THE EFFECT OF HEALTHY LIFESTYLE FACTORS ON POLYCYSTIC OVARIAN SYNDROME, CURRENT APPROACHES IN DIAGNOSIS AND TREATMENT, EVIDENCE-BASED PRACTICES

Yazar Merve Şen

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Abstract

Polycystic Ovary Syndrome (PCOS) is defined as both an endocrine and metabolic disorder. This syndrome is characterized by hirsutism, hyperandrogenemia, amenorrhea, irregular menstrual cycles, ovarian cyst formation and anovulation. The syndrome is grouped into 4 classes as Phenotype A, B, C and D, and there are various classification methods. The most commonly used of these methods is the Rotterdam criteria, and these criteria are determined as 3 items: physical-biochemical findings of hyperandrogenism, oligo/anovulation, and cystic structures seen by ultrasound/inspection. If at least 2 of these items are present, PCOS is diagnosed. The etiology of PCOS is not fully known, but it is thought to be characterized by environmental, genetic and insulin disorders. It has also been determined that PCOS is associated with important diseases such as Type 2 Diabetes, Infertility, Cardiovascular diseases, depression and hypertension. Although there is no universal treatment for PCOS, which negatively affects women's quality of life, planning is made according to the symptoms seen in the individual. Medication, surgery and supportive treatment methods can be applied to individuals, and healthy lifestyle factors are of great importance in treatment. The first step in treatment has been determined as prevention of obesity/overweight and physical activity. For this purpose, the review was conducted to examine the impact of healthy lifestyle factors on PCOS, current approaches and evidence-based practices in its diagnosis and treatment. In conclusion; It has been determined that healthy lifestyle behaviors in PCOS management have positive effects on improving quality of life and treatment effectiveness. In addition, effective and quality care services can be provided thanks to evidence-based practices. For this reason, it is recommended to conduct more evidence-based studies and provide evidence-based care services to individuals.

Key Words: Polycystic Ovary Syndrome, Diagnosis, Treatment, Healthy Lifestyle

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a comorbid disease of unknown etiology and can be defined as a hormonal and metabolic disorder manifested by symptoms such as insulin resistance, hyperandrogenism, and anovulation (Kim 2021) . Hormonal disorders and metabolic disorders result in conditions such as infertility, menstrual disorders and hirsutism in individuals. In addition, this syndrome is associated with various diseases, and these diseases can be listed as Type 2 Diabetes, cardiovascular diseases, hypertension, depression, anxiety, thyroid disorders and cancer (Lim et al. 2019a; Dondi et al. 2021; Khan et al. 2023) .

The quality of life of women with polycystic ovary syndrome is negatively affected due to both the symptoms and other diseases caused by the disease. Diagnosis and treatment of the disease is important in terms of the frequency of the disease and eliminating negative situations. Treatment is in three ways (pharmacological, surgical and supportive) and healthy lifestyle factors are seen as the first step in treatment. Although there is no universality in treatment, the treatment of individuals is planned by taking into account the symptoms and individuals (Glendining and Campbell 2023) .

This review was conducted to explain the endocrinology, pathophysiology, diagnosis and treatment of Polycystic ovary syndrome with evidence-based studies.

2. PCOS

PCOS is defined as a syndrome that occurs due to hormonal dysfunction. Hormonal dysfunctions result in hyperandrogenemia (hirsutism), amenorrhea, irregular menstrual cycle, cyst formation in the ovaries and anovulation. PCOS is also defined as a metabolic disorder after it was determined that it is one of the pathogens of insulin resistance (Khan et al. 2023) .

The prevalence of PCOS varies depending on the diagnostic criteria used, and the prevalence of PCOS is 6% according to NIH, 10% in Rotterdam, and 10% according to the diagnostic criteria of the AE-PCOS Association (Bozdag et al. 2016) ; In Turkey, the prevalence of PCOS was determined as 6.1% according to NIH, 19.9% in Rotterdam and 15.3% according to the AE-PCOS Association diagnostic criteria (Yildiz et al. 2012).

PCOS can be explained by 4 phenotypes: Phenotype A, B, C and D. The most common ones were identified as Phenotype A (44-65%), Phenotype B (8-33%), Phenotype C (3-29%) and Phenotype D (0-23%). The characteristics of the phenotypes are respectively (Khan et al. 2019) ;

- Phenotype A and B: Called Classic. It is associated with increases in insulin secretion, insulin resistance and metabolic syndrome, and marked menstrual irregularities. Obesity, hepatic steatosis, Atherogenic Dyslipidemia (AD) are commonly seen in the classical type. In the classical type, there are significant increases in antimullerian hormone levels.
- Phenotype C (Ovulatory): Serum insulin level is slightly high, atherogenic lipid, androgen levels and hirsutism are clearly observed
- Phenotype D (Non-hyperandrogenic): Increased sex hormone binding globulin, low levels of T3, T4 and very low FSH/LH ratios are observed. There are also normal androgen levels and low metabolic function. Although menstrual cycles are disrupted occasionally, the cycles generally occur regularly.

2.1. Diagnosis

The most popular criteria for defining PCOS are the Rotterdam criteria. These; Clinical (hirsutism, alopecia, acne) and biochemical findings of hyperandogenism (increase in serum androgens), oligo-ovulation or anovulation, polycystic ovaries seen with ultrasonography or direct inspection . PCOS is diagnosed when at least two of these three items are present (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004) . In addition, for a definitive diagnosis, congenital adrenal hyperplasia, hyperprolactinemia, endogenous Cushing's syndrome, thyroid dysfunction, tumor and diseases that have effects similar to PCOS must be excluded (Rosenfield 2020) .

2.2. Endocrinology and pathophysiology

Follicle stimulating hormone (FSH) and Luteinizing hormone (LH) hormones are effective on gonadal growth and function, therefore FSH and LH hormones are called gonadotropin hormones. These hormones are secreted from the anterior pituitary gland and are regulated by gonadotropin-releasing hormone (GnRH). Hypothalamic GnRH carries out the neural control of reproductive functions. GnRH stimulates the pituitary gonadotropes, ensuring the synthesis and secretion of LH and FSH. In polycystic ovary syndrome, primary pituitary/hypothalamic disorders and changes in Gn-RH secretion affect pituitary gonatropin, causing increases in LH secretion. Accordingly, estrogen level increases and FSH level decreases. Inhibin secretion, which is responsible for stopping FSH in the ovary, causes LH to be secreted more than FSH, thus disrupting the balance of FSH and LH. In GnRH dysfunction, hyperandrogenemia occurs due to the increase in LH, which provides androgen synthesis in the ovaries (McCartney et al. 2022) . Hyperandrogenemia can inhibit follicle development and maturation by inducing atresia in the follicles, causing permanent anovulation. In addition, excessively accumulated testosterone in fatty tissues turns into estrone, which prevents follicle development, changes LH and FSH balances, and results in ovarian dysfunction (Li et al. 2019) . As a result, with the disruption of the process between the ovary-pituitary and hypothalamus, ovulation cannot occur and estrogen is secreted from the cyst follicles that do not rupture. The irregular estrogen levels are not sufficient for the start of the menstrual cycle and cause anovulation (Taşkın 2021; McCartney et al. 2022) . Additionally, high levels of LH cause androgen secretion from the stroma and result in hirsutism. Increases in estrogen levels and decreases in progesterone levels cause cycle disorders. Rising androgen levels atresia the ovaries, causing the capsule tunica albuina surrounding the ovary to thicken, thus causing the ovaries to become polycystic (Taşkın 2021) .

Although the etiology of PCOS is not clearly known, it is thought that environmental and genetic factors have an impact on its formation and that it occurs with insulin disorders. Insulin resistance prevents glucose from being metabolized in the liver, muscle and fat tissue. This causes insulin levels to rise, resulting in hyperinsulinemia. Hyperinsulinemia increases androgen secretion in the ovaries and reduces globulin (sex hormone binding hormone) in the liver, causing the androgen level to rise. Therefore, hyperinsulinemia and increased androgen levels result in atresia in the ovaries and ovulation cannot occur (Taşkın 2021) .

Insulin resistance is defined as a condition that occurs due to impaired insulin action in basic target organs such as muscle, fat and liver, that is, the inability of insulin to bind to its receptors or due to ineffective activation (Khan et al. 2023) . Insulin

resistance causes pancreatic β cells to secrete excess amounts of insulin into the circulation, resulting in pancreatic stress. This resulting situation causes disruption of glucose homeostasis, causing Type 2 Diabetes (Pani et al. 2020) . PCOS is characterized by hyperandrogen, and in one study, high testosterone levels were detected in women with Type 2 Diabetes and were associated with insulin resistance, and high concentrations were determined to lead to the development of Type 2 Diabetes (Muka et al. 2017) . It has been found that insulin resistance is seen in obese and thin individuals with PCOS, but it is most seen in individuals with severe obesity (Stepto et al. 2013) . In a study, the risk of developing Type 2 diabetes in underweight women was compared with overweight and obese women, and it was reported that the risk was approximately 4 times higher in overweight/obese women (Livadas et al. 2023) .

With obesity, there is excess fat in the body. It increases insulin resistance and the resulting hyperinsulinemia, which increases adipogenesis and reduces lipolysis. Obesity also sensitizes theca cells to LH stimulation, causing functional ovarian hyperandrogenism . Additionally , obesity affects inflammatory adipokines, which increases insulin resistance and adipogenesis. As a result, insulin resistance, hyperinsulinemia, poor menstrual cycle and anovulation, and secondary amenorrhea are associated with androgen increases. This makes it difficult to both become pregnant and maintain the pregnancy. Anovulation, oligomenorrhea, luteal insufficiency or amenorrhea caused by androgen secretions results in infertility (Taşkın 2021) . Additionally, obesity is associated with high levels of testosterone secretion, resulting in greater androgen release, which prevents ovulation (Aggarwal and Chakole 2023) . With the development of insulin resistance, both obesity and obesity-related complications increase the risk of infertility (Khan et al. 2023) .

3. PCOS AND GENETIC

Genetics is involved as a risk factor for PCOS. Genome-wide association studies (GWAS) have found that PCOS is associated with certain genes. Genes have been explained to be associated with hyperandrogenism, ovulation disorder, hormone changes, and polycystic morphology (Welt 2021) . Additionally, Genetic variants that play an important role in PCOS susceptibility have been identified as GATA4, HMGA2, THADA, FSHR, LHCGR, CYP11A HSD17B5, FSHB, ERBB4, RAB5B/SUOX, INSR and H6PD (Eiras et al. 2022) . Other genes linked to PCOS are CYP11a, CYP17, CYP19, CYP21, Androgen receptor gene (AR), Sex hormone binding globulin gene (SHBG), Luteinizing hormone and receptor gene, Follicle stimulating hormone receptor (FSHR), AMH, Follistatin gene, Insulin receptor gene (INSR), Insulin receptor substrate genes (IRSs), CAPN10, Fat mass obesity gene (FTO), PPAR-γ genes (Siddiqui et al. 2022) . Even though it has been explained that genetic factors are important for PCOS, they cannot fully explain the clinically different changes that occur in PCOS, so more research is needed with large-scale studies that will examine variants and gene sequences (Eiras et al. 2022) .

4. PCOS AND METABOLIC SYNDROME

The pathology of metabolic syndrome is explained by insulin resistance, and this syndrome occurs with the combination of hypertension, high triglyceride, hyperglycemia and abdominal obesity. The frequency of metabolic syndrome is high in women with PCOS and has been reported to be 3 times higher in those with PCOS than in healthy individuals (Lim et al. 2019b) .

5. PCOS AND CANCER

PCOS is a risk factor for various diseases. It is thought that anovulation, which causes unmet estrogen, may lead to endometrium, ovarian and breast cancer. A meta-analysis explained that individuals with PCOS are at risk for endometrial cancer (Dumesic and Lobo 2013; Barry et al. 2014) .

6. PCOS ANXIETY AND DEPRESSION

Individuals with PCOS show more depression and anxiety symptoms than individuals without PCOS (Yin et al. 2021; Nasiri-Amiri et al. 2023) . Psychological problems are characterized by the disruption of both the endocrine system and the immune system in individuals with PCOS. This condition can cause low quality of life and reproductive dysfunctions (Patel and Shah 2018) . For this reason, individuals need to seek psychiatric help when they need to relax, reduce stress factors, and avoid anxiety and depression in order to maintain a healthy mood.

The most effective treatment for individuals with PCOS is cognitive behavioral treatments (Cuijpers et al. 2016) . Another intervention is mindfulness-based meditation programs. These programs are based on improving psychology in reducing stress in medical conditions and can be effective in reducing androgen hormones (Stefanaki et al. 2015) .

7. TREATMENT

It can be listed in three ways: drug treatment, supportive treatment and surgical treatment.

If we list the principles of PCOS treatment: There is no universal treatment, individual-specific and symptom-focused treatments are selected. Lifestyle modification recommendations are given for individuals with mild symptoms. The focus of treatment is on hyperandrogenism, insulin resistance and oligo/anovulation. Combined oral contraceptives for hyperandrogenism (hirsutism, alopecia and acne) and menstrual irregularity; For metabolic properties, it is applied in combination with body weight reduction, diet or oral insulin sensitizers. In addition, applications such as waxing, lighteners, hair removal laser for the treatment of Hirsutism; laser-light therapy for acne treatment; Procedures such as hair transplantation etc. are applied for alopecia (Escobar-Morreale 2018; Glendining and Campbell 2023)

7.1. Pharmacological treatment

Contraceptives: Hormonal contraceptives are preferred for menstrual irregularity, hirsutism and acne treatments. For those who do not want to get pregnant, oral contraceptives are a treatment option and reduce androgen levels and prevent hyperandorogenism. Oral contraceptives reduce adrenal androgen . However, oral contraceptives increase insulin resistance and may cause triglyceride levels, coagulation and inflammatory disorders . Progestins have androgenic effects , and it is important which oral contraceptive to use due to the progestin content of the selected oral contraceptives (Rashid et al. 2022)

Anti-androgens: Spironolactone, flutamide and finasteride are called anti-androgens and are used in the treatment of hyperandrogenism. These drugs are preferred to eliminate androgen-related symptoms and hirsutism. It functions by blocking the effects of testosterone. They are generally used together with oral contraceptives (Rashid et al. 2022)

Metformin: Known as insulin sensitizers. It is used to ensure ovulation, reduce insulin resistance, increase glucose uptake, insulin sensitivity, reduce androgen levels and regulate the menstrual cycle (Daneshjou et al. 2020) .

Oligo-ovulation management: In individuals not considering pregnancy, oral contraceptives, progestin can be used regularly or at certain intervals, or intrauterine devices (levonorgestrel-releasing) can be preferred. For those considering pregnancy, oral contraceptives are not preferred because they prevent ovulation. Medicines that help initiate ovulation are used and the focus is on losing weight. Letrozole is used first. Metformin is also used together with clomiphene citrate, which is effective on follicle development and is known as anti-estrogenic. However, these drugs increase the risk of endometrial cancer due to the increase in estrogen. Additionally, individuals using Letrozole and clomiphene citrate pose a risk for ovarian hyperstimulation syndrome (OHSS) (Sadeghi et al. 2022; Glendining and Campbell 2023) . In individuals considering pregnancy, the fertility of the partner should be evaluated first. If individuals have mild menstrual disorders, pregnancy can be achieved by informing the individual about the fertile periods. If in vitro fertilization is deemed appropriate in the evaluation, they should be referred to a doctor and gonadotropin-releasing hormone antagonist protocols should be applied. If agonists are used, they should be used in combination with metformin to prevent ovarian stimulation. If anovulation is a concern, drugs that will help initiate ovulation (clomiphene citrate or letrozole) should be preferred (Escobar-Morreale 2018)

7.2. Surgical treatment

Although there are risks of decreased ovarian cells and fertility, laparoscopic puncture of the ovaries has been considered as a bariatric surgery treatment option. It has been explained that bariatric surgery can increase ovulation while decreasing body weight and the risk of Type 2 diabetes. (Islam et al. 2022) . It has been found that the decrease in body weight due to surgery decreases testosterone levels, improves the menstrual cycle and reduces hirsutism in individuals with PCOS and severe obesity (Escobar-Morreale et al. 2017).

7.3. Supportive therapy

Obesity

Obesity is known to worsen PCOS. Lifestyle changes and some interventions are required to achieve weight control. A study explained that lifestyle interventions (exercise, diet, behavioral interventions for diet and exercise, or combined intervention) are effective in weight loss and reduce body mass index (BMI) (Lim et al. 2019a) . Lifestyle interventions are recommended to prevent excessive weight gain, manage weight, and prevent future reproductive and metabolic complications (Teede et al. 2019) .

Physical activity

It has been explained that exercise has an effect on insulin resistance, body composition and BMI. According to the PCOS guideline: ≥250 minutes of moderate-intensity or ≥150 minutes of vigorous-intensity exercise per week for weight loss and weight loss; It has been explained that ≥150 minutes of moderate intensity or ≥75 minutes of vigorous intensity exercise per week is required to prevent weight gain (Teede et al. 2019).

Yoga and Acupuncture

In a systematic review about yoga, it was concluded that yoga is more effective than traditional exercises, has positive effects on FSH prolactin, LH, cholesterol levels, reduces stress and depression rates, regulates menstrual cycles, is effective in reducing hirsutism, and has healing effects on metabolic syndrome and thyroid functions. It has been concluded that it can be a powerful tool for PCOS management (Thakur et al. 2021) . Another method that has positive effects on the sympathetic nervous system is acupuncture, and in a meta-analysis study, it was reported that it regulates the menstrual cycle (Wu et al. 2020) .

Diet

The Mediterranean diet is a diet that includes vitamin intake, low intake of unsaturated fatty acids, antioxidant intake, foods with moderate animal protein content, and carbohydrate consumption with low glycemic index. The Mediterranean diet is known to have anti-inflammatory effects and reduce body weight. A study on the subject found that unhealthy nutrition (high intake of simple carbohydrates, low intake of fiber and monounsaturated fatty acids) was associated with hyperandrogenemia, inflammatory state and insulin resistance. It has been explained that adherence to the Mediterranean diet, monounsaturated fat intake, and inflammatory status are effective on testosterone levels and will support the therapeutic role of the Mediterranean diet for PCOS (Barrea et al. 2019).

The ketogenic diet has important roles in reducing body weight, regulating blood sugar, regulating the menstrual cycle and improving liver function (Shishehgar et al. 2019).

Carbohydrates are indicators of blood sugar and insulin levels, such as glycemic index and glycemic load. Depending on carbohydrate consumption, increases in glycemic index and glycemic load occur. These increases have been associated with the risk of PCOS (Eslamian and Hekmatdoost 2019) . In addition, dietary preferences with high glycemic load and index are characterized by a higher risk of stroke, cardiovascular diseases and Type 2 Diabetes in obese/overweight people (Hardy et al. 2020) . Therefore, carbohydrates with low glycemic index and load should be consumed in the diet.

Thanks to dietary fiber intake, inflammation decreases, blood sugar is regulated, insulin sensitivity increases, systemic androgen levels decrease. It may be useful in conditions such as insulin resistance and hyperandrogenism, which are also included in PCOS pathology. Therefore, fiber consumption in the diet is important, and a study explained that fiber consumption has a negative correlation with insulin resistance, glucose tolerance, and fasting blood sugar in individuals with PCOS (Parker et al. 2022).

When the first studies on folic acid were examined, individuals who took folic acid (hf≥6) supplements had a lower risk of infertility than individuals who did not (Chavarro et al. 2008), and a recent study similarly found that folic acid supplements increased fertility (Cueto et al. al. 2022)

In a study evaluating the intake of Omega 3 supplements in the treatment of PCOS, it was explained that cholesterol and triglycerides decreased, lipoprotein increased, insulin resistance decreased, blood sugar was regulated and it was effective in decreasing CRP (Melo et al. 2022) . Therefore, it is important to include it in the diet.

In a meta-analysis review of cinnamon, it was determined that cinnamon is effective in reducing fasting blood sugar, insulin resistance and HbA1C. It has also been explained that cinnamon, known as an antidiabetic, can be used in treatment to control the glycemic index in individuals with Type 2 Diabetes and PCOS (Zarezadeh et al. 2023) .

It has been explained that probiotics have positive effects on insulin resistance, lipid balance and also reduce ovarian inflammation (Islam et al. 2022) . It has been reported that vitamin D supplementation does not affect androgen levels, but increases sex hormone binding globulin levels, decreases testosterone levels, and decreases testosterone levels when used with probiotics. It has also been found that vitamin D supplementation makes positive improvements in the menstrual cycle and increases fertility (Berry et al. 2022) .

Considering that immune cells affect ovarian functions and therefore PCOS is an inflammatory disease, protecting immunity is important for PCOS (Zhang et al. 2017) .

Sleep

Sleep problems have been associated with anxiety, depression, insulin resistance, melatonin decreases, Type 2 diabetes, and obesity (Szczuko et al. 2021) ; These problems seen in individuals with PCOS are explained as sleep disorders, decreased sleep quality, severe fatigue, sleep initiation problems, short or excessive sleep times, difficult/restless sleep situations (Cowan et al. 2023) . It has been found that cognitive and behavioral training in treatment increases the quality of life of individuals with PCOS and reduces psychological fatigue (Abdollahi et al. 2019) .

Cigarette

Although it is a risk factor for PCOS, it has been announced that the risk of developing PCOS in smokers is 38% (Tao et al. 2021) . It has also been explained that the smoking rate is higher in individuals with PCOS who have oligo-anovulation or reduced fertility (Zhang et al. 2020).

Scanning

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease and is closely related to Type 2 Diabetes and obesity (Khan et al. 2022) . Type 2 diabetes and obesity are characterized by hyperglycemic problems, which can cause permanent damage to the liver, so individuals with PCOS should be screened for NAFLD (Vassilatou 2014) .

8. CONCLUSION

It has been determined that PCOS negatively affects women's lives due to many factors. Difficulties in both diagnosis and treatment make the disease even more difficult. In addition, the fact that it is associated with many diseases shows that the management of the process is important. It has been revealed that healthy lifestyles such as protecting individuals from obesity, ensuring weight control , healthy and balanced nutrition, supplements and exercise positively affect the lives of individuals, facilitate the management of the disease and increase the quality of life of individuals.

For the provision of quality health care, evidence-based studies on the etiology, diagnosis and treatment of the disease will make it possible to provide quality care services in terms of disease management.

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