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Hemodynamic effect of danazol therapy in women with uterine leiomyomata

Uterine fibromyomas or leiomyomata are the most common neoplasm of the female genital system and are often associated with infertility, menorrhagia, and dysmenorrhea (1). In young women hoping to bear children, fibromyomas may be removed individually, whereas in women over 40 years of age, total hysterectomy has generally been the policy (2). Menorrhagia may be due to increased vascularization of the uterus (3). Acute pain may occur in cases of necrosis, torsion of pedunculated myomas, or degeneration that occurs spontaneously or during treatment (4).

Hypoestrogenism, as after menopause and during therapy with gonadotropin-releasing hormone (GnRH) agonist, induces a reduction in leiomyoma size, which indicates the estrogen dependence of the tumor (5). Similarly, marked regression of leiomyomata with the antiprogestin RU486 indicates a probable stimulatory effect of progesterone (P) on the tumor (6).

In the last 10 years, advances have been made in the treatment of these tumors, and medical therapy can now be regarded as a valid alternative to surgery (7, 8). It has been demonstrated that the etiology of fibromyomas is hormone dependent. Estrogens are the hormones principally involved in the pathophysiology of fibromyomas.

In a recent study, the efficacy of short-term danazol treatment in the management of uterine fibroids was investigated (9). Fibromyoma volume decreased significantly by an average of 24% at the end of the therapy. Three and 6 months after the end of treatment, the fibromyoma volume had only increased slightly with respect to the volume at the end of therapy but was still lower than the starting volume. The use of danazol (100 mg/day) for 6 months after 3 months of GnRH analog therapy in women with leiomyomata has been associated with a rebound of uterine volume that is 30% less compared with controls at the end of danazol therapy (10). The effects of danazol are mainly androgenic, with moderate progestogenic, antiprogestogenic, and antiestrogenic activity.

The aim of this study was to evaluate the effects of danazol on the volume of uterine myomas as well as on uterine artery blood perfusion in a 6-month period of administration in premenopausal women.

Informed consent to the study protocol was obtained from 15 women ranging in age from 34 to 42 years. Women were affected by uterine fibromyomas associated with abdominal pain and heaviness and menometrorrhagia. None of the patients had been on hormone therapy in the 3 months before enrollment in the study; all were healthy and without any type of hormonal dysfunction. Exclusion criteria were hepatic, renal, and endocrinological dysfunction and use of sex steroids or GnRH analogs (GnRHa) more recently than 1 year before the start of the study.

Danazol was administered at a dose of 100 mg/day for 6-month periods. The women underwent ultrasound examination in follicular phase to determine uterine and fibromyoma volume at enrollment and after 3 and 6 months. Ultrasound was performed in all patients transvaginally and transabdominally by the same examiner (A.L.) with a 6.5-MHz linear probe and a 3.5-MHz sectorial probe using a Hitachi EUB-415 CFM (Hitachi Medical Systems, Zug, Switzerland).

The main factor investigated was pulsatility index (PI), an indicator of impedance to downstream blood flow. Doppler ultrasound was performed before the start of the study and at intervals of 3 months throughout the study. The women rested for 5 minutes in the supine position before readings were taken. Tumor volumes were calculated using the formula for a sphere ($4\pi abc/3$, where a, b, and c represent the radii of the sphere in three dimensions). Doppler analysis of uterine artery flow velocity waveforms was performed by PI. The main branch of both uterine arteries was examined lateral to the cervix in a longitudinal plane. No significant differences between Doppler analysis of the left and right side were observed, and therefore the average value of both arteries was used.

For statistical analysis, the mean PI of the left and right uterine arteries was used. All values were normally distributed. Values were expressed as mean ± SD. The comparison of PI and uterine fibromyoma volume was made by analysis of variance and Student's t-test. $P<.05$ was considered statistically significant.

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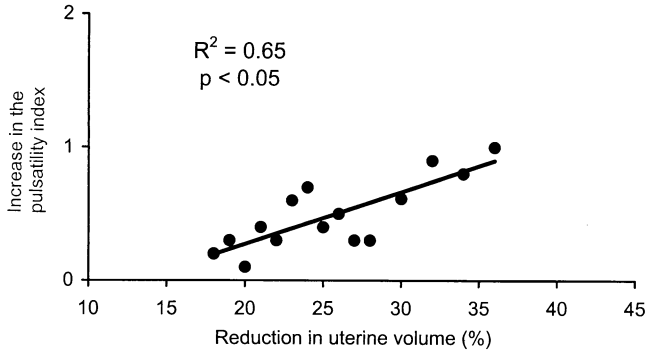
FIGURE 1

A significant correlation between the reduction in uterine volume and the increase in uterine artery impedance was found.



La Marca. Effect of danazol on leiomyomata. Fertil Steril 2003.

Three of the 15 women were amenorrheic during the 6 months of therapy. Mean basal uterine volume was 305 ± 31 cm^3. Ultrasound showed a 29% ± 6.8% ($P<.05$) reduction in uterine volume after 6 months of therapy. Mean basal myoma volume was 28 ± 8 cm^3. Mean myoma volume was reduced by 37.6% ± 10% ($P<.05$) after therapy.

The basal PI value in the uterine arteries was 1.60 ± 0.55. After 3 and 6 months of danazol administration, the PI value showed a significant increase (2.1 ± 0.6 and 2.3 ± 0.7, respectively; $P<.05$). There was a significant correlation between the size of reduction in uterine volume and the increase in PI ($r = .65$; $P<.05$); in other words, the higher the increase in PI, the greater the uterine reduction during therapy (Fig. 1).

No adverse effects were observed during the treatment. Hemoglobin concentrations and hematocrit significantly increased during treatment with danazol. Hemoglobin increased from 10.8 ± 0.9 g/dL before therapy to 11.5 ± 0.6 g/dL 6 months later. Hemocrit (%) increased from 33.8 ± 1.1 to 38.9 ± 0.9 after 6 months of treatment. Serum cholesterol increased slightly from 4.5 ± 0.7 mmol/L to 5.05 ± 0.7 mmol/L, but there was no change in serum triglycerides.

These results confirm the efficacy of danazol in reducing fibromyoma volume and demonstrate a significant increase in uterine artery impedance to blood flow, which could explain, at least in part, the therapeutic effect of danazol on leiomyomata. In a previous study, we demonstrated that danazol treatment for 3 months was followed by a significant reduction in uterine and myoma volume in premenopausal women and that 3 and 6 months after the end of treatment the fibromyoma volume had only increased slightly with respect to the volume at the end of therapy but was still lower than the starting volume.

Doppler ultrasound is the most accurate noninvasive method of evaluating vascular impedance. PI represents vascular impedance to distal flow with respect to the point of measurement. Uterine leiomyomata seem to affect uterine artery blood flow. Uterine arteries in women with uterine leiomyomata are characterized by low impedance (11, 12). Pharmacological treatment of uterine leiomyomata with GnRHa and mifepristone has been shown to result in decreased myoma size and in increased PI values in uterine arteries (13).

Danazol has been described as a "selective androgen" (14). However, many reports suggest that danazol binds to multiple classes of steroid receptors. Danazol binds to rat uterus and brain P receptors (15). Danazol does not bind to estrogen receptors in human endometrium, rat uterus, or rat brain. These findings are consistent with the observation that danazol has no estrogenic effects in various bioassay systems (14).

In vitro, danazol has been shown to inhibit multiple enzymes of steroidogenesis, including cholesterol cleavage enzyme, 3B-hydroxysteroid dehydrogenase, 17B-hydroxysteroid dehydrogenase, 17a-hydroxylase, 17,20-lyase, 11B-hydroxylase, and 21-hydroxylase (16). In cell culture, danazol has been demonstrated to inhibit gonadotropin-induced steroidogenesis in rat, porcine, and hamster granulosa and luteal cells and in rat leydig cells (15). It has been recently demonstrated that short-term danazol administration is associated with a significant increase in uterine artery PI in women affected by dysfunctional uterine bleeding (17). The investigators have concluded that the vascular effect of danazol may explain in part its efficacy in the management of dysfunctional uterine bleeding and in the preoperative preparation of women undergoing endoscopic endometrial ablation.

In the present study, we confirmed the beneficial effect of danazol treatment in women with leiomyomata and observed a positive correlation between the therapeutic efficacy and the increase in uterine artery impedance.

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