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Research Article

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Short Term Effects of the Vaginal Administration of Gestrinone and Miodesin™ on Endometriosis Pain

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Abstract

Introduction: *Gestrinone a 19 nor testosterone derivative with androgenic, anti-estrogenic and anti-progesterone properties was used either alone or associated with plant derived anti-inflammatory drugs to treat pain in deep endometriosis patients.*

Patient and Methods*: In the present study Gestrinone was used alone or in combination with either a higher (500 mg) or a lower (170 mg) doses of Myodesin™ in order to treat pelvic pain in patients with deep endometriosis . In the higher dose group Miodesin™ was dispensed without Astaxanthin. Miodesin is the trade name for a herbal complex prepared by Fagron Brazil whose composition contains a mixture of plant extracts from an amazon tree Uncaria tomentosa together other plants. In the lower dose group (170 mg), on the other hand, a novel composition of Miodesin™ was tested that also contained H. pluviallis extract containing Astaxanthin. Forty patients with deep endometriosis and severe pain were enrolled for this study. Patients were divided into 3 groups according to treatment scheme. In Group A (n=11) they were treated with vaginal Gestrinone alone (2,5mg/g twice a week). In Group B (n=17) the patients received Gestrinone (2.5 mg/g twice a week) together with Miodesin™ (500 mg/3g daily)(Fagron Brazil). In Group C (n=12) the patients were treated with a daily dose of 1 mg/g of Gestrinone together with a lower dose of Miodesin™ 170 mg/g containing H pluvialis extract as described above . All medications were dispensed vaginally dissolved in Pentravan® (Fagron, Netherland). In group C only 1g of Pentravan® was necessary to dissolve 170 mg of the new composition of Miodesin™ containing H. pluvialis extract while in group B it was necessary to use 3g to solubilize the 500 mg of traditional Miodesin™.*

Results: *In all 3 groups total pain scores reduced significantly after one month of treatment. However the post treatment scores were always significantly lower in patients who had used either the higher dose of Miodesin™ (Group B) or the new composition of Miodesin™ (Groups C) when compared to Gestrinone alone (Group A)($p<0.02$).*

Conclusion: *Although Miodesin™ was administered in a lower dose in group C the addiction of H.pluviallis extract standardized to contain Astaxanthin increased its efficacy to treat endometriosis pain when used together with Gestrinone. Miodesin™ is an inhibitor of NF-kappa-b activation while Astaxanthin is a carotenoid with potent antioxidant effects and their combined administration had a synergetic effect that allowed the reduction of the doses of Miodesin™ without compromising its efficacy.*

Introduction

Gestrinone is a 19 nor testosterone derivate with potent anti estrogenic and anti progesterone properties in addition to an important androgenic action.

These unique properties make it a perfect medication to treat endometriosis and leiomyoma as proposed by Coutinho several years ago [1]. However the occurrence of androgenic side effects may hamper its prolonged although this can be circumvented by using lower doses with herbal preparations or other routes of administration such as the vaginal mucosa [2]. Since the original observations in 1980 by Coutinho (1) that a Gestrinone pill when administered vaginally to treat endometriosis pain had a clinical efficacy comparable to the other routes of administration but with a lesser incidence of side effects, very little was published until 2 decades later with the introduction of Pentravan® [3]. Pentravan® is an oil in water emulsion that uses liposomal technology which permits not only transdermal drug delivery but also enables the use of other routes of administration such as the vaginal mucosa. Initial results showed that Gestrinone when administered vaginally in Pentravan® was very effective to treat endometriosis pain especially when associated with orally administered plant derived anti inflammatory drugs [4]. The combination of hormonal treatment with plant derived NF-kappa-b inhibitor was a novel approach in

endometriosis treatment since it permitted to diminish Gestrinone side effects without compromising its therapeutic efficacy [2]. The development and survival of endometriosis in the pelvis are dependent on inflammation. The constant exposure to a high inflammatory milieu will ultimately induces the necessary changes in the eutopic endometrium that will permit endometriosis to develop. These changes are achieved through the use of epigenetic mechanisms such as DNA methylation and histone acetylation. The development of a high estrogenic and inflammatory milieus necessary for the implantation and survival of endometrial cells outside the uterine cavity [5, 6]. NF-Kappa-b a transcription factor that triggers the inflammatory cascade after it's binding to DNA is constitutively activated in both endometriosis lesions and eutopic endometrium which will result in an augmented inflammatory milieu in both tissues [7, 8]. This heightened inflammation plays a pivotal role in triggering the epigenetic changes in the endometrium, necessary for both endometriosis aggressiveness and its resistance to progesterone treatment. Epigenetic changes also trigger the aberrant expression of aromatase p450 in both endometrium and endometriosis lesions [5, 9-11]. In this context the concomitant use of NF-kappa-b inhibitors associated with hormonal therapy would be a biologically plausible approach to improve endometriosis treatment. Miodesin™ is a trade name for a herbal complex composed by a mixture of a herbal extract prepared from an amazon tree Uncaria tomentosa with others plants developed by Fagron Brazil. Initial clinical studies showed that this herbal complex is endowed with potent anti-inflammatory properties that are mediated through the inhibition of the NF-kappa-b activation [12, 13]. Previous studies had shown that NF-kappa-b played an important role in the mechanism of break through bleeding and persistent endometrial inflammation in patients using oral contraceptives containing Gestodene in continuous regimens [14]. The suppression of inflammation by Miodesin™ could play a pivotal role in decreasing progesterone resistance and ultimately allowing the progestin to treat the endometriosis lesions [2, 4. 5]. Plant extracts from Uncaria tormentosa were shown to suppress the production of tumor necrosis factor (TNF alpha) a pro-inflammatory cytokine. This was achieved through the inhibition of a NF-kappa-b dependent pathway which will cause the suppression of the ensuing inflammatory cascade [11, 12, 13]. One immediate consequence of diminishing inflammation would be the decrease in progesterone resistance thus allowing the endometriosis lesions to respond to progestin therapy administered either locally or systemically [5].

The search for synergisms of Miodesin™ with other drugs in order to enhance its anti-inflammatory effects on endometriosis lesions would be highly desirable since it would allow the use of lower doses without compromising efficacy .This will likely improve long term patient adherence to treatment particularly when it is administered vaginally.

In the present report, a new composition of Miodesin™ with H. pluviall is extract containing Astaxanthin, a beta carotenoid, was investigated on endometriosis pain. Astaxanthin is endowed with strong antioxidants and anti-inflammatory properties, besides inhibiting the NF-kappa-b activation and this could be synergistically increase the anti inflammatory and analgesic effects of vaginal Miodesin [5].

Patient and Methods: The effect Gestrinone on pain scores was investigated in 48 patients with deep endometriosis and pain who were in the waiting list for laparoscopy surgery. In the present study Gestrinone was used either alone or associated with Miodesin™ or the new composition of Miodesin™ with H. pluvialis extract.

Miodesin™ is a trade name for a herbal complex developed by Fagron Brazil that was prepared by mixing extracts from an amazon tree Uncaria tomentosa with other plants. The new Miodesin™ used by Group C patients included in its composition 20mg of a H. pluviallis extract containing Astaxanthin. All medication were dispensed vaginally using Pentravan® an oil in water emulsion with liposomal matrix which allows greater rates of absorption than the other bases (Fagron Netherland) [3].

The inclusion criteria for this study were the presence of severe pelvic pain with self reported scores greater than [6]. The diagnosis of deep endometriosis associated or not with other forms of the disease was confirmed by image techniques. All patients were in the waiting list for laparoscopy either because of pain recurrence following a previous unsuccessful surgery or failure to respond to previous hormonal treatments with either oral dienogest or continuous oral contraceptives.In all patients endometriosis diagnosis was confirmed by vaginal ultrasonography with intestinal preparation when indicated or by magnetic resonance of the pelvis. Patient allocation to the three different treatment groups was based on patient preference after the three different treatment regimens were explained and their consent was obtained. The study was open in that both the patients and their attending physician were aware of the medications they were using.

The enrolled subjects were divided into 3 groups according to the treatment regimen chosen. In Group A (n=11) patients were treated with vaginal Gestrinone alone (2,5mg/g twice a week). In Group B (n=17) they received a treatment regimen that consisted of Gestrinonein the same dosage as in Group A (2.5 mg/g twice a week) together with Miodesin™ (500 mg/dose daily) (Fagron Brazil). In Group C (n=20) patients were treated with a daily dose of 1 mg/g of Gestrinone together with a lower dose of the new composition of Miodesin™. All medications were dispensed vaginally dissolved in Pentravan® (Fagron, Netherland) at bedtime as mentioned before. In group B 500 mg of Miodesin™ was only stable when 3g of Pentravan® was used but in group C the lower dose of 170mg of Miodesin™ with H pluvialis extract together and 1mg of Gestrinonecould be dissolved in lower volumes of Pentravan®. These compounds were stable in just 1g of Pentravan® and the final preparation was good for drug delivery even when stored at room temperature for at least two months.This greatly facilitated its vaginal application by the patient since lower volumes were used. All drug preparation was done by the same certified pharmacist in the same compound pharmacy (WSJ).

All patients were initially interviewed by the same investigator (HM) and pain scores were assessed using a visual analogic scale (VAS) in which zero corresponded to the total absence of pain and ten to the worst pain imaginable. A total pain score was calculated, which included dysmenorrhea, pelvic pain and dyschesia. When the patients gave different VAS scores for these different forms of pain, the one with the highest score was chosen for the purpose of evaluation. Pain scores were evaluated at the beginning of treatment and repeated again after the second month of therapy. Two patients in group C also had a sub mucous leiomyoma that was successfully removed by hysteroscopy using the Versa point (Gynecare USA) after the second month of treatment. The technique of hysteroscopy

myomectomy using bipolar energy has been previously described [16]. Another patient in group C had a video laparoscopy for a cholecystectomy done by a general surgeon when she was at the end of the first month of treatment. The removal of gallbladder was unrelated to endometriosis. During laparoscopy a through inventory of the pelvis was carried out and the lesions were photographed and evaluated by one of us (HM). It is important that in this study patients participated in the decision process of the treatment that was going to receive rather than being allocated randomly. This reflects more accurately which occurs in the real world when the patients are interacting with their physicians in the selection process of a specific treatment.

Statistical analysis was performed using Student's t-test to evaluate differences in mean pain scores among the different treatment groups before and after treatment. The chi square test was used to calculate differences in percentages. In both tests p-values <0.05 were considered statistically significant.

The study was conducted at the Instituto da Mulher, Itaigara Memorial Day Hospital, a private institution. Approval was obtained from the institute's internal review board. All patients gave consent to participate in the study and they were informed on the used medication by the same attending physician (HM)

Results: Gestrinone significantly decreased total pain scores in all patients after the first month of treatment as assessed by the visual analogic scale (VAS). In all three groups pain scores were the same before treatment was started with a mean value of 9. Even though total pain scores were reduced significantly by treatment after the first month in all groups significant differences were observed in the post treatment scores.Mean pain scores were significantly less in the group of patients who had used Miodesin™ (Group B) or the new composition of Miodesin™ (Groups C) when compared to those who had used Gestrinone alone (Group A). In the latter (Group A) although pain scores decreased significantly after the first month of treatment they were still higher than in the other two groups (p<0.02). These results are summarized in (Table I). The post treatment pain scores in groups B and C did not differ significantly despite a trend toward lower scores in group C(p=0.2).

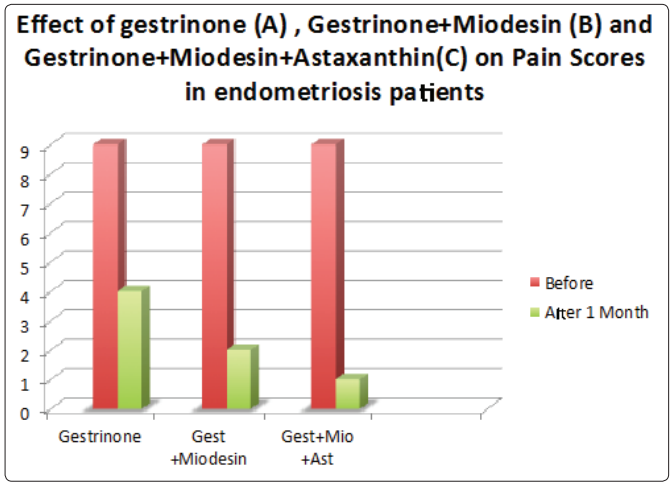

Table I

It is also noteworthy mentioning that the combined treatment of daily Gestrinone with the new composition of Miodesin™ (170 mg/g) rendered most of the patients pain free already after the first month (Figure 1). These results are summarized in (Table II). The percentage of pain free patients increased in all groups throughout treatment although in the first month they were significantly higher in group C than in the other two groups. This difference tended to level off with the continuation of treatment. Although the mean percentage of pain free patients was a little bit lower in group A than in Group B it did not reach statistical significance (p=0.4).

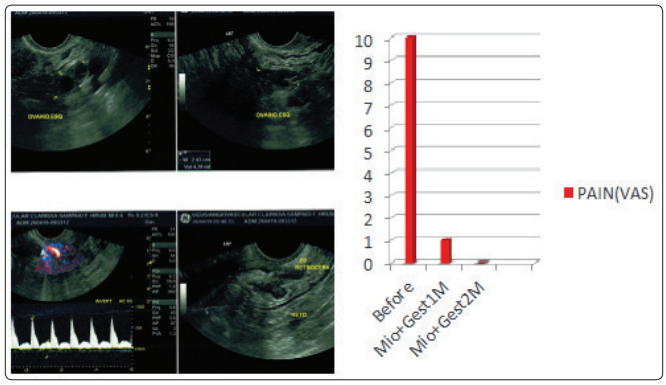

Figure 1: Patient with deep endometriosis in the retro cervical space. Pre treatment pain was 10 (VAS). She was treated with daily vaginal Miodesin™ (new composition) 170mg/mL and 1mg/mL of gestrinone in Pentravan®. The patient became pain free (VAS 0) after the first month treatment.

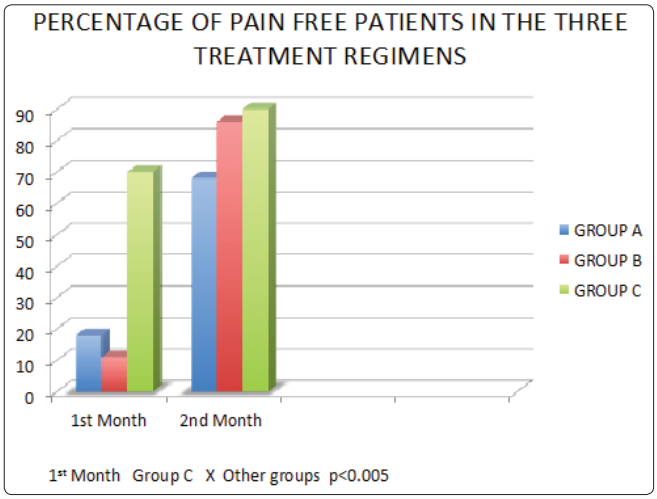

Table II

In one patient in Group C a video laparoscopy was carried two months after the initiation of treatment and all endometriosis peritoneal lesions had a dark brown appearance with no signs of inflammation. There were no red and vascularized lesions on the peritoneum (Figure 2). Two patients in Group C had sub mucous leiomyoma associated with deep endometriosis. A color Doppler transvaginal ultrasound showed a great reduction in vascularization that was confirmed when the hysteroscopy myomectomy was carried out using the bipolar Versa point. The pre operative administration for 2 months of Miodesin™ and astaxanthin extract (Group C) and daily Gestrinone was effective to reduce leiomyoma vascularization. This rendered the myomectomy procedure safer with minimal blood loss (Figure 3 ,4)

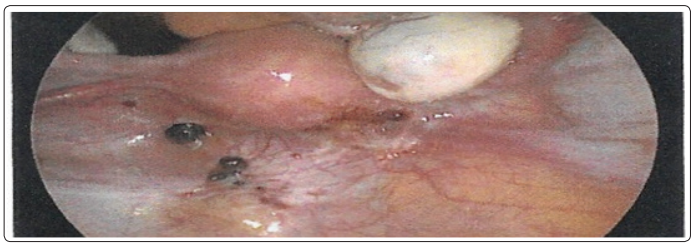

Figure 2: Reduction of vascularization in endometriosis lesions after one month of vaginal gestrinone with the new composition of Miodesin™. Pain scores decreased from 9 to 0

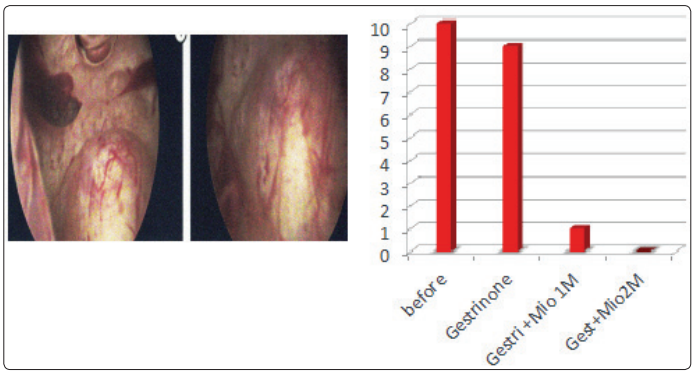

Figure 3: Patient with deep endometriosis and sub mucous leiomyoma. She was using a mirena® and having bleeding and pain . She started using gestrinone 2,5 mg/ml twice a week . Pain persisted (VAS 9). Treatment was changed to daily Miodesin™ (new composition) 170mg/g with 1mg/g of gestrinone in Pentravan® dispensed vaginally at bedtime. The patient became pain free (VAS 0) after 2 months of treatment. Myomectomy by hysteroscopy was then successfully performed. Leiomyoma vascularization was reduced.

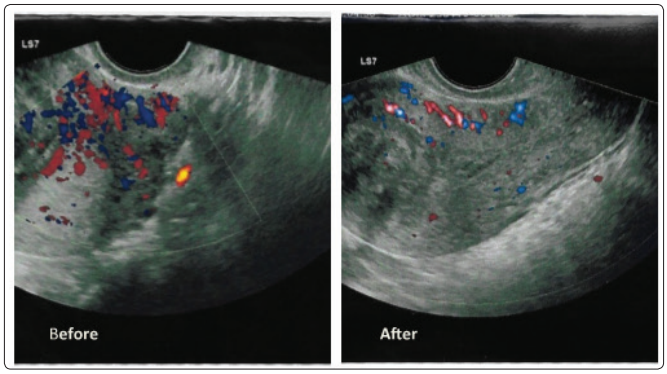

Figure 4: Reduction of vascularization in the leiomyoma after one month of vaginal gestrinone with the new formulation of Miodesin™.

It is important to mention that although Miodesin™ was administered in a lower dose in group C the association with H. pluviallis extracts containing Astaxanthin had synergistic effect thus allowing the reduction of the dose without compromising its efficacy.

Smaller doses of the new Miodesin™'s composition could be easily dissolved in lower amounts of Pentravan® thus making vaginal administration less messy and more acceptable by the patient since the volume of Pentravan® necessary to make a stable preparation with the new Miodesin™ composition of Miodesin™ could be reduced to just 1g.

Discussion

Miodesin™ a potent inhibitor of NF-kappa-b activation was effective to potentiate the pain ameliorating effects of Gestrinonein patients with deep endometriosis as reported here [13]. The addition of H. pluvialis extract containing Astaxanthin to the treatment scheme greatly enhanced the anti-inflammatory effects of Miodesin™ allowing the use of lower doses without compromising its efficacy. Patient acceptance to the treatment was also improved when lower volumes of Pentravan® were used in the vagina to deliver the active compounds.The daily use of Gestrinone with the new composition of Miodesin™ was able to render most of endometriosis patients pain free after the first month of treatment which made unnecessary to perform invasive laparoscopy surgery to control pain in all of them. However it is noteworthy mentioning that after the second month of treatment the differences in pain scores among the groups were not significantly different.

Due to frequent complications of radical laparoscopy surgery and the high rates of recurrence, clinical treatment with gestrinone and Miodesin™ should be offered as a first line of therapy even in patients who had previously failed to respond to either Dienogest or continuous oral contraceptives. In several patients with deep endometriosis the origin of pain, specially dysmenorrheal, can be traced down to the presence of adenomyosis, an uterine condition that is associated with a high grades of inflammation and progesterone resistance. Patients with this pathology are consequently less susceptible to respond to progestin therapy [17, 18].

Gestrinone proved to be an effective treatment for both endometriosis and pelvic pain when used by other methods of administration such as intradermal implants or oral pills [1]. There is only one paper in the literature comparing the three forms of administration and the results showed a similar efficacy but there were fewer side effects when the vaginal route was used [1]. However in this study Gestrinone was administered vaginally not only in the form of tablets but in higher doses than in the present report. Unfortunately there are no recent studies comparing the efficacy of vaginal gestrinone in Pentravan® when used either alone or associated with Miodesin™, with the other forms of administration of this hormone. Miodesin™ when used in the new composition with H pluvialis extract increased the efficacy of vaginal Gestrinone to reduce pain scores in symptomatic patients with deep endometriosis specially after the first month of treatment, when it rendered the majority of them pain free. This is consequence of the potent anti-inflammatory effect of the combination of Miodesin™ with H.pluvialis extracts which blocked synergistically the activation of NF-kappa-b in endometriosis. This in turn dismantled the vicious cycle of pain, oxidative stress, increased vascularization and augmented inflammation [5, 12-15]. A marked reduction in vascularization was indeed observed after the first month of treatment in both leiomyoma and endometriosis lesions and it coincided with the reduction in pain scores and inflammation.

The novel scheme of vaginal gestrinone administration using daily doses of gestrinone associated with a lower dosage of the Miodesin™' formulation containing H. Pluvialis extract (Group C) proved to be at least as effective as the traditional regimen with Miodesin (Group B). The resolution of endometriosis pain occurred much faster than with traditional regimen with the advantage of using lower volumes of Pentravan® in the vagina. The combination of a H. pluviallis extract containing Astaxanthin with Miodesin had a synergistic effect on endometriosis pain .This was likely caused by the concomitant

reduction in the oxidative stress and the inhibition of NF-kappa-b activation in the lesions and eutopic endometrium [13, 15]. The synergism of these medications in the treatment of endometriosis pain probably occurred through different mechanisms. Miodesin™ is an inhibitor of NF-kappa-b activation while Astaxanthin is carotenoid with potent antioxidant effects.For this reason their combined use reduced more efficiently both oxidative stress and inflammation thus leading to a faster resolution of pain [13, 15]. It is noteworthy to mention the rapid decrease in pain scores in deep endometriosis patients that was observed in all treatment groups albeit more rapidly when Gestrinone was combined with plant derived NF-kappa-b inhibitors. However these findings are still preliminary to draw any definitive conclusion but they do suggest that lower doses of vaginal Gestrinone in Pentravan® with Miodesin™ may represent an excellent clinical option to treat endometriosis instead of surgery. The combination with these herbal therapies with anti-inflammatory and antioxidant properties with hormones such as Gestrinone, a 19 nor testosterone derivative may have synergistic effects that will augment the efficacy of treatment and reduce the dose dependent androgenic side effects [1, 2, 4]. The use of vaginal mucosa as a route of administration to administer medications to treat endometriosis leads to a more efficient concentration of the sedrugs in the pelvic region because of the first uterine pass effect thus increasing the efficacy of treatment in the pelvis with less systemic side effects [19]. This is the consequence of higher tissue concentrations in the pelvis and lower blood systemic levels. This combination will result in better clinical responses in terms of pain control and a lesser incidence of side effects especially the androgenic ones which are frequently reported by Gestrinone users [1]. Unpublished ex vivo studies carried out in Brazil by Anderson group in Juiz de Fora using porcine vaginal mucosa showed excellent absorption rates for Gestrinone when Pentravan® was used thus corroborating our clinical findings showing that the vaginal mucosa is an excellent route to administer Gestrinone for endometriosis treatment [1, 2]. Previous animal studies had already shown that extracts of Uncaria tomentosa were able to reduce the experimental lesions of endometriosis in rats [20]. These results are in concordance with our findings that there was a great reduction in the vascularization of pelvic endometriosis in one patient in group C after the first month of treatment.

In conclusion, the concomitant use of the new composition of Miodesin™ with H.pluvialis extract in Pentravan® permitted the use of lower doses without compromising its efficacy. In fact the clinical response to Gestrinone in terms of pain control in deep endometriosis patients seemed to be improved with this combination at least in the first month of use. The use of lower volumes of Pentravan® to administer these drugs in the vagina will certainly have a positive impact on long term patience adherence to treatment.These results also support the conclusion that the use of vaginal mucosa is one of the best ways to administer medications to treat endometriosis. This is consequence of the high concentrations of active compounds in the pelvis that are achieved due the first uterine pass effect [19]. However this conclusion needs to be further confirmed in larger clinical trials.

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