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ASSESSMENT OF THE ROLE OF MELATONIN IN THE PATHOGENESIS OF HORMONAL INFERTILITY AND DEVELOPMENT OF A COMBINATION THERAPY SCHEME WITH ITS APPLICATION

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Abstract: The study of melatonin levels in women of reproductive age with PCOS is a promising direction, which makes it possible to more accurately determine treatment tactics for women with PCOS with different phenotypes. The results obtained demonstrate the need to include the determination of melatonin in women of reproductive age with PCOS as an additional diagnostic criterion for making a diagnosis and determining further management tactics.

Key words: *women of reproductive age, polycystic ovary syndrome, melatonin.*

Hormonal infertility is one of the most common endocrine pathologies in the population [3]. The etiology of the disease is largely controversial: every year new possible mechanisms of pathogenesis are discovered [1,2,6,9]. The results of research in recent decades have suggested the influence of melatonin and the body's biological rhythms on the development and progression of the disease. There is clear evidence that melatonin functions through receptors, both membrane and nuclear, and also neutralizes free radicals (a process that does not require the participation of receptors) [5,6]. Extensive evidence suggests a role for melatonin in ovarian physiology, including follicular development, ovulation, oocyte maturation, and corpus luteum maintenance. Melatonin ensures the adaptation of endogenous biorhythms to constantly changing environmental conditions. Biological rhythm is the basis of the body's vital activity [1,3,5,10].

Considering the high prevalence of metabolic disorders, the chronic nature of PCOS, and new data on the role of melatonin in folliculogenesis, there was a need to evaluate the role of this hormone in a woman's reproductive function, because The results obtained will improve the efficiency of treatment of patients and realize the ability to conceive using conservative methods of therapy without the use of assisted reproductive technologies [4,7,8].

Objective: to study the effect of melatonin on the development of anovulation and somnological disorders in patients with hormonal infertility, the possibility of its use in treatment regimens for this disease.

Materials and methods: study of two independent samples of patients from 20 to 35 years old. The first sample included women with hormonal infertility (n=60). The second sample (control group) consisted of healthy women without menstrual irregularities (n=30).

Criteria for including women in group 1: irregular menstrual cycle; detection of ultrasound signs of polycystic disease

ovaries; the presence of clinical signs of hyperandrogenism; absence of any hormonal therapy for 6 months before the study; obtaining informed consent for comprehensive examination and treatment.

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Exclusion criteria for group 1: presence of contraindications to the intended therapy; pregnancy, lactation; the presence of chronic extragenital diseases in the acute stage, subcompensation; the presence of decompensated endocrine pathology; identification of acute and exacerbations of chronic inflammatory diseases of the genital organs; smoking, alcohol abuse.

Research results:

In accordance with the objectives, 90 women were examined. The assessment of hirsutism using the Ferriman-Gallway scale gave the following results: 30 patients (50%) had a mild degree of hirsutism, 4 (6.7%) had a moderate degree and 1 patient (1.7%) had a severe degree. The remaining women (25 people, 41.7%) had no signs of increased male-pattern hair growth.

The duration of treatment for patients before contacting a gynecologist was: up to 1 year – 6 people (10%), 1-3 years – 41 people (68.3%), 4-6 years – 10 people (16.7%), more than 7 years – 3 people (5%), which corresponds to the general trend of long-term treatment of patients.

According to pelvic ultrasound data, 46 patients (76.7%) with PCOS showed signs of bilateral ovarian enlargement, 13 patients (21.7%) had unilateral enlargement, and 1 patient (1.7%) had ovarian volume that did not exceed normal. In all of them, multiple small follicles up to 10 mm in diameter were identified in the amount of 12-15 pieces in the ovarian structure. 27 patients (45%) showed signs of uterine hypoplasia, which could probably be associated with an irregular rhythm of menstruation. The results of a comprehensive examination made it possible to distribute patients according to phenotypes: classic (signs of hyperandrogenism + polycystic ovaries according to ultrasound + anovulation) - 29 people (48.3%), ovulatory (signs of hyperandrogenism + polycystic ovaries according to ultrasound) - 6 people (10%) , non-androgenic (polycystic ovaries according to ultrasound + anovulation) – 15 (25%), anovulatory (signs of hyperandrogenism + anovulation) – 10 people (16.7%).

Patients with PCOS were asked to select the main cause of sleep disturbances among all causes. The most common reason was stress (55%), followed by night or daily work, studying at night (29%), life events accounted for 10% and 6% - other reasons. According to the results of a questionnaire assessing the subjective characteristics of sleep, patients with PCOS were statistically significantly different from the control group in terms of the level of pathological abnormalities ($p = 0.0040$) - in the presence of PCOS, these disorders were more common.

When distributed by phenotype, the following feature of the somnological profile of the patients was revealed: with the classic phenotype, deviations were present in 82.8% of cases, with ovulatory - 16.7%, non-androgenic - 66.7%, and with anovulatory - in 70%. Although only the classical and ovulatory phenotypes differed statistically significantly ($p = 0.004$), which may indicate a more pronounced pathology of melatonin secretion in the classical phenotype, which is further aggravated by sleep deprivation due to life circumstances, while the presence of ovulation possibly smooths out the melatonin imbalance.

Questioning using the Hospital Anxiety and Depression Scale did not reveal statistically significant differences between the PCOS group and the control group, which may be explained by the high prevalence of secondary infertility in the control group, which affects the psychological status.

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Metabolic parameters. When studying carbohydrate metabolism, the level of fasting glucose was statistically significantly higher in the 1st subgroup compared to the 2nd, while both indicators were within the normative values. No statistically significant differences in glucose levels were found between the PCOS group and controls of the corresponding BMI category.

Hormonal parameters. A general trend towards an increase in LH concentrations in patients with PCOS was revealed, while FSH values did not differ significantly between subgroups, and testosterone levels were increased in both PCOS groups. The level of AMH was statistically significantly higher in both PCOS groups when compared with the control, and BMI did not affect the indicators. Determination of melatonin and its metabolite in biological fluids. Patients with polycystic ovary syndrome were characterized by higher levels of melatonin in the blood, levels of 6-sulfatoxymelatonin in 24-hour urine, and lower concentrations of melatonin in follicular fluid. A reduced concentration of melatonin in the follicular fluid with an accompanying increase in the concentration of the same parameter in the blood suggests a possible compensatory increase in the level of melatonin in the blood. Decreased melatonin concentrations in follicular fluid in women with PCOS can lead to anovulation. A consequence of melatonin deficiency in the ovary and its increase in the blood is also an increase in the content of 6-sulfatoxymelatonin in the urine according to the principle of a putative negative feedback. We assessed the level of melatonin in the blood of women in the control group (the presence of confirmed ovulation): a value of more than 51.2 pg/ml was not found in any participant. Subsequently, we assessed the presence of ovulation in patients with melatonin levels more than 51.2 pg/ml. In only 15% of cases, ovulation was absent when the melatonin level was more than 51.2 pg/ml; in the remaining patients, despite the melatonin level conventionally accepted as normal, anovulation was recorded. A statistically significant weak direct correlation between the level of melatonin in the blood and testosterone was found ($r = 0.277$, $p = 0.036$, Spearman rank correlation method), which may confirm their role as the most important factors

Conclusions:

1. Patients with PCOS have a statistically significantly lower concentration of melatonin in the follicular fluid with increased levels in the blood and saliva and its metabolite in the urine, regardless of BMI, compared to women in the control group without signs of anovulation. The highest level of melatonin in the blood was found in the classic phenotype of PCOS, and the lowest in the ovulatory phenotype, which confirms the connection between ovulatory dysfunction and the level of melatonin in the follicular fluid.

2. The frequency of somnological disorders in patients with PCOS (42.2%) exceeded that among women in the control group (10%). When distributing patients depending on the phenotype, statistically significant deviations were found in the subgroups of the classical and ovulatory variants, and in the first subgroup the changes were most pronounced. According to the questionnaire, women with PCOS had a worse somnological profile compared to the control group, regardless of BMI. There were no statistically significant differences in the degree of anxiety and/or depression in patients with PCOS and women in the control group.

3. Sleep disorders act as an additional factor that disrupts the metabolic profile of patients: deterioration of the somnological profile is associated with increased insulin resistance in patients with PCOS.

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4. The development of anovulation in PCOS is influenced by a violation of the relationship between melatonin determined in the blood and ovarian melatonin, as well as hyperandrogenism and increased AMH levels (correlates with the level of melatonin in the blood). A synthetic analogue of melatonin in combination therapy for PCOS makes it possible to increase the effectiveness of conservative therapy by 2.7 times and overcome clomiphene resistance in ovulation stimulation cycles.

References:

1. Absatarova J., Andreeva E., Sheremetyeva E., Grigoryan O. Melatonin and sleep disorders in polycystic ovary syndrome. Proceedings of the conference “Gynecological Endocrinology. World Congress". March 2-5, 2016 Italy, Florence.

2. Absatarova Yu.S., Sheremetyeva E.V., Andreeva E.N. Melatonin in human reproduction // Problems of reproduction. – 2016. – No. 1. – p.8-11.

3. Ikhtiyarova G.A., Kurbanova Z.Sh., Rozikova D.K. Causes and methods for diagnosing endocrine infertility and the role of vitamin D in its correction // Tibbiyotda Yangi kun 2020. No. 2(30/2). –C. 34-38.

5. Ikramova Kh.S., MAtrizaeva G.D., Razhabova Assess the cumulative effectiveness of monoovulation stimulation in women with Stein-Leventhal syndrome in different age groups Central Asian Journal of Pediatrics Volume 2/ Issue 2 6-20-2019/ Page 123-128 .

6. Kurbaniyazova M.Z., Matrizayeva G.D., Duschanova Z.A. ,Saparbayeva N.R Ovarian hyperstimulation syndrome – as a complication of ovulation induction Central Asian Journal of Pediatrics Volume 2/ Issue 2 128. 6-20-2019/ Page 123-128.

4. Ikhtiyarova G.A., Kurbanova Z.Sh., Shodiev B.V. Diagnosis and preparation of women with low ovarian reserve for assisted reproductive technologies // Tibbiyotda Yangi kun 2020. No. 2(30). -C. 123

7. Kurbanova Z.Sh., Rozikova D.K., Ikhtiyarova G.A. Anovulatory infertility and polycystic ovary syndrome //Tibbiyotda Yangi kun 2020. No. 2(30/2) – P.159-165.

8. Tamura H., Takasaki A., Taketani T., Tanabe M., Kizuka F., Lee L., TamuraI., Maekawa R., Asada H., Yamagata Y., Sugino N. The role of melatonin as an antioxidant in the follicle // Journal of ovarian research. – 2012. – Vol.5. – P.5.

9. Tamura H., Taksaki A., Taketani T., Tanabe M., Kizuka F., Lee L., Tamura I., Maekawa R., Asada H., Yamagata Y., Sugino N. Melatonin as a free radical scavenger in the ovarian follicle // Endocrine journal. – 2013. – Vol.60. – P.1–13.

10. Tan D., Manchester L., Fuentes-Broto L., et al. Significance and application of melatonin in the regulation of brown adipose tissue metabolism: relation to human obesity // Obesity Reviews. – 2011. – Vol.12. – P.167-188.

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