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OVARIAN FUNCTION IN DIFFERENT PHENOTYPES OF POLYCYSTIC OVARY SYNDROME IN WOMEN OF REPRODUCTIVE AGE

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✓ ***Resume***

This article analyzes the assessment of the functional state of the ovaries in women with various PCOS phenotypes by examining the hormones of the pituitary-ovarian system and evaluating the results of the functional test with letrozole. The results of the study indicate the existing differences in hormonal features and activity of the enzyme cytochrome p-450 ovarian aromatase in women with polycystic ovary syndrome of reproductive age.

Key words: PCOS, phenotypes, women of reproductive age, hormones, cytochrome P-450, aromatase.

ФУНКЦИОНАЛЬНАЯ АКТИВНОСТЬ ЯИЧНИКОВ ПРИ РАЗЛИЧНЫХ ФЕНОТИПАХ СИНДРОМА ПОЛИКИСТОЗНЫХ ЯИЧНИКОВ У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА

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✓ ***Резюме***

В данной статье приводиться анализ оценки функционального состояния яичников путем исследования гормонов гипофизарно-яичниковой системы и оценки результатов функциональной пробы с летрозолом у женщин с различными фенотипами СПКЯ. Результаты исследования указывают на имеющиеся различия в гормональных показателях и активности фермента цитохром р-450 ароматазы при синдроме поликистозных яичников у женщин активного репродуктивного возраста.

Ключевые слова: СПКЯ, фенотипы, женщины репродуктивного возраста, гормоны, цитохром Р-450, ароматаза.

TURLI FENOTIPDAGI TUXUMDONLAR POLIKISTOZI SINDROMI BILAN KASALLANGAN REPRODUKTIV YOSHDAGI AYOLLARDA TUXUMDON FUNKSIONAL FAOLLIGI

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Ushbu maqolada tuxumdonlar funksional holatini gipofiz-tuxumdon sistemasi gormonlarini tekshirish yo’li bilan va turli fenotipdagi tuxumdonlar polikistozi sindromi bilan kasallangan reproduktiv yoshdagi ayollarda letrozol bilan test natijalarini baholash tahlili keltirilgan. Tadqiqot natijalariga ko’ra, tuxumdonlar polikistozi sindromi bilan kasallangan faol reproduktiv yoshdagi ayollarda sterioidogenez ko’rsatkichlari va sitoxrom p-450 aromataza fermenti faolligida farqlar mavjudligini ko’rsatmoqda.

Kalit so'zlar: TPS, fenotiplar,reproduktiv yoshdagi ayollar,gormonlar, aromataza , sitoxrom P-450

Relevance

Polycystic ovary syndrome (PCOS) is one of the most pressing problems in gynecological endocrinology, being a widespread disease among women of reproductive age [1,7]. The frequency of PCOS according to various authors is detected in 4-10% of women of childbearing age, while there is a tendency to increase the prevalence of the disease. The mechanisms leading to endocrine disorders, and as a result, to failures in the proper functioning of all parts of the reproductive system in PCOS, have not been fully elucidated and are the subject of modern research. PCOS is a multidisciplinary problem and doctors of various specializations often have to deal with this disease in their clinical practice. The main complaints of women of reproductive age with PCOS are reproductive disorders, irregular menstruation, as well as various metabolic disorders and their manifestations.

When diagnosing this disease, according to the Rotterdam criteria of 2003, it is necessary to have two of three parameters: oligo- or amenorrhea, clinical and/or biochemical signs of hyperandrogenism and polycystic ovarian transformation according to the results of ultrasound (ultrasound) [4, 9].

According to the recommendations of the Society for the Study of Androgen Dependent Diseases (AES, 2006), the criteria of the US National Institutes of Health (NIH, 1991) and the ESHRE / ASRM criteria (2003), it is customary to distinguish 4 PCOS phenotypes depending on the combination of certain clinical manifestations: phenotype A [hyperandrogenism, chronic anovulation, polycystic ovarian morphology (PCO)], phenotype B (only hyperandrogenism and chronic anovulation), phenotype C (only hyperandrogenism and PCOS); phenotype D (chronic anovulation and PCOS, without signs of hyperandrogenism) [2,4].

PCOS is regarded as normogonadotropny ovarian insufficiency. Primary ovarian factors play an important role in its development. These include chronic adnexitis, autoimmune ovarian damage, as well as damage to the enzymatic system responsible for the synthesis of estrogens by the dominant follicle. The key enzyme in the conversion of androgens to estrogens is aromatase. Aromatase is a unique enzyme complex that is required in the body to complete the synthesis of estrogens by ovarian granulosa cells. Aromatase activity in the ovaries is manifested in the antral follicles of the 5th class, when the third stage of folliculogenesis begins - the selection and maturation of the dominant follicle. At this stage, the follicles reach a size of 2 mm or more in diameter and their growth becomes completely dependent on the follicle-stimulating hormone (FSH), which stimulates aromatase through the adenylate cyclase system. Aromatase activity is also determined in other tissues and organs involved in peripheral estrogen production, such as adipose tissue, skin fibroblasts, liver, stroma and parenchyma of the mammary glands, endometrium, placenta, muscle and bone tissue, etc. Therefore , there are sufficient reasons to believe that the aromatization reaction is one of the essential mechanisms for maintaining the estrogen-androgen balance in the relevant organs and can influence the formation of estrogen-deficient states during anovulation [2, 7, 5].

The conversion of androgens to estrogens is the last step in the multienzymatic transformation of cholesterol into estrogens. It is known that aromatase is involved in three successive stages of androgen oxidation using three oxygen molecules and NADP-H. In the 1980s, a number of authors isolated a human protein, cytochrome P450 aromatase, from placental microsomes and demonstrated the conversion of androstenedione to estrone using a purified enzyme. These studies proved that one enzyme is involved in the process of aromatization, and not several, as was originally assumed [3, 10].

Purpose of the study: to assess the functional activity of the ovaries in various phenotypes of polycystic ovary syndrome in women of reproductive age.

Materials and methods

Clinical and laboratory studies were carried out in 56 women aged 19 to 35 years with PCOS. Of these, patients with phenotype A were 16 women, with phenotype B - 18, with phenotype C - 12, with phenotype D - 10. The diagnosis and phenotypes of the disease were verified based on the recommendations of the Rotterdam Consensus (2003). The control group consisted of 12 women of identical age with a normal menstrual cycle. To clarify the diagnosis, the phenotype of the disease and exclude conditions similar to PCOS, hormonal studies were performed. ELISA using standard kits studied the content of hormones in blood serum. Hirsutism was assessed using the modified Ferriman – Galway score.

In 27 patients, the aromatase activity of the ovaries was studied by a functional test using the aromatase inhibitor letrozole. The study used the calculation method. The letrozole test was performed on the second day of the menstrual cycle. Before and 48 hours after taking mg of letrozole in the blood serum, the content of estradiol (E2), anti-Mullerian hormone (AMH) was determined. Then the absolute value of the change in the level of estradiol (ΔE2) was determined and calculated. To assess the aromatase activity of follicles, the following coefficient was used according to the formula: K = ΔE2/AMH, where K is the coefficient of aromatase activity of antral ovarian follicles; ΔE2 - decrease in estradiol in nmol / l in blood serum 48 hours after taking letrozole; AMH — blood levels of anti-Müllerian hormone in ng/ml. Depending on the K value, aromatase activity was assessed as low, normal, or high.

Ultrasound examination of the pelvic organs was performed on the SonoAce X4 device (South Korea) using a vaginal probe with a frequency of 5.0 MHz. The volume of the ovaries, the number, size and location of antral follicles were assessed. The data obtained were subjected to statistical processing using standard computer programs with the calculation of the arithmetic mean (M), standard deviation (σ), and the mean error of the arithmetic mean (±m).

Results and discussion

The examined patients were aged 19 to 35 years (mean age of patients 26.1 ± 2.3 years). The age of menarche ranged from 12 to 17 years and averaged 13.7 ± 3.3 years. The body mass index varied from 18.4 kg/m² to 32 kg/m² and averaged 23.98±8.02 kg/m². Overweight was determined in 6 patients. Obesity of the I degree was present in 2 patients, body weight deficiency was determined in 1 patient. The hirsute number in PCOS patients averaged 11.8 ± 2.3 and ranged from 5.0 to 19.0. In all patients with PCOS, menstrual irregularities were noted: secondary amenorrhea was diagnosed in 12 patients, oligomenorrhea in 34 patients, and the menstrual cycle was preserved in 10 patients. 24 patients sought medical help due to menstrual irregularities, 11 for primary infertility, 15 for secondary infertility, 10 for miscarriage.

Comparative assessment of hormonal parameters in patients with PCOS with different phenotypes revealed a number of intergroup differences (Table 1). The highest testosterone levels were in patients in the androgenic (phenotype B) and complete phenotype (phenotype A) groups. It was in these groups that the lowest levels of estradiol were detected. One of the frequent laboratory signs characteristic of patients with PCOS, but not a diagnostic criteria for the disease, is the LH/FSH ratio > 3. The average LH values were the highest in the group with the complete phenotype; more than 50% of patients had high levels of this hormone. Almost identical in the compared groups were the indicators of prolactin, but significantly increased in relation to the control group. Also, there were no differences in the average values of the serum FSH level. Patients in the groups with non-androgenic and complete phenotype had high DHEA values. Different signification of adrenal function may indicate an ambiguous role of the adrenal glands in the process of steroidogenesis in various phenotypes. The existing differences in hormonal parameters, indicating possible existing differences in the process of steroidogenesis, indicate the state of the target organs: in particular, differences in the values of the Ferriman-Golway score and other clinical markers of hyperandrogenism, as well as the varius frequency of uterine hypoplasia and endometrial hypertrophy in the examined patients with different phenotypes of PCOS.

A test with letrozole revealed some differences in aromatase activity in patients with different phenotypes. Taking 10 mg of letrozole in women with PCOS phenotype I caused a decrease in blood estradiol from 118.9 ± pmol / l to 49.2 ± pmol / l (by 31.2 ± 2.1%). In 67% of patients with phenotype II, in 28.5% of patients with phenotype III, in 11% of patients with phenotype IV of PCOS, the level of estradiol in the blood increased after the test with letrozole from 63.2 pmol / l to 82.4 pmol / l by (19.2). Serum content blood AMH in PCOS patients ranged from 2.5 ng/ml to 21.8 ng/ml and averaged 12.7 ± 0.8 ng/ml. Aromatase activity of follicles in PCOS patients varied widely: in 21.6 % of patients was within normal limits, in 29.6% of patients it was increased, in 48.8% of patients it was reduced.

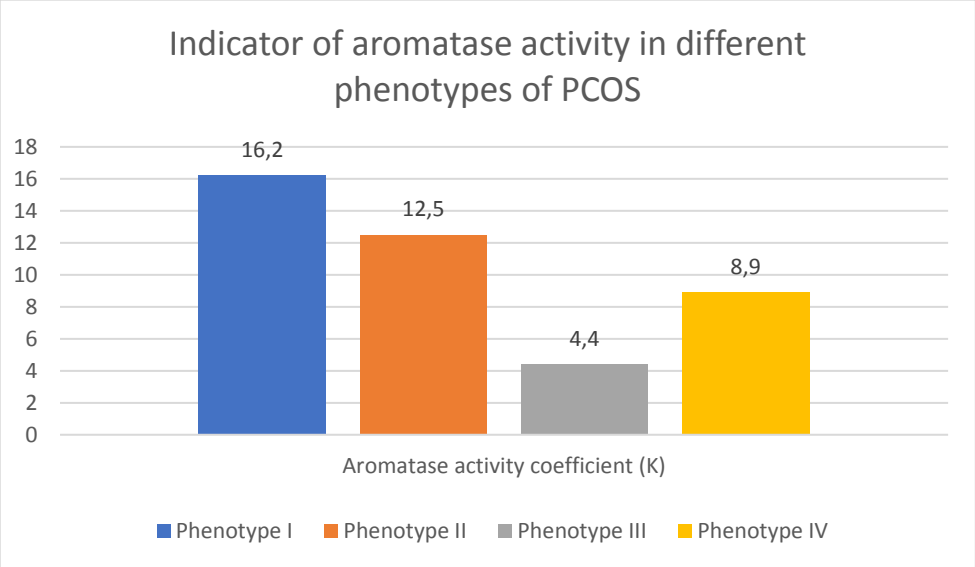
Analysis of the results of the study showed that the aromatase activity of the ovaries in various disease phenotypes is ambiguous (Fig. 1). The averaged data made it possible to establish that with a non-androgenic phenotype (Phenotype III), the aromatase activity is the lowest and is at a level corresponding to a low aromatase activity.

Table 1 **Researched hormonal values in PCOS phenotypes**

hormones	phenotype B (I)	phenotype C (II)	phenotype D (III)	phenotype A (IY)	Control group
PRL	37,1±8,9*	26,0±5,9*	11,8±1,4	23,5±5,7*	12,98±2,16
DHEA-S	10,5±4,4*◊	22,7±8,9*^◊	5,2±0,8*^#	39,3±15,9*^#◊	1,29±0,18
E2	53,9±5,9*◊	119,5,8±15,3*^◊	69,9±10,2*	51,5±3,8*#◊	75,81±4,50
T	1,5±0,3◊	0,8±0,1*^◊	1,2±0,2*	1,7±0,1*^◊	0,50±0,02
FSH	7,5±0,9	7,2±0,8	7,7±1,9	8,2±2,0	7,51±0,68
LH	11,6±1,1*◊	13,8±1,8*◊	9,5±1,9*^#	17,1±3,2*^#◊	4,69±0,84

*Note: * - reliability of data in relation to the control group (P<0.05-0.01); ^ - reliability of data between indicators of androgenic and other phenotypes (P<0.05-0.01); # - reliability of data between indicators of non-androgenic and other phenotypes (P<0.05-0.01); ◊- reliability of data between indicators of ovulatory and other phenotypes (P<0.05-0.01)*

With this phenotype, it was found that only 17% of the coefficient of aromatase activity was within normal values, in 83% of patients it was regarded as reduced. With the androgen phenotype (Phenotype I), individual K values in all cases, without exception, corresponded to the value of normal aromatase activity. The average K in the ovulatory phenotype (Phenotype II) is as close as possible to the value in healthy women. At the same time, in patients with the indicated phenotype, normal aromatase activity was detected in 68%, reduced - in 32%. We found the most ambiguous nature of aromatase activity in patients with IY, complete phenotype: normal aromatase activity was found in 72.2%, reduced aromatase activity in 24%, and increased aromatase activity in 3.8%.



To date, there are sufficient grounds to believe that the aromatization reaction is one of the essential mechanisms for maintaining the estrogen-androgen balance in the relevant organs and can influence the formation of estrogen-deficient states during anovulation. This pathogenic mechanism may occur in some forms of PCOS.

Conclusion

Thus, the conducted studies allowed us to identify some features of hormonal activity and differences in aromatase activity in different PCOS phenotypes. According to a number of modern studies, the activity of aromatase, as a key enzyme of steroidogenesis, can range from normal to values corresponding to a moderate deficiency. Aromatase deficiency, as a key factor in impaired

steroidogenesis in PCOS, is currently excluded. However, these studies have shown that the activity of ovarian aromatase may be various in different phenotypes of the disease. It may reveal a change in the activity of one of the key enzymes of steroidogenesis and the differences in pathogenetic ways of PCOS phenotypes.

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