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# Review Article

## Hepcidin, Polycystic Ovary Syndrome, and Sleep Disorder

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**ABSTRACT**

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women. In 2003, the Rotterdam criteria were developed and adopted in diagnosing polycystic ovary syndrome, which is characterized by: A) Lack of ovulation or its cessation, which causes a difference in the menstrual cycle. B) The presence of a clinical or biochemical sign of high androgens. C) When diagnosed with ultrasound, there is a clear appearance of the presence of polycystic ovaries in women. When the distinctive signs of the disease appear in adolescence, they continue during the years before menopause, and even after menopause, women with polycystic ovary syndrome are at greater risk of developing metabolic diseases such as diabetes, high blood pressure, and cardiovascular disease. The most concerning risk factor for infected women is age, so affected women must constantly follow up and treat when infected with any type of ovarian cysts to reduce the occurrence of malignant tumors and their risks. The causes of polycystic ovary syndrome are many and varied, but the exact mechanisms and pathophysiology have not been comprehensively understood and clarified yet. Hepcidin increases significantly in cases of inflammation, infection, and high iron levels, but in patients with polycystic ovary syndrome, a decrease in its level was observed. This may be due to an increase in the hormone's androgen and testosterone, which are signs of polycystic ovary syndrome, or its decrease may be due to an increase in the absorption of dietary iron. The hormone melatonin works to regulate the body's biological clock, and research indicates that its level is lower in patients with polycystic ovary syndrome compared to healthy people, which may be due to metabolic disorders or a high level of testosterone.

**Keywords:** Hepcidin (HP), polycystic ovary syndrome (PCOS), ovarian stimulating hormone (FSH), obstructive sleep apnea (OSA).

## INTRODUCTION

The uterus is the primary reproductive organ in mammals and is important for the health of the woman's fertility and her offspring. The hormonal and cellular functions that regulate and develop the uterus are very complex (Reiter *et al*., 2016). Adnexes of the uterus include the fallopian tubes and ovaries The ovary is the female reproductive gland responsible for the function of procreation and the continuation of offspring. A woman's body is affected by internal conditions (nervous and hormonal) and external factors (The environment and its effects) starting from puberty, and these factors affect future offspring (Terzic *et al*., 2021). The menstrual cycle is one of the variables that affect a woman's body after puberty, with the increase in the production of follicle-stimulating hormone (FSH) (which stimulates the ovaries to grow eggs), the production of estrogen increases which is the hormone responsible for the development of female secondary sexual characteristics such as puberty, breast size, and the distribution of fat in specific areas, etc. and with an increase in the hormone which causes. By releasing eggs from the ovaries to the uterus in the event of fertilization, pregnancy occurs and the hormones estrogen and progesterone rise (Rockfield *et al*., 2017) .Otherwise, the level of both hormones decreases and the menstrual cycle begins, and so on continuously. Ovarian cysts are the growth of many eggs instead of one egg and the eggs do not reach their required size, which leads to the woman being unable to become pregnant. This abnormal endocrine disorder, known as polycystic ovary syndrome, affects many women of reproductive age around the world. Its signs include swelling of the ovaries, disruption of their function, and increased levels of luteinizing hormone, which stimulates the ovarian follicles. Studies indicate that 3 out of 10 women develop polycystic ovary syndrome before menopause and suffer from its complications (Sadeghi *et al*., 2022). PCOS is a heterogeneous gynecological syndrome, associated with a wide range of endocrine and metabolic abnormalities such as hyperinsulinemia, hyperglycemia, dyslipidemia, obesity and hypertension. Excess insulin stimulates androgen synthesis in the ovaries and adrenal glands, and, besides, it can inhibit the synthesis of sex hormone binding globulin in the liver and increase the levels of free testosterone. There are many types of polycystic ovary syndrome. 20% of women in the world suffer from this disease, and it can cause a malignant or benign tumor in the ovary. It always occurs during the reproductive stage and an imbalance in reproductive hormones (Lee et *al.*, 2018). Many body hormones are affected by PCOS, and hepcidin is one of them. It is a Peptide composed of 25 amino acids and a mass of 2.7 kilodaltons. It was first discovered in human blood ultrafiltration (a method of filtering blood that passes through special filters outside the body) and later in other species such as mammals, amphibians and fish (Ajaj and Mikael, 2024). Studies conducted on mammals have shown that this protein has two functions: The first is to regulate iron balance and the second is to fight fungi and bacteria (Liu *et al*., 2022). The main source of its production is the liver, as well as in the kidneys, heart, bacterial cells, macrophages, pancreatic cells, and adipocytes, with a lower percentage compared to the liver. The cells targeted by hepcidin for iron metabolism are three enterocytes, hepatocytes and retinal macrophages. When hepcidin binds to ferroportin, it leads to the formation of erythrocytes by stimulating iron absorption and its degradation pathway (Fathi *et al*., 2022). Ferroportin is a source of iron through the membranes that produce iron and then from the tissues to the blood circulation to form the red blood cells that the body needs. It is a protein that acts as an iron transporter that allows the absorption of iron in intestinal cells. Ferroportin is also found in cells the liver, spleen, kidneys, and macrophages. Iron and oxygen deficiency, deposition of critical metals, or inflammatory causes affect the level of regulation of ferroportin. Ferroportin protein is affected by hepcidin, which is a peptide hormone (hormone formed by linking amino acids with peptide bonds) that has a significant relationship with the increase and deficiency of ferroportin. Hepcidin's size in the body reflects the level of formation of red blood cells in the organism, the production of which depends primarily on iron. Iron is an important and main iron for heme synthesis in the body. Body iron homeostasis is maintained by hepcidin through absorption in the duodenum, release from macrophages, and from hepatocytes. Also, hepcidin is regulated by serum

iron levels and hepatic iron stores (Krygier *et al*., 2022). In normal cases, renal excretion is the main route for removing hepcidin from the body. Only 5% of plasma hepcidin is filtered by the kidneys, and this is explained by the lack of filtration by the renal glomeruli or the reabsorption of the filtered hepcidin in the proximal renal tubules. For a mechanistic explanation of the increase and decrease of hepcidin. It is preventing the absorption of intestinal iron and the release of iron from phagocytic cells that recycle old red blood cells. When an increase in hepcidin occurs in the stages of fetal development during pregnancy, the fetuses become afflicted with anemia resulting from severe iron deficiency, and most of them die at birth, and this indicates hepcidin stops the transfer of iron across the placenta to the fetus. As for hepcidin, which is formed from sources outside the liver, iron within the tissues may control the production of hepcidin in them (Hernik *et al*., 2019; Taha *et al*., 2024).

**The most important risk factors causing polycystic ovary syndrome**

1- High levels of blood Lipids of all types (cholesterol, triglycerides, low-density lipoprotein) and this has been confirmed through research and studies conducted on 70% of women with polycystic ovary syndrome, which causes an increase in insulin and thus weight gain or obesity, especially in the abdominal area, which is called fat. Visceral heart disease, which causes high triglycerides, leading to weakness of the heart and its vessels (Hanson *et al*., 2017).
2- Blood sugar variation resulting from insulin resistance or hyperinsulinemia is a condition strongly affected by the process of androgen elevation in the pathophysiology of polycystic ovary syndrome (Yu *et al*., 2016).
3- Metabolic syndrome and weight loss.
4- Depression and anxiety accompany most affected women) Damone *et al*., 2019).
5- High blood pressure has been associated with polycystic ovary syndrome, and this relationship is somewhat complex and affected by many other factors) Cooney and Dokras، 2018؛ Kumarendran *et al*., 2019).
6- Chronic infections and weakness of the sympathetic nervous system, which is responsible for involuntary vital processes in the body such as breathing, digestion, and others (Manique and Ferreire، 2022).
7- Obstructive sleep apnea (OSA) it means the abnormal disturbed sleep that accompanies patients with polycystic ovary syndrome, and this may be accompanied by problems with lack of oxygen and difficulty breathing. This may be due to the vitamin D deficiency that sufferers suffer from (Jesintha *et al*., 2016).
8- Pregnancy complications linked to PCOS, namely preeclampsia, gestational diabetes, pregnancy-induced high blood pressure, and even miscarriage (Khan *et al*., 2019). Studies have shown that pregnancy-related complications are part of the already existing metabolic and endocrine effects of PCOS in women long before pregnancy, such as androgen excess and obesity) Goodarzi *et al*., 2015) .
9- Endometrial cancer and malignant tumors are also serious complications associated with polycystic ovary syndrome and result from infertility caused by polycystic ovary syndrome in women. Studies have shown an increase of 2-6 times in women with polycystic ovary syndrome. (Abdulla and Ismael, 2022). This may be due to lack of ovulation, as the uterine lining is exposed to a continuous flow of estrogen, so routine examination is recommended to avoid the disease and detect it early (Witchel *et al*., 2019).

**Hormone hepcidin**

Hepcidin is known as one of the important hormones in the body that is mainly secreted by the liver. Hepcidin controls the way accumulated iron is stored in all organs of the body. The function of hepcidin is to transport cellular iron through ferroportin to the body's plasma and other

extracellular fluids .It is a receptor for hepcidin and the most important source of iron for living organisms. Ferroportin among the cells that make iron in the body and ferroportin are present, which are the intestinal and duodenal cells that absorb dietary iron, the macrophages that rebuild old red blood cells in the spleen and liver, the liver cells that store iron, and the placenta that transfers iron to the fetus during pregnancy (Witchel *et al*., 2019). Hepcidin level is regulated by iron and erythropoietic activity. Increased hormone concentrations prevent the absorption of dietary iron and thus the level of iron stops, and in the case of iron deficiency, it causes hepcidin inhibition, which allows increased absorption of dietary iron and replenishment of iron stores. Increased erythropoietic activity also inhibits hepcidin production (Khalifa and Hasan, 2024). If iron absorption is increased, this allows rapid release of stored iron from macrophages and hepatocytes and increases the supply of iron needed for erythropoiesis blood cells and thus a disruption in the functioning of the hormone. The molecular mechanisms underlying hepcidin regulation by iron and erythropoiesis are areas of intense research but are still not fully understood. Hepcidin also increases in the case of inflammation and infection, and it works to raise genes involved in immunity as a defense strategy for the body (Zhao *et al*., 2013).

**Hepcidin levels and polycystic ovary syndrome**

Polycystic ovary syndrome, which is a heterogeneous hormonal disorder that affects. At least 7% of adult women. It is characterized by signs and symptoms of increased testosterone and ovulatory dysfunction, disrupting the function of the hypothalamic-pituitary hormone (HPO). Its prevailing clinical symptoms include excessive hair or baldness, acne, irregular menstruation, cysts in one or both ovaries, enlargement and dysfunction of the ovaries, chronic anovulation, and infertility. Persistent hyperandrogenism is associated with dysfunction of the hypothalamus and pituitary gland, increased secretion of luteinizing hormone, and abnormal oogenesis (Hakimi, 2017). Low serum hepcidin has been identified in patients with polycystic ovary syndrome. Although research has shown that hepcidin increases significantly in response to excess iron, inflammation, and infection (Sadeghi *et al*., 2022). There are also many studies that show its decrease for various reasons, such as an increase in the male hormone, which is considered one of the causes of polycystic ovary syndrome. The reason for low levels of hepcidin in plasma may be an increase in the absorption of dietary iron in the intestine, and also macrophages secrete iron derived from hemoglobin into the blood circulation more effectively, which leads to an increase in iron in the blood circulation. Iron binds to transferrin. When plasma iron levels are higher than normal, transferrin saturation increases. Research has shown an increase in iron in patients with polycystic ovary syndrome (Luque-Ramíre *et al*., 2011). The various discrepancies in hepcidin levels in numerous studies and with the fact that iron overload in PCOS is almost a constant fact may be due to the complex relationship between this hormone and iron status. Conditions in which the level of hepcidin decreases cause an increase in iron in the body, and conversely, in pathological conditions in which the level of iron decreases, the hormone hepcidin increases. High hepcidin levels may be due to another condition accompanying polycystic ovary syndrome, such as obesity, which leads to inflammation. It may bind to ferroportin, prevent iron absorption, release iron from cells, and prevent iron from entering the plasma. In previous studies, low levels of hepcidin were observed in people with abnormal obesity and those with iron deficiency (Nikonorov *et al*., 2015).

Blood hepcidin levels appear to be elevated in obese women despite iron depletion. This indicates the body's tolerance for inflammation rather than iron status. Inflammation may perpetuate this condition through inhibition of hepcidin-mediated iron absorption. Factors such as the degree of obesity and duration of obesity influence the stimulation of hepcidin release. Hypoxia, anemia, increased erythropoiesis, and decreased iron stores are associated with hepcidin (Nemeth and Ganz, 2021).

**Sleep disorders and melatonin and their association with the pathophysiology of polycystic ovary**

A shift in bedtime, a delayed start to sleep, trouble falling asleep, or an early wake-up time are all considered sleep disturbances. These behaviors can have a detrimental impact on mood, cognitive function, and psychomotor performance during the day, which can significantly impact everyday activities and well-being. Human experience sleep and wakefulness as a result of the interaction of two processes called the S process. It prompts sleep, while the C process prompts wakefulness. Over the course of your awake time, the C process accumulates and symbolizes your need for sleep. The biological clock process controls the C process, which involves coordinating wakefulness and sleep cycles with light and dark environmental cues (Fernandez *et al.*, 2018). Internal rhythmic signals are created from the environment's cycle of light and dark. Its cycle, which lasts roughly twenty-four hours, enhances the chronology of life's events. The suprachiasmatic nucleus of the hypothalamus is the central coordinator of the circadian system, which synchronizes with environmental stimuli (Mojaverrostami *et al*., 2019). Circadian information is transmitted by the suprachiasmatic nucleus. Additional brain regions like the pineal and pituitary glands. Mammals use bodily fluids and nerves to control the function of surrounding tissues and organs after receiving suprachoroidal nucleus (CSN it is a small area of the brain under the thalamus) light signals from the retina. The synchronization of the hypothalamic-pituitary-ovarian axis circadian signal is essential for female reproductive function (Li *et al*., 2020). The primary hormone secreted by the pineal gland to control circadian rhythms, reproduction, and the sleep cycle is melatonin (N-acetyl-5-methoxytrypamine). In the presence of light, its secretion decreases during the day and increases at night. Melatonin can also be secreted by the surrounding reproductive cells, such as eggs, cumulus cells, and granulosa cells (Li *et al*., 2022). While low melatonin concentrations may be the cause of PCOS patients' fewer and worse-quality eggs, high melatonin levels in follicular fluid are necessary for ovulation and egg health. It has been proposed that melatonin directly lowers the production of testosterone, thereby having an antigonadal effect. Studies have revealed that polycystic ovary syndrome patients' sleep differed from that of their peers without the condition (Jain *et al*., 2013). Numerous studies support the link between polycystic ovarian syndrome, circadian rhythm abnormalities, and metabolism. According to a cross-sectional study, patients with polycystic ovary syndrome have a circadian rhythm that is marked by a delay in melatonin displacement with respect to clock time and sleep time (Ayob *et al*., 2024). This delay has been linked to increased levels of serum free testosterone and insulin sensitivity given that PCOS is typified by a disrupted metabolism and that the endocrine system plays a significant role in regulating the sleep-wake cycle, it is plausible that PCOS either interferes with arousal and sleep, or that the relationship between the two is more intricate. Researchers became interested in the ovaries' impact on melatonin because it was discovered that melatonin controls the reproductive system both centrally and peripherally (Yi *et al*., 2020). Melatonin is a systemic hormonal agent that acts through activating a receptor to influence sexual maturation and reproductive function. Melatonin in the follicular fluid has a far higher concentration than in the blood because it is derived from the surrounding reproductive cells and serum in the follicle (Rijal *et al*., 2020). Melatonin concentration in the surrounding fluid rises with the growth of the eggs and peaks just prior to ovulation. It has been demonstrated that melatonin can lessen oxidative stress in tissues by acting as a free radical scavenger. Egg development and maturation are facilitated by the external environment provided by follicular fluid. In patients with polycystic ovary syndrome, deficiencies in maturation and ovulation may be directly linked to a lack of melatonin in follicular fluid. Arrhythmia has been identified as one of the pathological causes of polycystic ovarian syndrome and is thought to impact ovarian function (Wang *et al*., 2021). There are two possible causes of decreased melatonin concentration in follicular fluid: One is reduced absorption from serum. The second is reduced ovarian secretion in PCOS due to follicular atresia. Women with polycystic ovary syndrome are more likely to experience nighttime sleep, which increases their

susceptibility to light exposure at night, which suppresses the production of melatonin. While it's unclear if melatonin causes PCOS and sleep disorders directly, women produce higher levels of melatonin than men do. This demonstrates unequivocally that melatonin is a potent endogenous antioxidant and free radical scavenger that has protective effects, particularly on the female reproductive system (Alizadeh *et al*., 2021; Hamasaeed *et al*., 2019).

## CONCLUSIONS

In this article, it was concluded that hepcidin levels increase significantly in cases of inflammation, infection and high iron levels, but in patients with polycystic ovary syndrome, a decrease in its level was observed, which may be due to an increase in the hormone's androgen and testosterone, which are signs of polycystic ovary syndrome, or its decrease may be due to an increase in the absorption of dietary iron. Melatonin hormone regulates the body's biological clock, and research indicates that its level is lower in patients with polycystic ovary syndrome compared to healthy people, which may be due to metabolic disorders or high testosterone levels. In this article, it was concluded that hepcidin levels increase significantly in cases of inflammation, infection and high iron levels, but in patients with polycystic ovary syndrome, a decrease in its level was observed, which may be due to an increase in the hormone's androgen and testosterone, which are signs of polycystic ovary syndrome, or its decrease may be due to an increase in the absorption of dietary iron. Melatonin hormone regulates the body's biological clock, and research indicates that its level is lower in patients with polycystic ovary syndrome compared to healthy people, which may be due to metabolic disorders or high testosterone levels.

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest with respect to the publication of this manuscript.

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## الهيبسيدين، ومتلازمة المبيض المتعدد الكيسات، واضطراب النوم

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**الملخص**

متلازمة تكيس المبايض (PCOS) هي اضطراب او اختلال بالغدد الصماء الأكثر شيوعا بين النساء. في عام 2003 تم تطوير واعتماد معايير روتردام في تشخيص متلازمة المبيض المتعدد الكيسات والتي تتميز بالتالي: أ) قلة التبويض أو توقفها مما يسبب اختلاف في الدورة الشهرية. ب) وجود علامة سريرية وبايوكيميائية لارتفاع الأندروجين. ج) عند التشخيص بالموجات فوق الصوتية يظهر بشكل واضح وجود تكيس المبايض عند النساء. عندما تظهر العلامات المميزة للمرض في مرحلة المراهقة، فإنها تستمر خلال السنوات التي تسبق انقطاع الحيض، وحتى بعد انقطاعه، تكون النساء المصابات بمتلازمة المبيض المتعدد الكيسات أكثر عرضة للإصابة بالأمراض الأيضية مثل مرض السكري وارتفاع ضغط الدم وأمراض القلب والأوعية الدموية. أكثر عوامل الخطر التي تقلق المرأة المصابة هو العمر، لذلك يجب على المرأة المصابة المتابعة والعلاج بشكل مستمر عند الإصابة بأي نوع من أكياس المبيض لتقليل حدوث الأورام الخبيثة ومخاطرها. ويوضح هذا المقال وظيفة هرمون الهيبسيدين بتنظيم مستويات الحديد في الجسم ومستوى هذا الهرمون عند مريضات تكيس المبايض. ولان متلازمة تكيس المبايض تتميز باضطرابات التمثيل الغذائي، وبما أن نظام الغدد الصماء له دور مهم في التحكم في دورة النوم والاستيقاظ، فمن المحتمل أن تتداخل متلازمة تكيس المبايض مع الإثارة والنوم أو أن هناك علاقة متبادلة أكثر تعقيدا. يزداد الهيبسيدين بشكل ملحوظ في حالات الالتهاب والعدوى وارتفاع مستويات الحديد، لكن عند مريضات متلازمة المبيض المتعدد الكيسات، لوحظ انخفاض في مستواه، وقد يكون ذلك بسبب زيادة في هرموني الأندروجين والتستوستيرون، وهي من علامات تكيس المبايض، او وقد يكون انخفاضه بسبب وجود زيادة في امتصاص الحديد الغذائي. هرمون الميلاتونين يعمل على تنظيم ساعة الجسم البيولوجية وتشير البحوث الى انخفاض مستواه عند مريضات متلازمة تكيس المبايض مقارنة مع الاصحاء قد يكون بسبب اضطرابات التمثيل الغذائي او ارتفاع مستوى هرمون التستوستيرون.

**الكلمات الدالة:** الهيبسيدين (HP)، متلازمة المبيض المتعدد الكيسات (PCOS)، الهرمون المنشط لمبيض (FSH)، اضطراب النوم (OSA).