PROSPECTS FOR THE USE OF MELATONIN IN COMPREHENSIVE TREATMENT FOR WOMEN WITH HORMONAL INFERTILITY

Ikramova Kholidzhon Sakhibovna
Urgench branch of the Tashkent Medical Academy
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Summary: The study of melatonin levels in women of reproductive age with PCOS and endometriosis is a promising direction, which makes it possible to more accurately determine treatment tactics for women with PCOS with different phenotypes and external genital endometriosis. The results obtained demonstrate the need to include the determination of melatonin in women of reproductive age with PCOS and external genital endometriosis as an additional diagnostic criterion for making a diagnosis and determining further management tactics.

Key words: women of reproductive age, polycystic ovary syndrome, external genital endometriosis, melatonin.

Infertility in marriage remains the most pressing problem of our time, despite a significant amount of research devoted to its various aspects. In the third millennium, the frequency of infertile marriages increased from 10 to 18% and tends to further increase [8].

P. Török, T. Major (2013) [107] note that female infertility accounts for 40%, male infertility – 40%, and a combination of both female and male factors occurs in 20% of infertile couples.

The use of melatonin in the treatment of external genital endometriosis is a promising direction, given the pleiotropic effect of this hormone. In the studies conducted, data were published that described a decrease in the size of endometriosis lesions compared to the control group when melatonin was administered intraperitoneally to animals [3]. The authors also noted a lower level of lipid peroxidation products - malondialdehyde (a marker of oxidative stress) and higher activity of superoxide dismutase and catalase - enzymes of the antioxidant system. Another study showed an increase in the volume of endometriotic heterotopias in rats in an experimental model of endometriosis that underwent pinealectomy.

The “sleep hormone” has a significant effect on the reproductive system: it is necessary for folliculogenesis, affects the synthesis of steroids in granulosa cells and changes in cellular signals in target tissues. Presumably, it regulates the time of onset of puberty and ovulation, helps maintain pregnancy, and plays a role in the processes of restructuring the body during menopause [2]. The hormone

controls the expression of luteinizing hormone (LH) mRNA, the production of apoptosis regulators - Bcl2 and Casp3 proteinase, the activity of insulin-like growth factor (IGF) and growth factor TGF-b, as well as the expression of the LH receptor gene and the expression of the gonadotropin-releasing hormone receptor gene in granulosa. and luteal cells [1,4].

Often, patients are repeatedly examined and treated for diseases of the pelvic organs by related specialists: neurologists, urologists, proctologists. It is also known about multiple courses of anti-inflammatory therapy in these women. Only the ineffectiveness of the therapy leads the doctor to think about the possible presence of endometriosis. Before the correct examination and management plan is chosen, the patient often needs to visit at least 3 specialists. Thus, diagnosis is delayed by approximately 7-8 years from the moment of the first visit to diagnosis.

Endometriosis is difficult to diagnose. Transvaginal ultrasound can detect endometriomas and retrocervical endometriosis, however, in relation to small forms of endometriosis, ultrasound is “blind”, the same can be said about high-tech methods: CT and MRI. As for biochemical markers, today they are guided by the level of oncoantigen CA-125 in the blood, but the sensitivity of this test is only 28% (Loginova O.N., Sonova M.M., 2011). Immunological markers, indicators of oxidative stress, and also various genetic markers, in the form of functional gene polymorphisms, are also considered, but the use of molecular genetic methods is rare due to the high cost (Evdokimova V.V., 2011).

Thus, the effect of melatonin on human reproductive function and metabolism is multifaceted. The system of oxidants and antioxidants in the ovaries, sensitive to many factors, controls the maturation of the dominant follicle and the development of a full-fledged egg. The slightest violations lead to pathological changes. The use of melatonin preparations (as pathogenetic therapy), which replenish the deficiency of this hormone in the ovaries as part of a personalized approach to the treatment of patients with PCOS, may become a new stage in the management algorithms for patients with problems with reproductive function and currently unexplained causes of infertility. The use of combined management regimens for anovulatory infertility will solve one of the most important problems of reproductive endocrinology.

The purpose of the study is to evaluate the role of melatonin in the pathogenesis of hormonal infertility and to develop combination therapy regimens with its use.

Research materials: To complete the tasks, 120 women, aged 18-35 years, were examined. In the control group there were 30 healthy women who applied for a preventive examination. The main group consisted of 90 women with hormonal infertility. Based on the reasons for the development of infertility, 3 groups were formed: 1-group 30 women with PCOS and endometrioma; 2-group 30 women with PCOS; Group 3 with external genital endometriosis. At the second stage, all groups are further divided into subgroups a and b. All subgroups A took additional melatonin 3 mg in complex treatment for 5-6 months. Subgroup B received only standard therapy without melatonin.

Research results:

All women included in the study were of reproductive age, on average 27.9±0.2 years.

Body mass index was statistically significantly different in group 3 (patients with infertility due to NGE) from BMI in group 1 (infertility due to a combination of PCOS and NGE) and group 2 (patients with infertility due to PCOS) with $p < 0.0001$ in both cases and was the lowest in patients with external genital endometriosis – 21.447±1.547 with a minimum of 19.3 kg/m2 and a maximum of 24.3 kg/m2. And for patients with PCOS and a combination of PCOS and OGE, the body mass index was, respectively, 24.47±2.585 kg/m2 (with a minimum of 18.3 kg/m2 and a maximum of 28.8 kg/m2) and 24.287±2.561 kg/m2 (with the minimum is also 18.3 kg/m2 and the maximum is 28.8 kg/m2). Thus, patients of groups 1 and 2 who have either PCOS or a combination of PCOS and NGE are characterized by increased body weight, which leads to insulin resistance and suppression of ovulation. Today there is evidence for the association of increased BMI with type 2 diabetes mellitus, which also leads to dysfunction of adipocytes [8, 33, 61].

There is a connection between childhood infections during prepuberty and puberty with PCOS (group 2): in this group there were 91.07% of such patients, and in group 1 there were 9.3% (a combination of PCOS and NGE) fewer (83.33 %). At the same time, in the 3rd group (patients with infertility due to NGE) in comparison with the 1st group, the frequency of childhood infections suffered during puberty was 21.8% less and in comparison with the 2nd group less by 33.1%. Thus, childhood infections suffered during puberty were more often encountered with PCOS or its combination with NGE. Compared to the control group, in group 1, in prepuberty and puberty, childhood infections occurred 8.5 times more often, in group 2 9.3 times more often, and in group 3 7.0 times more

often. Thus, patients with polycystic ovaries more often suffered from infectious diseases during the formation of the menstrual cycle.

According to the duration of infertility, as the main diagnosis among all examined groups 1, 2 and 3, primary infertility was most often among patients of group 2 (96.87%) - patients with PCOS, then among patients of group 3 (75.9%) - patients with NGE and completed the group 1 patients (70.87%) - a combination of PCOS and NGE. Thus, in all groups there were significantly more patients with BI, but still this figure was highest among patients with polycystic ovaries, but among patients with external genital endometriosis, BI was 20.97% less common, and among patients with a combination of external genital endometriosis and polycystic ovary syndrome are less common by 25.9%.

In terms of the frequency of concomitant gynecological pathology, patients in group 3 were in the lead - 53.13%, then in group 1 - 35.48%, and in group 2, gynecological concomitant pathology was in 21.21%, while in the control group only 14.28%. Among gynecological pathologies, the first place was bilateral salpingoophoritis (18.8%): in group 1 - 25.81%, in group 2 - 12.12% and in group 3 - 31.25%.

In addition to the clinical signs of hyperandrogenism, PCOS is also characterized by biochemical signs of hyperandrogenism, indicated in the consensus [1,3], the authors discuss the opposition of androgens and the effect of estrogens on cell proliferation [3], but the significance of androgens in the pathophysiology of endometriosis is not clear to this day [49, 53]. The level of androgens is influenced by the level of gonadotropic hormones and their ratio is important. Regarding the FSH level, there is a statistically significant difference between groups 1-2, 1-3, 2-4 at $p<0.0001$, as well as between groups 3-4 at $p<0.01$. Regarding PH, a statistically significant difference was found between groups 1-3, 2-3 and 2-4 at $p <0.0001$; between the 1st-4th ($p<0.01$) and 3rd-4th ($p<0.05$) groups. The LH/FSH ratio in group 1 was 1.67, in group 2 2.49, which is 1.5 times higher than in group 1. In groups 3 and 4, LH/FSH was 1.44 and 1.31, respectively. In group 3 (infertility due to NGE), the LH/FSH ratio is 1.2 times lower than in group 1 and 1.8 times lower than in group 2; in group 4, the LH/FSH ratio was 1.3 times lower than in group 1 and 1.9 times lower than in group 2.

The study of ovarian reserve in emerging hyperandrogenism is very important. The role of anti-Müllerian hormone (AMH) in PCOS, NGE, and their combination is not fully understood. The following AMH gradations are used: high level more than 6.8 ng/ml; normal – from 4.0 to 6.8 ng/ml; normal low - from 2.2 to 4.0

ng/ml and low from 0.3 to 2.2 ng/ml. The difference in the indicator is statistically insignificant only in groups 1 and 2, 3 and 4, with $p>0.05$. significant difference between AMH indicators in groups 1-3 ($p<0.0001$) and 1-4 ($p<0.01$); and also between 2-3 ($p<0.0001$) and 2-4 ($p<0.0001$) groups. AMH in group 1 was 6.327±3.965 ng/ml with a minimum of 0.97 ng/ml and a maximum of 12.5 ng/ml; in group 2 AMH=7.895±2.73 ng/ml with a minimum of 3.12 ng/ml and a maximum of 12.5 ng/ml; in group 3, respectively, 2.363±0.5 ng/ml with a minimum of 1.5 ng/ml and a maximum of 3.2 ng/ml; in group 4 – 2.363±0.5 ng/ml with a minimum of 1.8 ng/ml and a maximum of 3.5 ng/ml. Thus, the AMH level varied from low to high in group 1, in group 2 from normal low to high, in groups 3 and 4 it was low and normal low. At the same time, the average values in group 2 (infertility due to PCOS) were high (2.363±0.5 ng/ml), in group 1 (infertility due to PCOS and NGE) were normal - 2.363±0.5 ng/ml, in group 3 and 4 groups were normally low: 2.363±0.5 ng/ml and 2.363±0.5 ng/ml, respectively. The role of AMH as a regulator of ovarian function is not yet completely clear. But we see that there are risks of hyperstimulation in groups with PCOS (groups 1 and 2). AMH characterizes not only ovarian reserve, but also the degree of reproductive aging, as well as the quality of oocytes [5]. There are indications in the literature that endometriosis causes a decrease in AMH levels when compared with tubal infertility [13], which corresponds to our data on the AMH level in NGE (2.363±0.5 ng/ml). In the combination of NGE and PCOS, AMH was normal (6.327±3.965 ng/ml), in contrast to its increased level in the group with isolated PCOS (7.895±2.73 ng/ml). The increase in AMH in PCOS is due not only to the number of follicles, but also to the production of hormone by the granulosa cells of these follicles, which increases AMH levels [67]. We found a direct high correlation in patients with PCOS and OGE between AMH and the number of follicles: $R = 0.446$, as well as between AMH and ovarian volume $R = 0.488$.

Thus, the found correlation between AMH and the number of follicles can be used to reflect the morphology of polycystic ovaries, which allows us to recommend its use as a determination of the outcome of stimulation.

In our study, the level of 6-sulfatoxymelatonin in the urine of patients with PCOS was reduced and amounted to 30 [23.55 – 46.5] ng/ml compared to the data in patients of the control group without endometriosis 30 [37.02 – 49.6] ng/ ml ($p<0.05$).

When conducting a correlation analysis of the content of 6-COMT with the studied bioregulators using the Spearman criterion, we found that there is an

average statistically significant relationship with catalase activity: the correlation coefficient is 0.52 (p = 0.047) for stage I-II NGE.

Correlation analysis showed that at stages I-II of NGE in women in the blood serum there is an average positive correlation between the activity of SOD-NOS (r=0.6) (p<0.05); and strong - arginase and NOS (r=0.7) (p<0.05); and an average negative was also revealed between the level of NO and TGFβ1 metabolites (r=-0.6) (p<0.05). Also significant is the strong positive relationship in women of this clinical group between the activity of catalase and SOD (r=0.77) (p<0.05), the level of NOx and NOS activity (r=0.89) (p<0.05) . Our data confirm the existence of certain patterns that allow us to consider the studied factors of cellular regulation and the antioxidant system to be significant for the formation and progression of NGE.

Conclusions: In case of infertility against the background of PCOS and NGE, the trend in increasing the LH/FSH ratio corresponds to increased ovarian androgen production, leading to ovarian hyperplasia, closing a vicious circle, which is confirmed by the level of ISA 2.39 ± 0.6%, SHBG 40.90 ± 8, 73 nmol/l, 17-OP 2.09±0.42 nmol/l. PCOS promotes an increase in AMH not only due to the increased number of follicles (R = 0.446), but also due to the large number of granulosa cells in them. A strong correlation was found between AMH and ovarian volume (R=0.488), which allows us to recommend its use as a predictor of the outcome of ovulation stimulation.

External genital endometriosis stages I-II is characterized by a significant decrease in the level of melatonin (6-COMT) relative to the data of the control group and the values obtained at stages III-IV of the disease.

Correlation analysis showed the presence of many relationships between cellular regulators and factors of the antioxidant system. The largest number of bonds was determined in the enzymes: catalase, arginase and SOD. At the same time, a statistically significant average negative relationship between catalase activity and 6-COMT levels was revealed.

The developed and implemented algorithm for the management of patients with infertility against the background of a combination of PCOS and NGE contributed to the onset of pregnancy 1.4 times more often compared to standard management, which led to pregnancy in 73.5%.

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