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Selective progesterone receptor modulator as an alternative for long-term therapy of uterine fibroids in women of reproductive age

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Abstract

Uterine fibroids are the most common benign uterine tumors in women of reproductive age. They are the most frequent cause of profuse uterine hemorrhage, which significantly decreases the quality of life of women of reproductive age^[1, 2]. In 20 to 30 % of cases, fibroids are an etiological factor of infertility and in 15 to 30 % of cases – the cause of miscarriage. The highest incidence of uterine fibroids – over 50 % – is observed in the premenopausal period^[3, 4].

At present, women's reproductive health is a topical issue of obstetrics and gynecology, therefore, great importance is attributed to timely diagnosis and prevention of diseases that influence fertility^[5, 6, 7].

In recent years, various medicines have been suggested for the treatment of uterine fibroids, including nonsteroidal anti-inflammatory drugs, tranexamic acid, progestogens (intrauterine devices that release levonorgestrel), gonadotropin-releasing hormone antagonists, progesterone receptor modulators, including mifepristone. The use of modern conservative methods of treatment of uterine fibroids enables a decreased incidence of complications, the preservation of uterus and of women's reproductive function, an improved efficiency of treatment and quality of patients' life^[8, 9, 10].

Keywords: Fibroids, reproductive age, fertility

Introduction

According to E.M. Vikhlyayeva, uterine fibroids should be regarded as benign hormone-controlled hyperplasia of muscular elements of mesenchymal origin^[3]. From 20 to 40% of women above 35 suffer from uterine fibroids (UF). The incidence of this pathology in women of the late reproductive age (from 35 to 45 years) and the premenopausal age (from 46 to 55 years) grows. UF tend to occur more frequently during pregnancy. Up to the moment of menopause, UF develop in 50 to 80 % of women (with clinical manifestations or an asymptomatic course)^[1-4]. Epidemiological studies found a number of risk factors for the development of UF – genetic, anthropometric, racial, reproductive, vascular and hormonal. Obesity contributes to an increase in the level of estrogens circulating in blood. Hypertension often goes with the general pathology of nonstriated muscular tissue, which contributes to the proliferation of nonstriated muscle cells of uterus and vessels. Such changes directly damage myometrium or vascular structures of uterus^[2, 5].

UF are benign tumors of monoclonal origin that develop out of nonstriated muscle cells and contain various quantities of fibrous connective tissue. UF develop as a result of incorrect division of one nonstriated muscle cell^[1, 2, 5]. The majority of scientists believe that UF develop as a result of multiple somatic mutations in normal myometrial cells, which lead to a gradual decrease in the control of their growth.

Aim of research: Improvement of the quality of treatment of infertility in women with uterine fibroids, reduction of the recurrence rate and restoration of the reproductive function.

Materials and methods. We have carried out clinical and laboratory examination of 60 women with small uterine fibroids (basic group), who were divided into two subgroups: Subgroup I – 30 women who underwent the suggested treatment for 6 months – and Subgroup II (comparison group) – 30 women who refused to undergo the suggested treatment. The reference group consisted of 20 healthy women without any pathology of the female reproductive system.

Research results: In women from the basic group, uterine fibroids did not manifest themselves in any apparent clinical symptoms for a long time. According to the estimate, symptoms characteristic of UF were observed in 20 to 50% of women in both Subgroup I and Subgroup II. The presence of symptoms depends on the quantity, size and location of myomatous growths as well as on the degree of secondary degenerative and inflammatory changes in the tissue of growths. The main UF symptoms are profuse uterine hemorrhages that cause weakness, fatigue and lead to the development of iron-deficiency anemia; nagging pain in the lower abdomen (in 20 to 30% of patients); infertility, miscarriage, complicated labor, which are observed in every third patient with multiple location of myomatous growths. UF significantly reduce the likelihood of conception, the implantation rate and the live birth rate. Besides, it increases the incidence of spontaneous abortion and preterm labor. Before prescribing the course of treatment, we carried out examinations of the hormonal profile (estradiol, progesterone) and ultrasonography in women from both the basic and the reference group. The levels of ovarian hormones (estradiol and progesterone) were measured on the 7th and the 21st day of the menstrual cycle. To assess and analyze the levels of estradiol and progesterone in women with small uterine fibroids, the obtained results were compared to the results of the same indicators in the reference group. The concentration of estradiol on the 7th day of the menstrual cycle was 0.436 ± 0.07 nmol/l in women from the basic group and 0.351 ± 0.03 nmol/l in women from the reference group ($p=0.05$). Thus, we can see higher levels of estrogens in women from the basic group, yet the difference is not significant. No significant difference in the levels of estradiol was found on the 21st day of the menstrual cycle either. The measurement of progesterone levels on the 7th and the 21st day of the menstrual cycle did not show any significant difference. The main instrumental methods of UF diagnosis are ultrasonography and Doppler ultrasonography, less often computed tomography and magnetic resonance imaging are used. The analysis of the results of ultrasonography of internal reproductive organs of women from the basic group showed the presence of subserous, intramural and submucous growths of up to 2 cm in diameter requiring no surgical treatment according to the indications. 11 women (36.7 %) from Subgroup I presented submucous growths, which clinically manifested themselves in hyperpolymenorrhea, 9 women (30%) – intramural growths, which also caused excessive uterine hemorrhages, 10 women (33.3%) – subserous growths, which did not show any clinical symptoms in 8 women and manifested themselves in dysuric disorders in 2 women. In women from Subgroup II, the location of myomatous growths most likely did not differ from those from Subgroup I: 9 women (30%) presented submucous growths, with manifestations of hyperpolymenorrhea, 10 patients (33.3%) – intramural growths, with manifestations of hyperpolymenorrhea, and 11 women (36.7 %) – subserous growths without any clinical manifestations. Women from the reference group presented no pathological changes of uterus. Nowadays, many women choose to postpone pregnancy to a later age, when the risk of UF is, unfortunately, much higher. Therefore, the improvement of medicinal treatment is the main trend in the contemporary treatment of women with UF. Medicinal treatment is only possible in cases of absence of symptoms and with small (up to 12 weeks) tumors and

implies active outpatient observation: dynamic ultrasonography, cytological control of the condition of cervical epithelium and of endometrium. In such cases, one recommends antiprogesterin with a high affinity for progesterone receptors. Its relative ability to bind to human progesterone receptors is from 2 to 10 times higher than that of progesterone. After oral administration, mifepristone is rapidly absorbed and its bioavailability is 69%. According to a number of scientists, it is safe to administer mifepristone for 3 to 12 months. Mifepristone is administered starting from the 1st-3rd day of the menstrual cycle, i.e. in the early follicular phase before the formation of the dominant follicle. The use of mifepristone in the late follicular phase leads to the collapse of the dominant follicle and breakthrough bleeding. Mifepristone causes reduction of the size of uterus by 27 to 49% and of the size of myomatous growths by 26 to 74 %. Depending on the drug dose (5-10-100 mg), amenorrhea was observed in 40-70-100% of patients respectively. The drug reduces the volume of menstrual loss of blood; increases the level of hemoglobin ^[2], which has a favorable influence on the condition of patients with concomitant anemia; decreases the manifestations of dysmenorrhea and pelvic pain in 75% of women after 2 months of treatment. The research results have shown a broad range of patients' responses to treatment. All the patients had their menstrual cycle restored from 2 to 6 weeks after the end of treatment. Uterus enlargement was observed in fewer than 20% of women after treatment and its maximum sizes were 42% smaller than before treatment. The women from the basic group underwent a control examination after 6 months of drug administration. Women from the basic group presented a lower level of estradiol (0.398 ± 0.05 nmol/l) measured on the 7th day of the menstrual cycle, while the level of hormones on the 21st day of the menstrual cycle did not differ significantly from that in the reference group. The ultrasonography of women from the basic group showed reduction of the size of growths in 5 women (16.7%) from Subgroup I, while in the other 25 women (83.3%) from Subgroup I, the size of growths did not change but these patients noted a decrease in the intensity and duration of menstrual hemorrhages. Women from Subgroup II, who refused to undergo the suggested treatment, presented no positive changes. In 9 of them (30%), the size of growths increased.

Overall, we have noted a significant improvement of the quality of life of patients due to a decrease in adverse symptoms.

Conclusions

1. Uterine fibroids are the second most common gynecological disease after inflammatory diseases of uterus and appendages. In 20 to 30 % of cases, fibroids are an etiological factor of infertility and in 15 to 30 % of cases – the cause of miscarriage. Women's reproductive health is a topical issue in the contemporary gynecology and obstetrics, therefore, the solution to this problem lies in a step-by-step etiopathogenetic approach taking into consideration the patients' age, reproductive anamnesis and concomitant genital and somatic pathologies.
2. The use of the contemporary methods of conservative and surgical treatment of uterine fibroids enables a decreased incidence of complications, the preservation of uterus and of women's reproductive function, an improved efficiency of treatment and quality of patients' life.

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