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GENITAL ENDOMETRIOSIS: CHOICE OF THERAPY

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ABSTRACT

Aromatase is a key enzyme in the conversion of androgens to estrogens in the ovaries and other tissues and organs. To study the role of aromatase in the pathogenesis of external genital endometriosis (NGE) 57 patients with NGE were examined and 15 healthy women of reproductive age. Aromatase activity was determined by the reaction of estrogens to the aromatase inhibitor letrozole. The ovarian source of the determined aromatase activity was determined by the suppression of the reaction to letrozole against the background of the use of the gonadotropin releasing hormone agonist. Aromatic activity in terms of antral. The follicle in patients with grade II–IV NE was higher than in healthy women, however, the total aromatic activity of the ovaries due to the low number of antral follicles did not differ from the indicator in the control group. Violation of folliculogenesis in NGE is probably associated with the revealed hyperestrogenemia of ovarian and extra-gonadal origin.

Endometriosis is an estrogen-dependent disease. Gonadotropin-releasing hormone (aGRH) agonists are currently most commonly used in the treatment of external genital endometriosis (OGE). Gonadotropin-releasing hormone (GRH) was discovered in 1971, and since then its agonists and antagonists have been used to treat diseases such as prostate cancer, breast cancer, endometriosis, uterine fibroids, as well as in assisted reproductive technology protocols [17]. GRG is a decapeptide that is synthesized and accumulated in the medio-basal hypothalamus and released into the portal system in a pulsed mode. Connecting with plasma receptors of pituitary gonadotrophs, GRH stimulates the synthesis and secretion of luteinizing (LH) and follicle-stimulating (FSH) hormones by them. Mammalian GRH receptor is a seven—component portal-type transmembrane receptor associated with a G protein consisting of 328 amino acids [2,4,6,8,10,12].

In addition to pituitary gonadotrophs, this receptor is expressed on many other human tissues, including the placenta, uterus, ovaries, prostate, mammary gland, liver, heart, skeletal muscles and kidneys [9, 11, 17]. Gonadotropin-releasing hormone agonists differ from natural

GRH by replacing amino acids at position 6 (at the site of proteolysis) and often by the presence of an ethylamide group instead of glycine-amide at the C end of the molecule, which leads to greater stability of the molecule and increases the half-life in circulation [1,3,5,7,9,11]. The mechanism of action of HRH agonists includes two phases: a short-term phase of stimulation, manifested by an increase in the blood content of FSH and LH and, as a consequence, an increase in estradiol and, to a lesser extent, progesterone in the blood; and a phase of pituitary desensitization, when gonadotrophs remain resistant to stimulation and the level of gonadotropins in the blood decreases. The intensity and duration of the second phase depends on the dose of GRH agonists [14,16,18,20,22,25]. The therapeutic effect of HRH agonists in endometriosis may be associated with the following factors: a decrease in the level of estrogens in the blood, an increase in apoptosis in endometrial cells through increased expression of the Fas ligand and a decrease in the activity of the anti-apoptotic protein Bcl 2, with a violation of implantation of rejected endometrial cells on the peritoneum [13,15,17,19,21,23].

By a number of authors [1, 5] absolute or relative hyperestrogenemia was found in women with endometriosis. Subsequently, an increased activity of ovarian aromatase in this pathology was established even before the formation of the dominant follicle [2]. It was of interest to compare the therapeutic efficacy of HRH agonists in endometriosis with the activity of ovarian aromatase.

The aim of the work was to study the therapeutic effect of a GRH agonist depending on the activity of ovarian aromatase.

Materials and methods of research. 64 patients with external genital endometriosis (OGE) were examined. The age of the patients ranged from 24 to 39 years and averaged 30.3±0.4 years, the body mass index (BMI) was on average 21.1±0.4 kg/m2. Within normal values, the body mass index was in 57 women (89.1%), excess body weight — in one (1.6%), obesity — in two (3.1%), body weight deficit — in four patients (6.2%). The average age of menarche onset in the study group was 12.9±0.2 years. A regular menstrual cycle was observed in 56 (87.5%) of the women studied, menstrual disorders manifested by opsomenorrhea were observed in 8 (12.5%) patients. 38 (40.1%) women had a history of pregnancy, 7 patients had urgent labor. Artificial abortions in the anamnesis were in 13 (20.4%) patients, miscarriage in the anamnesis was in 12 (18.8%) patients. Primary infertility was observed in 35 (54.7%) women, the duration of primary infertility ranged from 1 to 10 years (on average 3.6 ± 0.4 years), and the presence of male factor infertility in this group was noted in 9 (25.7%) patients. Secondary infertility was noted in 17 (26.6%) patients, its duration ranged from 1 year to 7 years (on average 2.9± 0.4 years), the male factor of secondary infertility was noted in 7 (41.2%) women. Ovulatory menstrual cycle was preserved in 22 (34.4%) women, 42 (65.6%) patients had ovarian insufficiency (36 — anovulation, six — luteal phase insufficiency). The menstrual cycle was preserved in all patients. 28 (43.7%) of them had perimenstrual spotting, 47 (73.4%) women had algomenorrhea, 21 (32.8%) women had dyspareunia, 11 (17.2%) patients had pelvic pain unrelated to the menstrual cycle. The prevalence of NGE was determined according to the revised classification of the American Fertility Society [6]. Nine women (14.1%) had grade I NGE, 40 (62.5%) patients had grade II NGE, 10 (15.6%) patients had grade III NGE, and five (7.8%) patients had grade IV NGE.

Surgical intervention for NGE was performed once in 58 (90.6%) patients, twice in five (7.8%) women and three times in one patient (1.6%). The control group consisted of 15 women with a full ovulatory menstrual cycle. The age of women in the control group ranged from 23 years to 31 years, averaged 26.7±0.8 years. The BMI in the control group averaged 21.3±0.5 kg/m^2, one woman had a body weight deficit, the rest had a body weight within the normal range. The average age of menarche onset in the control group was 13.1±0.2 years. Five (33.3%) women of the control group had a history of pregnancies that ended in urgent labor. All women had a regular menstrual cycle. The ovulatory menstrual cycle was confirmed by ultrasound examination of the pelvic organs, the level of progesterone in the blood on the 20th-21st day of the menstrual cycle.

All women of the main group underwent laparoscopy according to the generally accepted method using a laparoscope from Karl Storz (Germany) to confirm the diagnosis of external genital endometriosis and excision and coagulation of endometrioid heterotopias, followed by their histological examination. Ultrasound examination of the pelvic organs was performed on the Sonoace X4 device (Korea) using a transvaginal sensor with a frequency of 4-9 MHz. Ultrasound examination determined the size of the uterus, the thickness and structure of the endometrium, the size of the ovaries, the condition of the follicular apparatus, the presence of the dominant follicle and corpus luteum, their sizes. Hormonal examination included determination of estradiol (E_2), estrone (E_1), androstenedione (A4), FSH, LH, prolactin, anti-muller hormone (AMH) in blood serum by enzyme immunoassay. Prolactin, FSH, LH, progesterone were determined using Alkorbio test systems (Russia); estradiol, estrone, androstenedione - using DRG diagnostics test systems (Germany); AMG — using the Beckman Coulter test system (USA). All women were tested with the aromatase inhibitor letrozole on the second day of the menstrual cycle. The content of gonadotropins and sex steroid hormones was determined initially and 48 hours after oral administration of 10 mg of the aromatase inhibitor letrozole. The activity of ovarian aromatase was assessed by reducing the level of estradiol in the blood under the influence of letrozole in absolute values (pmol/L) and as a percentage of the baseline level. To assess the aromatase activity of one antral follicle, the coefficient was used: DE2 / AMG, where DE2 is a decrease in the level of estradiol in the blood in pmol / l 48 hours after taking letrozole, AMG is the content of AMG in the blood in ng /ml. An indirect method for assessing aromatase activity was the coefficient: E_1 /A4 , where E_1 is the level of estrone in the blood in nmol/l, A4 is the level of androstenedione in the blood in nmol/L. Fifty-five women received postoperative gonadotropin-releasing hormone agonist triptorelin acetate (diferelin, Ipsen Pharma, France) at a dose of 3.75 mg intramuscularly once every 28 days for 6 months. Thirty patients with NGE were tested with letrozole twice: the first time before the start of therapy, the second time 2 months after the start of AGR therapy. The effectiveness of therapy was evaluated according to the following criteria: elimination of pain syndrome, effect on the menstrual cycle (disappearance of perimenstrual secretions), restoration of the ovulatory menstrual cycle.

Statistical processing of the obtained results was carried out using the tools of Microsoft Office Excel 2003 and Statistica 10.0 for Windows, the Student's t criterion and criterion χ^2 were used. Significant differences were considered at p coefficient E_1 /A4 and with the reaction of estradiol to letrozole. After completing the course of the HRH agonist, a full

ovulatory menstrual cycle was restored in 37 out of 51 patients (72.5%), seven of whom became pregnant. The results obtained indicate a high efficiency of combined therapy of endometriosis (laparoscopic coagulation of endometrioid heterotopias followed by a six-month course of agonist HRH). The therapeutic effect of the GRH agonist is probably associated with inhibition of gonadotropin secretion by the pituitary gland, suppression of aromatase activity and a decrease in the production of estrogen by the ovaries. At the same time, the effectiveness of treatment did not depend on the aromatase activity of the predominant antral follicles. It is known that the highest aromatase activity is determined in the dominant follicle [4], and the therapeutic effect of HRH agonists can be associated with the suppression of the growth of the dominant follicle. Conclusions Hyperestronemia and an increase in the E_1/A4 ratio indicate an increased total aromatase activity in endometriosis. The aromatase inhibitor letrozole causes a comparable decrease in estradiol in the blood of healthy women and patients with endometriosis, and the suppression of the reaction against the background of a GRH agonist indicates the ovarian origin of the determined aromatase activity. Aromatase activity in terms of one antral follicle in endometriosis exceeds the corresponding indicator in healthy women and directly depends on the prevalence of endometriosis. Combination therapy of endometriosis (laparoscopic coagulation of endometrioid heterotopias followed by a six-month course of a GRH agonist) leads to a significant reduction in clinical manifestations of the disease and restoration of a full-fledged ovulatory menstrual cycle in 72.5% of patients. The effectiveness of combination therapy is not significantly related to the initial estrogenemia and the activity of ovarian aromatase.

Conclusions: 1.In endometriosis, the aromatase activity of antral follicles is increased compared to the aromatase activity of antral follicles of healthy women. At the same time, the total aromatase activity of the ovaries is close to the indicator in healthy women due to the low number of antral follicles in the ovaries of patients with endometriosis.

4. Basal (prior to the initiation of the dominant follicle) aromatase activity does not depend on the presence or absence of ovulation in patients with endometriosis.

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