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EFFECT OF UTERINE FIBROIDS ON HORMONAL PARAMETERS IN WOMEN OF ADVANCED REPRODUCTIVE AGE

ABSTRACT

The aim of this study was to investigate the level of steroid and gonadotropin-releasing hormone in women of reproductive age older to identify early markers predicting uterine fibroids. The study included 140 patients aged 35-55 years with uterine myoma, corresponding in size 6-10- and week-aged pregnancy with interstitial, submucosal and subserous localization of uterine fibroids. The main group included 60 patients treated with hormonal therapy, in the form of the drug, "Ulipristal acetate". There were 40 patients in comparison group (II group), including 12 patients taking gestagen ("Djufaston", "Utrozhestan"), at 10 VMS-"Mirena" for more than 1 year, 18 patients received hormone therapy with different drugs. The control group (III group) consisted of 40 patients, which were carried out various surgical interventions on the occasion of the diagnosis "Uterine fibroids." We have recognized "Ulipristal acetate" ("Esmiya", Hungary), as the most effective drug, for the conservative treatment of uterine fibroids. An in-depth study of the clinical and laboratory, including hormonal parameters will improve the tactics of directing patients, develop indications and contraindications for the use of the drug, increase their efficiency, develop an algorithm for the treatment of patients with a diagnosis of "uterine fibroids."

Keywords: uterine fibroids, hormonal parameters, ulipristal acetate, hormone therapy.

Despite numerous studies of domestic and foreign authors, devoted to the diagnosis and treatment of uterine fibroids, the problem still remains not fully solved [1,3]. Uterine fibroids are diagnosed in 20-25% of women of reproductive age and over the age of 40 years, it is diagnosed in 40-50%.

The development of uterine fibroids – is a hormone-dependent process. Numerous studies confirm that one of the most important factors affecting the molecular genetic processes of proliferation, apoptosis, hypertrophy and hyperplasia and uterine myometrium cells are estrogen and progesterone [2].

The most important aspect of the etiology of uterine fibroids – the initiator of tumor growth - remains unknown, although there are theories of initiating its tumorigenesis. One of them confirms that the increase in the level of estrogen and progesterone leads to increase in mitotic activity, which can promote the formation of fibroids, increasing the likelihood of somatic mutations. Along with traditional views on the leading role of estrogen in the pathogenesis of hormone-dependent diseases, it is reviewed the relation to progesterone in recent years, as a stimulator of tumor growth [8]. An importance is attached to the role of tissue receptors of steroid hormones, synthesized under the influence of many factors: the number and ratio of sex hormones, the menstrual cycle, the degree of pathological lesion of body, metabolic disorders [7].

Knowing the factors of predisposing allows an understanding of the etiology of uterine fibroids and to develop preventive measures.

Purpose of the study. In this regard, we aim to assess the level of steroid and gonadotropin-releasing hormone in women of advanced reproductive age to detect early prediction markers of uterine fibroids.

Materials and methods. The survey included 140 patients in the age from 35-55 years, with uterine fibroid, corresponding to size of 6-10- and week-long pregnancy with interstitial, submucosal subserous localization of uterine fibroids.

The work was performed at the Department of Obstetrics and Gynecology 1, of the Azerbaijan Medical University. To achieve this goal, we have examined 140 patients with uterine fibroids in the period from 2012 to 2015.

Exclusion criteria: young and average reproductive age, abnormal uterine bleeding, suspicion to endometrial hyperplastic processes, organic pelvic pathology, concomitant extra genital pathology.

The main group consisted of 60 patients treated with hormonal therapy, in the form of the drug, "Ulipristal acetate" ("Esmiya" Gedeon Richter, Verngiya). The drug was administered on the first day of the menstrual cycle on a daily basis, continuously at a dose of 5 mg. The course dozing of the drug was 1-2 courses for 3 months. Among the surveyed women, 45 of them took the drug during the 1st course, 15 patients took the drug during the 2nd course. The comparison group (II group) included 40 patients, including 12 patients taking gestagens ("Djufaston", "Utrozhestan"), at VMS "Mirena" for more than 1 year, 18 patients received hormone therapy with different drugs. The control group (III group) consisted of 40 patients, which were carried out various surgical interventions on the occasion of the diagnosis "Uterine fibroids."

Among the examined ones it was conducted a questionnaire survey, analysis of medical records, general clinical and gynecological examination.

To evaluate the hormonal status before treatment, during the treatment course and the subsequent menstrual cycle in different phases of the cycle: in follicular phase, periovulation period and average luteal phase – it was conducted determination of estradiol (E), progesterone (PG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL) and cortisol (K). Determination of these hormones in the blood plasma was carried out using a radioimmunoassay by using Bio-Rad Laboratories Inc. (USA) company standard sets for radioisotope analyzer Immunochem-2100 Microplate Reader using the procedure recommended by the manufacturer.

Results and discussion. Based on the data of comprehensive survey in the study group, under the influence of conservative treatment, after 3 months of treatment, the number of complaints of pain was reduced in the lower abdomen and sacrum and lumbar spine in almost all patients in the study group. The pain decreased in 7.5% of women in the comparison group taking the treatment, and in the control group, positive dynamics was insignificant - in 5.7% of the patients.

Violation of the menstrual cycle returned to normal condition in the main group in 40% of cases, the duration of menses reduced by an average of 2.2 + 0.5 days, menstrual blood loss decreased by 17%. In the comparison group, the recovery cycle was observed in 52.2% of patients, cycle time decreased by an average of 1.5 ± 0.5 days, blood loss decreased by 9.2%. However, in the main

group, the effect of blood loss lowering was significantly higher than in the comparison group.

Dysuric disorders and constipation in the study group and the control group decreased slightly, but in the control group it remained unchanged.

Complaints about the anxiety in the main group were observed in 55% (p <0,05), irritation - 33.3%, instability in mood- in 51.7% of patients. In the comparison group, after the treatment course, which included diet and gestagens, the complaints of anxiety and irritability were without any significant changes. In the control group, the psycho-emotional state had a tendency to increase.

At the end of 12 months treatment, the study group showed improvement of mental and emotional status: complaints on anxiety were observed in 30%, irritability - 15%, mood instability in 16.7%.

Clinical examination includes a detailed examination of the nature of the menstrual cycle, namely the volume of long-term blood loss in patients with uterine fibroids.

It was determined the level of estradiol (the E), progesterone (the P), free testosterone (T), prolactin (nR), follicle-stimulating (FSH) and luteinizing hormone (completion LH), cortisol (K) in the first, sixth months and after 12 months of patients follow-up.

The presented data show that in the majority of patients, menstruation was abundant, in all groups. Scanty menstruation was observed in only 65%, 2.5%, 12.5%. Also different was the length of menstrual bleeding. Thus, in 61.7%, 67.5% and 42.5%, menstruation lasted more than 7 days.

After 12 months of treatment, the average content of estradiol in the main group maintained the reduction dynamics from the initial indicators, in the I and VI months (pI-VI <0,001, pVI-XII <0,005).

It should be noted that in the 6th months, there was a significant decrease in this indicator by 1.2 times compared to the beginning of treatment. The concentration of estradiol in the comparison group also tends to decrease, but not significantly at 70 units. Analyzing the data table showed that the first and second studied groups, there was a statistically significant increase in the level of estradiol - 17β serum. Among the patients who received "Ulipristal acetate", the average content of this indicator decreased from 323.73 to 113,4 + 5,91 (p <0,001), for the studied who were treated with combined oral contraceptive estradiol 296.15 to 210.92 nmol / l (p <0,001).

The study of progesterone concentration showed a progressive increase in progesterone in the main group and the comparative group of survey (p <0,001). (21.51 + 0.48 and 20.38 + 1.05 compared with 5.71 + 0.32 and 8.02 + 0.66).

In carrying out surgery in the control group, the content of Pr in the VI month increased 15,06 + 0,41 (p <0,001), but in the 12th months almost three times it was decreased 5,23 + 0,35 (p IV-XII <0, 01 and p I-XII <0,01). The values of the indicators after the treatment were significantly higher compared with the comparison group.

Thus, we found significant reduction of estradiol - B17 and increase the concentration of progesterone in the main group, which corresponds to the data of various authors.

Our studies have shown that taking the drug "Ulipristal acetate" (Esmiya) causes significant changes in the concentration of progesterone and estradiol, approaching the performance of healthy women, promotes regression of fibroids.

The content of prolactin was significantly reduced in patients receiving the drug "Ulipristal acetate" from 24.46 + 0.83 down to 17,27 + 0,47 (p I-VI <0,001). In the second group, it was observed positive dynamics of prolactin in the blood, but the changes were not statistically significant (p I-VI <0,001).

In the study of the concentration of free testosterone (T) in the study and control groups, in the I and XII months, we found no significant changes. However, among the patients of the comparison group, there was a significant increase in testosterone from 1.73 to 2.94 + 0.19.

One of the fundamental risk factors for fibroids development is stress, which manifests itself in violation of the cortisol hormone secretion. The level of cortisol of the main group patients before the treatment was 454.38 + 0.33 and in the VI month, the concentration already decreased down to 377,50 + 7,99 (pI-III <0,001). A year after the start of treatment, the respondents noted a reduction down to 252.45 + 6.50, ie, the findings were consistent with standard indicators. When comparing with the clinical presentation 1, there is a significant improvement in the study group patients on the part of the psycho-emotional background.

The mean FSH content was significantly reduced in the case of "Ulipristal acetate" 36.77 + 0.38 to 18.76 + 0.21 and after a 36.31 + 0.52 to 28.32 +1.55.

Thus, a complete or partial clinical response to taking "Ulipristal acetate" is observed in the majority of patients of the main group. The downward trend of oestradiol-17 and progesterone increase is a reflection of the normalization of

Hormonal study in the patients with uterine fibroids (study group)

Hormones	Frequency of research		
	1 month	6 month	112 month
Estradiol (n = 60)	323,73±10,74 302,25-345,21	201,13±9,08 182,97-219,28 P I-VI< 0,001	113,4±5,91 101,59-125,21 P I-XII< 0,001 P VI-XII< 0,05
Progesterone (n = 60)	5,710±,32 5,07-6,35	16,42±0,31 15,79-17,04 P I-VI< 0,001	21,510±,48 20,54-22,47 P I-VI< 0,001 P VI-XII< 0,001
Testosteron (n = 60)	1,980±,09 1,80-2,15		1,7±0,06 1,57-1,82 P I-XII< 0,05
Prolactin (n = 60)	24,46±0,83 22,79-26,12		17,27±0,47 16,32-18,22 P I-XII< 0,001
FSH (n = 60)	35,89±0,50 34,88-36,90	23,26±0,17 22,92-23,61 P I-VI< 0,001	13,82±0,34 13,15-14,49 PI-XII< 0,001 P VI-XII< 0,001
LH	45,53±0,69 44,15-46,91	26,59±0,30 25,88-27,19 PI-VI< 0,001	13,35±0,50 12,33-14,35 PI-XII < 0,001 PVI-XII< 0,001
Cortisol (n = 60)	454,38±0,33 433,72-475,05	377,50±7,99 361,52-393,48 PI-VI< 0,001	252,45±6,50 239,45-265,45 PI-XII< 0,001 PVI-XII< 0,001

hormonal balance. On the background of the drug treatment it was significantly reduced the frequency of menstrual disorders, the psycho-emotional disorders, in this, a more expressed clinical benefit was observed in patients of the main group.

Changes in the indicators of hormonal status, discovered by us in case of dynamic observation regardless of the choice of therapy in the examined patients, confirm the importance of studying in hormonal balance, as a method for early diagnosis of uterine fibroids.

As early diagnostic criteria at the preclinical stage of uterine fibroids detection, we suggest using indicators Pg levels, E2, K in the peripheral blood of high-risk groups on the development of uterine fibroids.

Currently, the most effective drug for conservative treatment of uterine fibroids is “Ulipristal acetate” (“Esmiya”, Hungary). Several publications of foreign researchers also confirmed the high efficiency of this method.

An in-depth study of the clinical and laboratory parameters, including hormonal parameters, will improve the tactics of directing patients, to develop the indications and contraindications of the drug application, improve their performance, to develop an algorithm of therapy of patients with a diagnosis of “Uterine fibroids.”

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