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THE ROLE OF MELATONIN IN OBESE WOMEN OF REPRODUCTIVE AGE AND ITS RELATIONSHIP WITH OVARIAN DYSFUNCTION

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Abstract
Today, as a new direction in the study of reproductive problems in obese women, the effect of melatonin on the gonadotropic function of the pituitary gland and the process of ovariogenesis is being widely studied. In addition, obesity, which is a concomitant disease in polycystic ovary syndrome, and its relationship with melatonin secretion are of interest to many today. In this article, we discussed the importance of the above-mentioned problem.

Keywords: Polycystic ovary syndrome, melatonin, obesity.

Introduction

Today, among the causes of female reproductive problems, including various manifestations of menstrual cycle disorders, infertility, polycystic ovary syndrome and obesity occupy a leading position. Based on the data provided by the World Health Organization for the period 1980-2013, we can see that the percentage of people with a body mass index above 25 increased from 29.8% to 38% among women and from 28.8% to 36.9% among men.

As is known, obesity is a chronic disease that is currently recognized as a “social pandemic”, occurs due to hereditary factors, metabolic disorders and lifestyle, and can lead to many serious complications and even death. Android-type obesity in women causes a number of diseases and clinical conditions. Abdominal fat deposition in women indicates a serious violation of fat-carbohydrate metabolism in the female body. In this article, we discussed a number of disorders related to reproductive function in obese women and the role of the melatonin hormone in their development and their interrelationships.

Polycystic ovary syndrome (PCOS) is one of the most studied problems in gynecological endocrinology. Currently, its incidence among women is 4-12%. This disease is a heterogeneous disease that is transmitted from generation to generation, and its clinical manifestations include menstrual irregularities, chronic anovulation and infertility, hyperandrogenism, and enlarged ovaries. There are currently many hypotheses about the mechanism and pathology of the disease, but none of them has been able to fully resolve this problem. [14]

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In almost half of women with PCOS, the cause of the disease is obesity. Women with PCOS are mainly characterized by android-type obesity (visceral obesity). In 70% of cases, insulin resistance is also observed in such women. In addition to body mass index, it is advisable to measure waist and hip circumference in such patients. [14]

Today, there is growing interest in studying the daily concentration of melatonin in the blood and its effects in women with polycystic ovary syndrome. We know that melatonin is a sleep hormone, which is mainly produced during night sleep. Currently, two different mechanisms have been proposed for studying the etiopathogenetic relationship between polycystic ovary syndrome and sleep disorders: the hypothalamic-pituitary and psychophysiological mechanisms. The first mechanism is based on hyperandrogenism, which leads to insulin resistance, increased secretion of cortisol and melatonin. The second mechanism is based on chronic stress (depression), negative behavior and harmful habits (smoking, alcohol consumption, hypodynamia).[7]

In women with PCOS, melatonin concentration may not be correlated with the duration of night sleep. In this case, it may be associated with hyperandrogenism. We can observe that the decrease in the concentration of melatonin in the blood plasma occurs in parallel with the decrease in the level of testosterone. [5,6] This is due to the pronounced antiandrogen effect that occurs due to the regular use of combined oral contraceptives. [5,6] In a clinical study conducted in this regard, it was observed that when women with polycystic ovary syndrome were treated with melatonin (2 mg / day for 6 months), the level of testosterone in the blood decreased and the menstrual cycle was restored. This allows us to say that there is a feedback relationship between melatonin secretion and the concentration of androgens in the blood. [3,5] In addition, a number of clinical studies have been conducted in this regard, of which we reviewed 2 studies. [4] In these studies, the level of 6-sulfotoxymelatonin, the primary product of melatonin metabolism, was studied in the blood/urine of women with polycystic ovary syndrome and women in the control group. [4,5] The results showed that urinary excretion of 6-sulfooxymelatonin was higher in women with polycystic ovary syndrome (n=35 in study 1, n=26 in study 2) than in women in the control group (n=35 in study 1, n=26 in study 2). [5] However, as mentioned above, the concentration of 6-sulfooxymelatonin may also be related to the antiandrogen effect of combined oral contraceptives.

The hormone melatonin and its importance and role for the body, mainly for the reproductive system.

The hormone melatonin is formed in the pineal gland from the amino acid tryptophan, which is involved in the synthesis of the neurotransmitter serotonin, with the participation of the enzyme N-acetyltransferase.[15] The main functions of this hormone in the body are to regulate the circadian rhythm and act as an antioxidant. It is the main hormone that transmits signals from rhythm controllers located in the suprachiasmatic nuclei of the hypothalamus to organ tissues. [15] Therefore, the

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concentration of this hormone in the blood and its nocturnal secretion are important. The hormone melatonin is synthesized during the night hours when light does not reach the retina, and during the day its synthesis is significantly reduced or stops. [15] Melatonin synthesis begins during the hours of late sleep and reaches a maximum between 2-4 am. Its synthesis is minimal from 7-8 am to 8 pm.

Studies of the effect of light on human lifestyle began hundreds of years ago. It has been observed that excessive nighttime light, or “light poisoning,” can cause serious problems in human health and lifestyle. [2] According to this hypothesis, the body’s “circadian rhythm disruption” is caused by the effect of light in the evening hours, which leads to a disruption of the endogenous circadian rhythm, a decrease in the nighttime synthesis of melatonin, and, as a result, a decrease in the concentration of the hormone in the blood.

A number of scientific studies have shown that 1 lux of monochrome blue light or 100 lux of white light can significantly reduce the synthesis of melatonin from the pineal gland. [2] The results of scientific studies have shown that women are more sensitive to the incorrect distribution of light than men, which is precisely what causes the occurrence of endocrinological diseases in women, mainly obesity. [2]

The effect of the sleep hormone on the functioning of the reproductive system is of great importance. This hormone is essential for folliculogenesis, the synthesis of steroids and granulosa cells. In addition, the sleep hormone is involved in regulating processes such as puberty and ovulation, maintaining pregnancy, and the body's adaptation to menopause.

To date, the theory of "light poisoning", that is, reproductive changes resulting from insufficient synthesis of the hormone melatonin, has been tested in animals (rats and mice). It has been observed that increasing the duration of daylight hours to 2-4 hours per day causes an increase in the duration of the estrous cycle in rodents and various disorders of the cycle. [2] If the daylight hours are increased to 24 hours, this causes estrus persistence syndrome in mice and rats in a short time. Under physiological conditions, this condition is observed in "old" representatives of rodents (in rats at 15-18 months), and then they go into anestrus. This condition corresponds to the climax or menopause in humans. [2,3] Under the influence of the above-mentioned conditions, estrus persistence syndrome occurs in rodents, which causes follicular cysts and theca cells to hyperplasia in the rodent ovary, as well as the loss of the corpus luteum.[3] At the same time, acyclic production of gonadotropins, prolactin, estrogen, progesterone, and as a result, hyperplastic processes in the mammary glands and uterus can be increased and oncological problems can occur. Constant exposure to light leads to an increase in the sensitivity threshold of the hypothalamus to the inhibitory effect of estrogen in female rodents. This mechanism, in turn, can cause accelerated aging not only in female rodents, but also in women.[3]

A clinical study was conducted to study reproductive disorders observed in women of fertile age with high TMI of melatonin and ovarian dysfunction. [16]The study included 30 women aged 18-35 years with obesity and non-organic menstrual

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disorders and 30 healthy women with normal TMI and menstrual cycles. All of them were tested for salivary melatonin and urinary 6-sulfoxymelatonin. The results were compared in both groups. [16]In the obese group, 47% of cases had sleep disorders and 30% had sleep apnea. Based on the results of laboratory analysis, it was determined that the concentration of melatonin and 6-sulfoxymelatonin in urine and saliva in the study group was significantly lower than in the control group. [16] According to the study, sleep disorders are more common in women with high TMI and menstrual disorders, and melatonin in saliva and urinary 6-sulfoxymelatonin - sulfooxymelatonin levels were found to be low. [16]

Obesity and polycystic ovary syndrome – Currently, obesity is a chronic metabolic disorder that can develop at any age. According to the World Health Organization in 2016, 41 million children aged 0-5 years were overweight and obese. Among children aged 5 to 19 years, the number was 340 million. The United States and the Russian Federation occupy the leading positions in terms of the number of people suffering from obesity and overweight. The lowest prevalence of obesity is recorded in India - 3.9% and China - 4.2%. Based on the above figures, it can be understood that this disease has taken on the form of a social pandemic today.

As a concomitant pathology of polycystic ovary syndrome, we can say that the result of metabolic stress caused by relative hyperandrogenism, which is characteristic of this disease. Based on the studies conducted in this regard, it can be said that among the 54% of women with abdominal obesity, 49% had polycystic ovary syndrome.[]9 The frequency of obesity in polycystic ovary syndrome is 2 times higher than in other endocrinopathies that can occur in women. As evidence of this, we can cite the results of a large-scale study conducted in Australia over many years.[10] A total of 9145 women were taken for examination. Of these, 4478 women had polycystic ovary syndrome, and it was found that this group of women had a higher average BMI and a higher rate of body weight increase over a 10-year period compared to the rest of the women.[11,12] In women with polycystic ovary syndrome and obesity, the amount of testosterone and luteinizing hormone is higher than in women with normal body weight. According to the results of a scientific study conducted by a group of Italian scientists among the population of the Mediterranean[17], the percentage of impaired glucose tolerance and the development of type 2 diabetes mellitus in women with polycystic ovary syndrome and obesity was 15.7% and 2.5%, respectively.[17] Women with impaired glucose tolerance had high blood insulin levels, pronounced insulin resistance, pronounced hyperandrogenism, and a significantly higher response of cortisol and androstenedione to ACTH stimulation. [17]

1.2 Conclusion

Based on the above data, we can conclude the following:

- Among the diseases that are most likely to cause problems with reproductive function in women, polycystic ovary syndrome has a much higher incidence, causing menstrual irregularities, infertility, and external cosmetic problems.

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- The incidence of obesity among women with polycystic ovary syndrome is 2 times higher than in other endocrinopathies. The cause of obesity in polycystic ovary syndrome is mainly metabolic stress due to hyperandrogenism.
- The phenomenon of "light poisoning", which is currently of great interest to many, i.e. a decrease in the secretion of the hormone melatonin due to an increase in the number of daylight hours and the resulting disruption of circadian biorhythms, causes a number of systemic disorders in the human body, including reproductive disorder

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