positive effects on libido and on well being reported by these patients. Unlike other treatments for endometriosis that may adversely affect sexuality, this does not seem to occur with vaginal gestrinone. The therapeutic efficacy of gestrinone depends on its absorption through the vagina, which is greatly enhanced with the use of Pentravan®. This ultimately results in high concentrations of gestrinone in the pelvis, with systemic blood levels lower than those achieved by the oral route, thus decreasing endometriosis-related pain without too many androgenic side effects [8-10]. The concomitant use of oral pinus pinaster extract and resveratrol will further decrease inflammation by blocking NF-Kappa.b activity and lowering oxidative stress, not only locally in the lesions and in the endometrium but also systemically. The association of resveratrol with pinus pinaster extract may also potentiate the

inhibitory effect of gestrinone on aromatase expression, as previously shown when they were used in association with continuous oral contraceptives to treat endometriosis. Our initial results showing that the combination of androgenic hormones such as gestrinone with plant-derived anti inflammatory agents that act through NF-Kappa.b inhibition is effective for the treatment of endometriosis-related pain in patients in whom previous treatment with progestins was unsuccessful provide a novel approach to solving the problem of progesterone resistance in these patients. The vaginal mucosa may be the best route for the delivery of active pharmacological agents for the treatment of endometriosis because of the uterine first pass effect [10]. The use of Pentravan® (Fagron, the Netherlands) to deliver these agents vaginally has proven effective ever since its first use with danazol for the treatment of endometriosis [19]. Gestrinone was not only effective for the treatment of dysmenorrhea and other forms of pelvic pain, but the combination with oral pinus pinaster extract and resveratrol induced amenorrhea after the second month of treatment in 90% of the patients. In gestrinone-treated patients, aromatase and VEGF expression was greatly diminished in the endometrium during treatment. Since gestrinone acts by activating the androgen receptors, the inhibition of aromatase and VEGF expression may be a consequence of the reduction in inflammation, since gestrinone has been shown to have no direct effect on aromatase expression in cultured cells from endometriotic cysts [20]. Inflammation plays a pivotal role in the progression of endometriosis [12] and the activation of the androgen receptors may represent an alternative for those patients in whom progestin therapy was unsuccessful.

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