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THE CONTENT OF ANDROSTENEDIONE IN THE BLOOD OF WOMEN WITH OBESITY AND OVARIAN INSUFFICIENCY

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ABSTRACT

To reduce the pain syndrome and restore the ovulatory menstrual cycle, it is advisable to prescribe GnRH agonists to patients with external genital endometriosis after surgical removal of endometrioid heterotopias.

Endometriosis is a disease characterized by the growth of tissue similar in structure and function to the endometrium, beyond its normal localization. External genital endometriosis (OGE) affects from 12 to 80% of women of reproductive age, occurs in adolescents and postmenopausal women [1,3,5,7,9,11,24]. There is a steady increase in this pathology. It is generally recognized that genetic factors, as well as hormonal and immune homeostasis disorders are among the most important pathogenetic links in the development and progression of the disease. It is known that NGE is accompanied by an increased content of estrogens in the peritoneal fluid and relative or absolute hyperestrogenemia. The increase in the local content of estrogens is caused by enzymes involved in the biosynthesis of estrogens, namely 17p-hydroxysteroid dehydrogenase (17P-HSD) and aromatase. There are several types of 17/3-HSD: type 1, which catalyzes the conversion of estrone into estradiol, and type 2, which is responsible for the reverse reaction; it is 17P-HSD that regulates the level of active estrogens in tissues [14,16,18,20,22,25].

Hyperexpression of transcripts of 17P-HSD type 1 genes and estrogen sulfatase, which converts sulfated estrogens into biologically active estrogens, was found in endometrioid heterotopias compared with normal endometrium. It is known that prostaglandins (PG) Eg, can enhance the expression of aromatase, which, in turn, leads to increased biosynthesis of estrogens in the endometrium and endometrium-like tissue. It was determined that the expression of aromatase in endometrioid heterotopias and eutopic endometrium of patients with NE4 was significantly higher compared to this indicator in the endometrium of healthy women. Impaired expression of aromatase P450 in endometrioid tissue, in contrast to the eutopic endometrium, leads to increased estrogen biosynthesis, which contributes to the growth of endometrioid heterotopias and, possibly, determines resistance to traditional hormonal treatment methods). Endometrioid heterotopias differ from the surrounding endometrium not only in morphology, but also in the expression of sex steroid hormone receptors (estrogen (ER), progesterone (PR) and androgen. Data on the role of ER-alpha (ERa) in endometriosis are contradictory and few. A number of studies have shown reduced

expression of PR in endometrioid heterotopias and endometrium of patients with endometriosis compared with this indicator in the endometrium of healthy women. None of the existing methods of endometriosis therapy can guarantee the absence of a relapse of the disease.

The frequency of relapses within 2-5 years after surgical treatment ranges from 20 to 43.5% [13,15,17,19,21,23].

One of the effective methods of treating endometriosis is considered to be a combined approach (surgical followed by hormone therapy using gonadotropin-releasing hormone (GnRH) agonists, however, relapses of the disease within a year after the end of treatment are observed in 12-25% of cases [2,4,6,8,10,12].

The main mechanism of action of GnRH agonists is associated with induced hypoestrogenemia. There is evidence of suppression of the activity of aromatase P450 against the background of the use of GnRH agonists. In recent years, one of the promising and pathogenetically justified methods of therapy for NE is the use of aromatase inhibitors, as well as the progestogen dienogest, which has not only a pronounced antiproliferative effect, but also the ability to suppress the expression of aromatase and prostaglandin. Currently used methods for determining aromatase are associated with surgical intervention, therefore, the development of a less invasive method for determining aromatase seems relevant for choosing the optimal pathogenetically justified therapy.

The aim of the study was to study ovarian aromatase in polycystic ovarian syndrome using various methods for its determination.

Materials and methods: 49 women with normogonadotropic anovulation caused by polycystic ovarian syndrome were examined. The average age of the patients was 25.7±3.3 years, the average body mass index was 23.6±0.7 kg/m^2. 12 patients were overweight, 5 women were obese of the I degree, one was obese of the II degree. The diagnosis of polycystic ovarian syndrome was made on the basis of clinical manifestations (menstrual cycle disorders, androgen-dependent dermopathy (hirsutism, acne)), hormonal disorders (hyperproduction of luteinizing hormone (LH) by the pituitary gland and androgens by the ovaries) and the results of ultrasound examination of the ovaries (increased volume, thickening of the capsule, the presence of a large number of small antral follicles in them). The control group consisted of 33 healthy women aged 20 to 37 years (average age — 27.0 ±3.5 years) with a full ovulatory menstrual cycle, confirmed by ultrasound examination of the pelvic organs (presence of dominant follicle and corpus luteum) and progesterone levels on the 22nd day of the menstrual cycle (average progesterone level — 44.3±6.0 nmol/l). The body mass index averaged 21.1±0.3 kg/m^2, one woman had a moderate body weight deficit (17.6 kg/m^2). In the past, 12 women have had childbirth. All women on the second day of the menstrual cycle were determined by the enzyme immunoassay the level of estradiol in the blood using kits from DRG Diagnostics (Germany) and the content of AMH using test systems from Beckman Coulter (USA). Patients with polycystic ovarian syndrome were tested with letrozole. During the test, 10 ml of blood was taken on the second day of the menstrual cycle from the ulnar vein at 9 a.m., the level of estradiol and AMH was determined in the obtained blood serum. Next, the patient took 10 mg of the aromatase inhibitor letrozole orally. After 24 hours, repeated blood sampling and determination of estradiol levels were performed. On the

fifth day of the menstrual cycle in women of both groups, the number of antral ovarian follicles was calculated using ultrasound on the SonoAce X4 device (South Korea) using a vaginal sensor with a frequency of 5.0 MHz. The coefficient of aromatase activity of antral follicles was calculated by the formula $K = E^2/n$, where K is the coefficient of aromatase activity of antral ovarian follicles in pmol/l; E^2 is the level of estradiol in the blood on the second day of the menstrual cycle in pmol/l; n is the number of antral follicles in both ovaries. Statistical processing of the obtained results was carried out using standard software packages for applied statistical analysis (Statistica for Windows 7.0, Microsoft Excel). The analysis of the dependence and the strength of the connections between the signs were evaluated by the value of the nonparametric correlation coefficient — Spearman's rs-criterion. The directionality of the links was assessed by the sign of the correlation coefficient. The critical confidence level of the null statistical hypothesis was assumed to be 0.05. Results and discussion The basal level of estradiol in the blood of patients with polycystic ovary syndrome practically did not differ from the content of estradiol in healthy women, while the level of AMH in the blood was significantly $p < 0.05$ were: lower — 8.1 pmol/l, upper — 28.3 pmol/L. It follows that the value of K28.3 pmol/l corresponds to the high aromatase activity of the antral follicles of the ovaries. The aromatase activity of the antral follicles of the ovaries of women with polycystic ovary syndrome varied widely: in 39% of patients it was within the reference interval for healthy women, in 59% of patients it was reduced and in 2% of patients it was increased. The obtained data were compared with the previous results of determining the aromatase activity of ovarian follicles by the methods proposed above. A positive reliable ($p<0.05$) correlation was revealed between the method of determining the aromatase activity of the follicle calculated by the formula E^2/ AMG [3], and a method for determining aromatase activity calculated by the formula $KA = E^2$ / AMG. The correlation coefficient was 0.9. A positive reliable ($p<0.05$) correlation was also observed between the results of determining the aromatase activity of the follicle, calculated by the formula E^2 /AMG [8], and the method of determining aromatase activity using the coefficient E^2 /n. The correlation coefficient was 0.7. The proposed method allows to estimate approximately the aromatase activity of antral ovarian follicles noninvasively without the use of letrozole aromatase inhibitor and determination of AMH in the blood. The method is easy to use and can be applied in everyday practice.

Recent literature data indicate the pathogenetic significance of partial aromatase deficiency of antral follicles in the development of normogonadotropic anovulation. Reduced aromatase activity of antral follicles according to the results of the letrozole test is detected in 22.8% of patients with normogonadotropic anovulation, and 56% of them have clinical, echographic and hormonal signs of polycystic ovarian syndrome [2]. In normogonadotropic anovulation caused by polycystic ovarian syndrome, low aromatase activity is determined in 48.8% of patients [4], in 82% of patients — by the E^2 / AMH coefficient and in 59% of patients — by the E^2 /n coefficient.

The results indicate that ovarian aromatase deficiency is a common, but not the only cause of polycystic ovarian syndrome. Another important link in the pathogenesis of polycystic ovarian syndrome may be insulin resistance, which leads to increased insulin secretion by the pancreas [4]. Hyperinsulinemia may be responsible for increased secretion of

LH by the pituitary gland, high sensitivity of the ovaries to LH, hyperproduction of ovarian androgens and relative deficiency of ovarian aromatase. To date, the ratio of aromatase deficiency and insulin resistance in the development of polycystic ovarian syndrome has not been studied. Clarification of this issue will optimize therapy aimed at eliminating the clinical manifestations of polycystic ovarian syndrome and overcoming infertility.

Conclusions.

1. Estradiol coefficient/number of antral follicles allows to estimate approximately ovarian aromatase activity.
2. Aromatase deficiency of ovarian follicles is detected in 59% of patients with polycystic ovarian syndrome.
3. Absolute or relative deficiency of ovarian aromatase is the central link in the pathogenesis of polycystic ovarian syndrome.
4. External genital endometriosis in 64.7% of patients of reproductive age is characterized by normogonadotropic ovarian insufficiency (of which anovulation - in 55.9% of women, luteal phase insufficiency - in 8.8%).

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