ORIGINAL ARTICLE: GYNECOLOGY AND MENOPAUSE

Ulipristal acetate decreases transforming growth factor β3 serum and tumor tissue concentrations in patients with uterine fibroids

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Objective: To evaluate and compare transforming growth factor β3 (TGF-β3) serum concentration in patients with uterine fibroids (UFs) without hormone treatment, treated with ulipristal acetate (UPA), and controls; to evaluate TGF-β3 concentrations in UF tissue in patients without hormone treatment and those treated with UPA; and to evaluate the correlations of age and body mass index (BMI) with TGF-β3 serum and UF tissue levels between the groups.
Design: Retrospective cohort study.
Setting: University teaching hospital.
Patient(s): A total of 141 patients divided into three groups: UFs non-UPA, UFs, and UPA, controls.
Intervention(s): Medical history and examination, genital ultrasound scan, blood and tissue sampling, and measurement of TGF-β3 serum and tissue concentrations.
Main Outcome Measure(s): Evaluation of the impact of UPA (3 months treatment), age and BMI on TGF-β3 serum and UF tissue levels.
Result(s): The values of TGF-β3 serum and tissue concentrations statistically significantly differed between the non-UPA and UPA groups. The mean TGF-β3 serum concentrations were non-UPA group 32.24 ± 34.55 pg/mL, UPA group 10.88 ± 7.15 pg/mL, and controls 11.97 ± 10.30 pg/mL. The mean TGF-β3 tissue concentrations were non-UPA group 171.29 ± 91.81 pg/mg and UPA group 99.99 ± 60.63 pg/mg. Statistically significantly lower mean TGF-β3 serum and tissue concentrations were observed in patients treated with UPA. No statistically significant correlations between TGF-β3 concentrations and age or BMI were found.
Conclusion(s): Reduction of serum and tissue TGF-β3 concentrations in UFs may be an important component of the effect of UPA on UF biology. Further research in this area is necessary. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Leiomyoma, selective progesterone receptor modulator, transforming growth factor beta 3, ulipristal acetate, uterine fibroid

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Uterine fibroids (UFs) are benign tumors arising from uterine smooth muscle cells. The prevalence of UFs ranges from 20% to even 80% of women depending on several factors (mainly age and ethnicity). The spectrum of fibroid-related symptoms comprises abnormal uterine bleeding, anemia, abdominal and pelvic pain, gastric disorders, voiding symptoms, female infertility (including implantation failure), and numerous obstetric pathologies (1–3). Symptoms associated with those tumors depend mostly on the tumors' size and

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location, but they may also have a paracrine effect on the adjacent tissues (4).

All over the world fibroids are the leading cause of hysterectomy and hospitalization due to gynecologic problems. The total load caused by UFs on the national health care budget is enormous (5). This burden is not just the price of medicines, medical staff salaries, or surgery costs, but also the preoperative diagnosis, subsequent gynecologic visits, and work absences (6).

There are many reports on the risk factors for UF occurrence. Higher levels of steroid hormones are one of the most important factors inducing the formation and growth of UFs (2, 3). Other well-known risk factors include advanced age, increased body mass index (BMI), low parity, family history, and genetics (3, 7, 8). According to recent studies, these factors may also include reduced hypovitaminosis D (8–11) and increased transforming growth factor $\beta 3$ (TGF-$\beta 3$) serum levels (8, 11). These are not all the possible risk factors and further studies are still necessary to determine the other patients who are at an increased risk for developing UFs.

According to expert opinion and laboratory studies, fibroid growth depends on steroid hormones (2,12–15). Studies on the estrogen and progesterone effect on the UFs are numerous. Regardless, their growth was not obtained with the external administration of these hormones only, thus indicating that there must be several additional links in the complex pathophysiological network of UF.

Genetic studies have demonstrated fibroids to be monoclonal tumors. The process of UF development starts with the creation of a pathologically changed, primary myometrial cell with a tendency for abnormal growth. In the next step, these transformed cells and all secondary cells divide, making the tumor grow further (16, 17). Modified cells need adequate stimulation to divide and produce the extracellular matrix (ECM). Fibroid tumors predominantly consist of smooth muscle cells embedded in the ECM (17, 18). Excessive ECM production is believed to be one of the most important mechanisms of fibroid enlargement (19–21).

A growing number of investigators are of the opinion that progesterone is a major factor in the initiation of fibroid differentiation and stimulation of further growth (2, 22). Some researchers even coined the term “progesterone hypothesis” to emphasize the role of progesterone in the process (23). Progesterone-induced activation of the uterine smooth muscle cell division is a well-known fact, especially in the second stage of the cycle, when progesterone levels are significantly elevated (12). The luteal phase is the time when higher levels of progesterone receptors are found in the tissues. This phenomenon is accompanied by a slowdown in the process of apoptosis within the normal and abnormal uterine smooth muscle tissue (2, 12, 15, 24). The main mechanism of progesterone influence appears to be based on the effect of increasing concentrations of selected growth factors and overexpression of the cytokine genes. These factors are secreted and act directly in the UF, making it an autostimulating process (2, 12). The positive influence of progesterone on UF growth is implied by the efficacy of its antagonists in pharmacologic therapy. Application of selective progesterone receptor modulators (SPRMs) results in evident reduction of tumor size and alleviation of the associated symptoms (25–28).

As mentioned, growth factors are one of the key players in the development and proliferation of UFs. Each of them has its individual effect on the tumor, but all of them combined create a mysterious network of simultaneous connections, synergisms, and antagonisms. Transforming growth factor β is a polypeptide consisting of three isoforms: TGF-$\beta 1$, TGF-$\beta 2$, and TGF-$\beta 3$ (20). Transforming growth factor β controls proliferation and differentiation in most types of human cells and is considered to be one of the most relevant factors in the pathogenesis of fibrosis-associated diseases (20). An accumulating body of research has confirmed the participation of different TGF-β isoforms in the pathophysiology of UFs (21, 29, 30). Transforming growth factor β is of particular importance in increasing the number of cell divisions and ECM production in UFs. Transforming growth factor $\beta 3$ is considered to be the most important isoform of TGF-β in UF biology as it occurs in three- to fivefold higher concentrations in UFs than in a normal myometrium (30–32). It also plays a role in the overproduction of ECM by stimulating gene expression—such as collagen type I, fibronectin, laminin, or versican (33, 34). On the other hand, TGF-$\beta 3$ has also a substantial impact on ECM degradation (30–32).

Selective progesterone receptor modulators are substances that influence the progesterone receptor (PR). These substances differ from the full agonist (progesterone) and full antagonists (e.g., aglepristone) in their various receptor effects (35). Selective progesterone receptor modulators may act as an antagonist in certain tissues while simultaneously acting as an agonist in others (36).

Progesterone effect modulation represents a possible pathway in UF therapy. Clinical trials have demonstrated that ulipristal acetate (UPA), a SPRM with tissue-specific antagonist and agonist activities, is efficient in controlling excessive uterine bleeding caused by fibroids and reducing fibroid size. Studies using UPA in the long regimen proved a very good effect on bleeding and UF size reduction (25–27). Patients receiving UPA reported a significant reduction in UF-derived symptoms, resulting in improved quality of life. Based on these studies, Donnez et al. (27, 28) proposed several UF treatment regimens, including the use of UPA and surgery. In those regimens, UPA is usually administered as first-line therapy to prepare the uterus for the operation or, in cases of high efficacy of this treatment, to lead to a condition when surgical treatment is no longer necessary. However, further studies are necessary as knowledge about the mechanisms of UPA action, its tissue effects, long-term efficacy, and overall safety remains limited (28, 37).

The main goals of our study were [1] to evaluate and compare the serum TGF-$\beta 3$ concentration in patients with UFs without hormone treatment, with UPA treatment, and in controls; [2] to evaluate the TGF-$\beta 3$ concentration in UF tissue in patients without hormone treatment and in those treated with UPA; and [3] to evaluate the correlations of age and BMI with TGF-$\beta 3$ serum and UF tissue levels between the groups.