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Treatment of endometriosis by vaginal administration of gestrinone*

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The effectiveness and acceptability of gestrinone administered by vaginal route was evaluated in a group of 110 patients with endometriosis. Patients were divided into four groups. The first three groups were treated by vaginal route. Group I (n = 17) received two 2.5-mg tablets weekly; group II (n = 31) received three 2.5-mg tablets weekly; group III (n = 35) received two 5.0-mg tablets weekly. Group IV consisted of 27 patients who received 2.5 mg of gestrinone orally twice weekly. Ninety-eight women completed the 6- to 8-month treatment period. Amenorrhea developed in all treatment groups, including group I (34%). The disappearance of both dyspareunia and dysmenorrhea occurred in most patients in all treatment groups soon after the second month of therapy. Patients treated by vaginal route had significantly less seborrhea and acne than those treated by oral route. Weight gain was also significantly less in vaginally treated women than in those treated orally. Pregnancy rate following discontinuation was not significantly different for the various groups. Fertil Steril 49:418, 1988

The use of antiestrogen, antigonadotropin drugs in the treatment of endometriosis is well established.[1] Several such compounds have been used to treat endometriosis with varying degrees of success.[2,3] The most widely used antigonadotropin is danazol, a synthetic isoxazol derivative of ethynyltestosterone. Recently, however, gestrinone, a trienic derivative of ethynyl-nor-testosterone, which is also an antiestrogen, antiprogesterone, has been shown to produce the same end results at much lower doses.[4] While the effective therapeutic dosage of danazol is between 200 and 800 mg daily, gestrinone is effective with dosages between 5 and 7.5 mg, usually administered in 2.5-mg doses, two or three times weekly. With this convenient schedule, gestrinone-treated patients may find long-term treatment more acceptable, while the development of side effects is correspondingly reduced.[5] Despite the undeniable advantage of reduced dosage, prolonged oral administration in the treatment of endometriosis may be poorly tolerated, even by some patients on gestrinone. Undesirable side effects, such as acne and seborrhea, develop in many patients, and gastrointestinal intolerance may preclude the use of this drug by a small but significant number of women. In order to overcome the difficulty of treating these patients by oral route, and based on our extensive experience with vaginal administration of contraceptive pills,[6,7] we decided to investigate the efficacy of gestrinone administered by vaginal route in patients with endometriosis. It was expected that absorption by the vaginal epithelium would result in greater concentrations of the drug in the pelvic area where it was needed, whereas avoidance of the first pass through the liver would reduce side effects associated with the impact of the steroid as a bolus on the liver cell.

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PATIENTS, MATERIALS, AND METHODS

One hundred ten patients with varying degrees of endometriosis were admitted to the clinical trial. Most patients (75) were infertile and all had either dysmenorrhea, dyspareunia, or both. Diagnosis in every case was confirmed by laparoscopy. Patients were divided into four groups, evenly distributed according to the stage of endometriosis. The first three groups were assigned to the vaginal route: group I, two 2.5-mg tablets weekly; group II, three 2.5-mg tablets weekly; group III, two 5-mg tablets weekly. Women in group IV were treated orally with two tablets of 2.5-mg weekly. Forty patients had mild endometriosis (stage I), 34 had moderate (stage II), and 36 had severe (stage III). Distribution of patients by group and stage of endometriosis, according to classification by The American Fertility Society, is shown in Table 1.[8]

Tablets of gestrinone were made specially for this trial by Silva Araujo Roussel Laboratories (SARSA) in Rio de Janeiro, Brazil, and contained either 2.5 mg or 5.0 mg of the compound in lactose as excipient. Patients assigned to the vaginal route were instructed to insert a tablet deep in the vagina either twice (groups I and III) or three times (group II) weekly.

RESULTS

Only 11 patients of group I completed 6 months of treatment. Six women abandoned treatment because it failed to stop menstruation or to reduce pain. Of those completing 6 to 8 months of treatment, only 5 developed amenorrhea (34%). The other 6 patients had either irregular bleeding or continued to menstruate regularly.[2] Eight patients increased body weight during the treatment. Two patients lost weight. One had her body weight unchanged. Mean weight increase was 1.33 kg. Patients in group I were virtually free of acne and seborrhea. Only one patient complained of these side effects, but inspection confirmed only mild seborrhea and no acne.

Table 1 Stages[a] of Endometriosis in Patients of the Various Groups

Group	Patients	Stage I	Stage II	Stage III
I	17	6	5	6
II	31	12	9	10
III	35	12	11	12
IV	27	10	9	8
Total	110	40	34	36

[a] Stages according to The American Fertility Society classification.

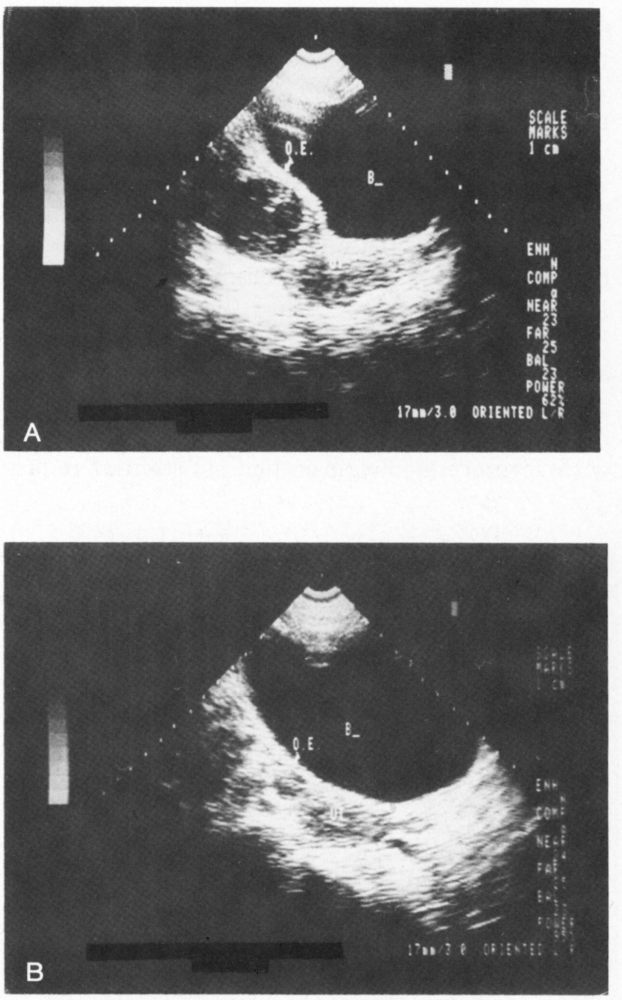

Figure 1 Thirty-one-year-old patient. Endometriotic cyst on the left ovary (*OE*) was diagnosed by laparoscopy. Real-time ultrasound image of cyst measuring 68.2 cm^3 is shown before treatment (**A**) and after 6 months of gestrinone treatment by vaginal route, 2.5 mg three times weekly (**B**), when ovarian volume was restored to normal (11.6 cm^3).

Of the 31 patients in group II, only 1 abandoned treatment before 6 months. Amenorrhea developed in 16 patients (51%). Nine patients developed oligomenorrhea, whereas the remaining 5 retained a regular menstrual pattern. Patients reported reduced or no pain whenever a bleeding episode occurred during the treatment. Most patients were symptom-free by the end of the second month of treatment. In patients with severe endometriosis, regression of lesions could be seen at the end of 6 months of therapy (Fig. 1). Mild acne and seborrhea developed in only 5 women (16%). Cramps

associated with leg pain were reported by 5 women (16%). Four women complained of pruritus (13%). Twenty-two women (73%) had a moderate increase in body weight. Three women lost weight (3%), whereas the remaining 5 women (16%) had no weight change. Mean body weight increase was 2.0 kg.

In group III, 5 patients discontinued treatment before 6 months. Of the remaining 30 patients, 16 (51%) developed amenorrhea. Seven women had oligomenorrhea. One patient had hypermenorrhea, and the remaining 6 retained a regular menstruation pattern. Patients reported reduced or no pain during bleeding episodes. As in group II, patients with severe endometriosis had substantial reduction of lesions at 6 months of therapy (Fig. 2). Only 3 women (10%) developed seborrhea and acne. Cramps associated with leg pain were reported by 5 patients (16%). Four women complained of pruritus. Eighteen women (60%) had weight increases. Six women lost weight (20%), whereas another 6 had no change. Mean increase in weight was 1.5 kg.

Table 2 Side Effects of Gestrinone by Either Vaginal or Oral Administration

	Group I	Group II	Group III	Group IV
	%	%	%	%
Amenorrhea	34	51	51	58
Acne, seborrhea	0	16	10	48[a]
Cramps, leg pain	2	16	0	16
Allergy	0	6	0	0
Edema	0	3	0	0
Chloasma	0	0	3	0
Hirsutism	0	0	0	15
Hoarseness	0	0	0	7
Hair loss	0	0	0	3
Pruritus	0	13	13	7

[a] Statistically significant.

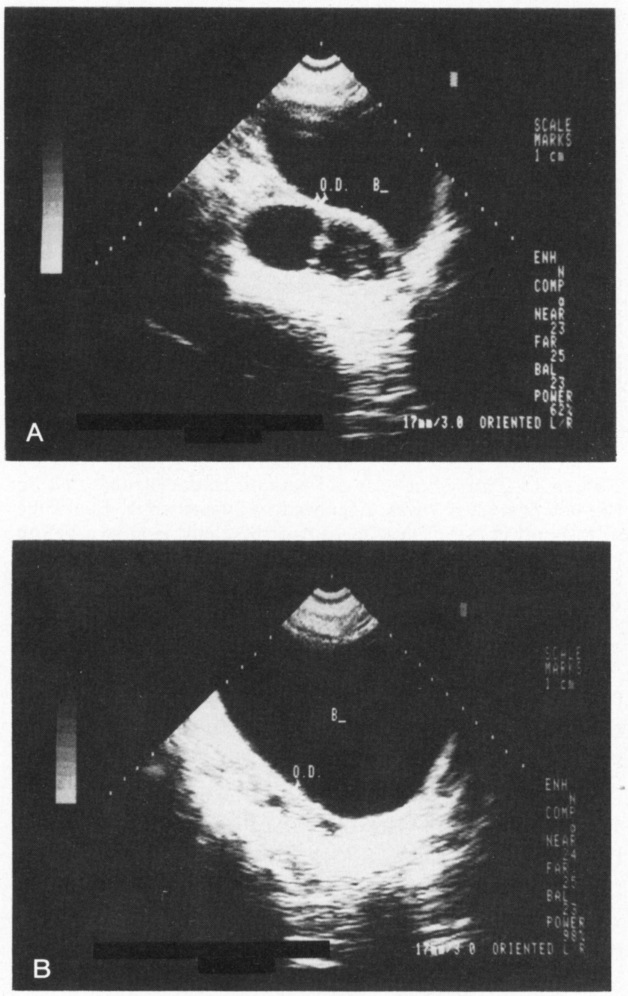

Figure 2 Thirty-one-year-old patient with endometriosis and chocolate cyst on the right ovary (*OD*) diagnosed by laparoscopy. Real-time ultrasound image of large (72.7 cm^3) cyst before (**A**) and after 6 months of gestrinone therapy by vaginal route, 5.0 mg twice weekly (**B**). Note the disappearance of the cyst. Ovarian diameter after treatment was 13.2 cm^3.

None of the 27 patients in group IV abandoned treatment before the end of the trial. Amenorrhea developed in 15 women (58%). Oligomenorrhea was reported by 9 women, whereas regular bleeding patterns were retained by only 3 women. Bleeding episodes were painless. Acne and seborrhea were more common in this group than in the other three groups. Almost half (48%) of the patients reported these skin alterations. The higher incidence of seborrhea and acne in group IV is statistically significant when compared with all three vaginal administration groups. The difference between groups I and IV was significant at $P < 0.0003$; between groups II and IV at $P < 0.006$; and between groups III and IV the difference was highly significant at $P < 0.0008$. Hirsutism developed in 4 patients (15%), and hoarseness was reported by 2 patients (7%). These differences in the occurrence of hirsutism and hoarseness were not statistically significant. Incidence of cramps with leg or joint pain was reported by 5 women (18%; Table 2). Only 2 patients complained of pruritus (7%). Twenty-four women (88.8%) of group IV had weight increases during treatment; two were unchanged and only one lost weight. Mean weight increase for group IV was 2.44 kg. The differences in weight increase were statistically significant only between groups III and IV ($P < 0.03$).

By the end of the first year of follow-up, recurrences developed in all four groups: 2 in group I, 8

in group II, 10 in group III, and 14 in group IV. Differences in recurrence rate among the various groups were not statistically significant. Pregnancies occurred in all four groups: 2 of a possible 7 (28%) in group I, 9 of a possible 14 (61%) in group II, 13 of a possible 19 (72%) in group III, and 4 of a possible 12 in group IV (33%). Abortions occurred in all groups, except in group IV: two in group I, two in group II, and four in group III. The occurrence of abortions reduces the rate of successful pregnancies to 0 in group I, 50% in group II, 47.8% in group III, with group IV remaining at 33%. Differences in pregnancy rate among groups II, III, and IV are not significant, although the values between groups III and IV were close to significance level ($P = 0.05$). Table 3 shows how these various events compare for the four groups.

DISCUSSION

We have shown in a series of clinical studies that several steroid contraceptive pills are effective when administered by vaginal route.[6,7] Vaginal contraceptive pills seem to achieve the same effectiveness as orally administered contraceptives with lower blood levels and fewer side effects.[9] A moderate success also has been achieved with gestrinone administered by vaginal route in the treatment of leiomyomas.[10] Apparently, absorption by the vaginal mucosa allows greater concentration of the compound in the pelvic area and saturation of receptors in the various organs of the reproductive tract in the region. We found that blood levels of gestrinone in patients treated by the vaginal route are lower than in patients receiving the same dose orally. In addition, the drug introduced by the vaginal route bypasses the liver in the first pass, thereby reducing the impact of the synthetic steroids on the liver cells. Side effects associated with the action of synthetic steroids on protein carbohydrates and lipid metabolism, which alter the synthesis of lipoproteins, may be reduced by the avoidance of the first pass through the liver.[9] The present study shows that the vaginal route also can be used successfully in the therapy of endometriosis. Administration by oral route should be avoided, for example, when the patient has gastritis, gastrointestinal ulcer, hyperacidity, or simply gastric intolerance to steroids. Patients who develop side effects such as seborrhea, acne, or hirsutism, which are associated with a decrease of sex hormone binding globulin (SHBG) or reduced binding of testosterone to SHBG, should also benefit from the vaginal route. In young patients with both endometriosis and acne, the decision to prescribe a compound such as gestrinone, whose prolonged use may markedly worsen the seborrhea and acne, is a particularly difficult one.

Comparison between the two routes of administration of gestrinone in the present study shows that the vaginal route may be used with equal success as the oral route in both suppression of symptoms and pregnancy rate following discontinuation. The significantly lower incidence of seborrhea and acne confirms the expectation that vaginal absorption allows better tolerance by patients who already have acne and seborrhea or who are more susceptible to developing these conditions under long-term treatment with an antiestrogen. Hirsutism, although mild and reversible, has developed in four patients from group IV (15%), but not in vaginally treated groups. Hoarseness also was reported by two patients in group IV (7%), but not at all in the other three groups. Cramps and leg or joint pain was reported by groups II and IV, and edema was reported by one patient in group II, but by none in the other groups. Only pruritus, which may be caused by lowered estrogen, appeared more common in groups II and III than in group IV. Weight gain, which is another undesirable side effect of most hormonal treatments, seems to be significantly reduced by vaginal administration. It therefore seems that the vaginal route compares favorably with the oral route in regard to undesirable side effects, while being as effective with regard to suppression of symptoms and pregnancy rate.

The higher drop-out rate for vaginal route users may reflect the lack of familiarity of patients with this route of administration. In the present study, as in other clinical trials involving long-term administration of vaginal contraceptive pills, the main reason given for discontinuation was "inconvenience," "strangeness of the technique," or simply "distrust" in its effectiveness. Only when gas-

Table 3 Pregnancies, Outcome of Pregnancies, and Recurrences per Group

	Group I		Group II		Group III		Group IV	
	n	%	*n*	%	*n*	%	*n*	%
Pregnancies	2	28	9	61	13	72	4	33
Abortions	2	100	2	22	4	30	0	0
Deliveries	0	0	7	50	9	47	4	33
Recurrences	2	18	8	26	10	33	14	41

trointestinal side effects precluded the use of the drug by the usual oral route did patients accept the vaginal route.

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