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REVIEW ARTICLE

Polycystic Ovary Syndrome: Definition and Management

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a complex metabolic, endocrine disorder characterized by hyperandrogenism and menstrual abnormalities affecting 8.7%-17.8% of women of reproductive age. Although the etiology of PCOS is not known, environmental and genetic factors are thought to be factors in the emergence of this disease. Women with PCOS suffer from hair loss, hair growth, acne, facial fat, inflammation, irregular menstruation, darkening of the skin, headaches, infertility, depression, insulin resistance, infertility, obesity and polycystic ovaries. Lifestyle or diet, genetics, gut dysbiosis, environmental pollutants, neuroendocrine changes and obesity are among the risk factors that predispose women to PCOS. Although there is no definitive treatment for this disease, pharmacological and non-pharmacological methods are used to manage PCOS. Nonpharmacological treatment options include weight loss, improvement of sleep patterns, smoking cessation, exercise, psychological treatment, healthy nutrition, alternative medicine treatments, supplementary food and probiotic use. Oral contraceptives, antiandrogen drugs, drugs that increase insulin sensitivity, statins, medroxyprogesterone acetate, GLP-1 receptor agonists are pharmacological treatment options.

Contents

1. Introduction

Polycystic Ovary Syndrome (PCOS) is a complex metabolic, endocrine disease that affects 8.7%-17.8% of women of reproductive age and is characterized by hyperandrogenism and menstrual abnormalities (oligoovulation or anovulation) [1,2]. The prevalence of PCOS in different age groups in 1990 and 2019 is given in Figure 1.

Although the etiology of the disease is unknown, it is thought to occur as a result of the interaction of environmental and genetic factors [4]. It has been reported that the risk of developing endometrial hyperplasia and cancer increases in patients with PCOS, and this may change endometrial receptivity and/or the chance of future pregnancy [5,6].

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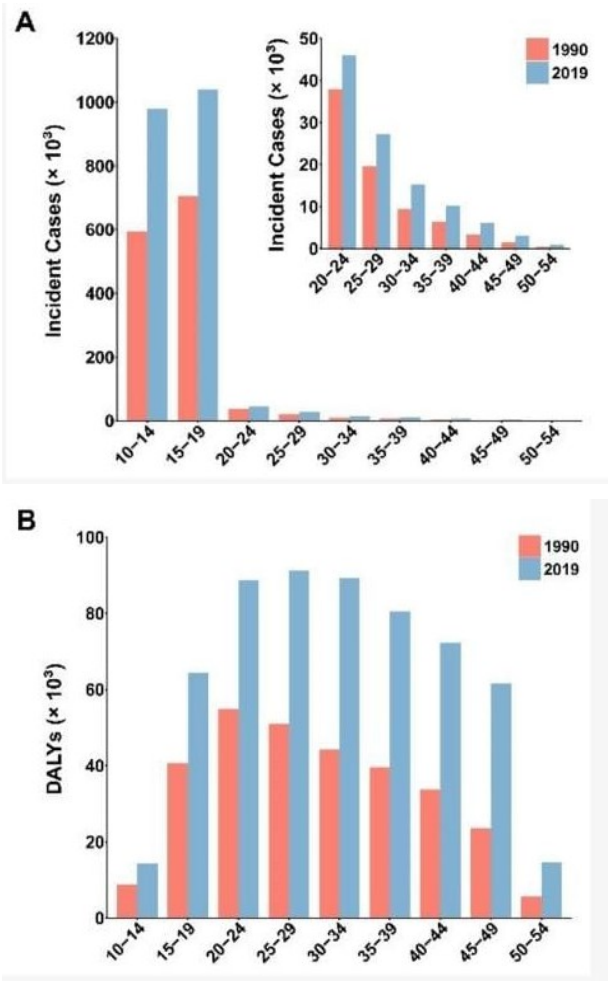

Figure 1 Prevalence of PCOS in different age groups in 1990 and 2019 [3]

Most treatments for PCOS address the current symptoms, such as ovulatory dysfunction and infertility, rather than the long-term risks caused by PCOS, such as diabetes and cardiovascular disease. For this reason, there may be delays in the implementation of preventive strategies such as lifestyle changes [7].

PCOS is characterized by hair loss, hair growth, acne, facial fat, inflammation, irregular menstruation, darkening of the skin, headache, infertility, depression, insulin resistance, infertility, obesity and polycystic ovaries. Lifestyle or diet, genetics, gut dysbiosis, environmental pollutants, neuroendocrine changes, and obesity are among the risk factors that predispose women to PCOS. These factors may contribute to increased metabolic syndrome by causing oxidative stress, hyperandrogenism, hyperinsulinemia, impaired folliculogenesis, and irregular menstrual cycles. Dysbiosis in the intestinal microbiota plays a pathogenic role in the development of PCOS [8]. According to the Endocrine Society Guidelines, proper management of this disease is primarily achieved through lifestyle changes, weight loss, increased physical activity, and healthy nutrition. In order to achieve a significant clinical improvement in women with PCOS, 5-10% of body weight must be lost [9].

Emotional health is also very important for women with PCOS. Anxiety, psychosexual dysfunction, depression, eating disorders, poor body image, and hirsutism are closely related to PCOS, and screening, evaluation, and treatment strategies should be developed for this [10].

In this review, the definition of PCOS disease, risk factors of the disease, clinical symptoms, non-pharmacological and pharmacological treatment options are explained.

2. Polycystic Ovary Syndrome

PCOS is an endocrine disease that affects 8.7-17.8% of women of reproductive age [1,2]. The exact cause of PCOS is unknown. It is considered a genetically based, multifactorial condition [7]. Based on this, it can be said that the history of PCOS is common in these families; but the familial link to PCOS is unclear. [11].

2.1. Diagnosis of PCOS

If PCOS is suspected in a patient, a complete medical history, physical examination, blood tests, and pelvic ultrasound are required. Medical history and physical examination provide the doctor with information about unexplained weight gain, male pattern hair loss, menstrual cycle abnormalities, skin changes and high blood pressure. Blood is drawn to evaluate hormone, glucose, and lipid levels, and a pelvic ultrasound is performed to screen for ovarian cysts [12–14].

2.2. Risk Factors for PCOS

Oligoamenorrhea means having at least 45 days between menstruations or having six or fewer menstruations in a year. Polycystic ovaries on ultrasonography are defined as ≥12 follicles of 2-9 mm in size in at least one ovary and/or increased ovarian volume >10 mL [15].

It is characterized by high levels of total or free testosterone, increased androstendione or dehydroepiandrosterone sulfate. PCOS occurs as a result of excessive androgen secretion from both the ovaries and adrenal glands [16]. Excess luteinizing hormone (LH) stimulates androgen production in the ovaries. Follicular stimulating hormone (FSH) deficiency impairs the growth of follicles. The resulting imbalance between LH and FSH causes the theca cells in the ovaries to be stimulated to proliferate. This causes increased steroidogenesis and, as a result, hyperandrogenism in women with PCOS [17].

Insulin helps regulate ovarian function. The ovaries respond to excess insulin by producing androgens, leading to anovulation. Arrest of follicular maturation is a clear sign that an ovarian abnormality exists [11]. Insulin resistance affects 30%-40% of PCOS patients. It is characterized by increased circulating insulin levels both at baseline and after the glycemic load. As a result of the inadequacy of insulin in its functions such as glucose production and uptake, a greater amount of insulin is required for metabolic effect [18]. This situation has a significant impact on the formation of PCOS. It can cause various metabolic and reproductive abnormalities [19,20]. Insulin resistance occurs in thin women in a mechanically different way than insulin resistance caused by excess weight. In obese individuals, weight further exacerbates hyperinsulinemia [21]. Therefore, preventing excessive weight gain in insulin resistance is among the main goals in PCOS management [22].

Women with PCOS experience an increase in weight. This is a serious problem as weight gain contributes to

reproductive pathogenesis. In a study, it was observed that the prevalence of insulin resistance in obese women with PCOS (64%) was higher than in non-obese (20%) women with PCOS. Obesity causes and exacerbates insulin resistance [23]. The resulting hyperinsulinemia may trigger hyperandrogenism [24]. Obesity is the key to low-grade chronic inflammation [25]. A positive correlation was observed between weight gain and the number of adipocytes present. Adipocytes accumulate in visceral fat, which first causes hypoxia and then necrosis. As a result, the amount of inflammatory cytokines increases [26]. Increased androgen leads to increased estrogen concentration in the body. This triggers a negative feedback loop that suppresses gonadotropin production. Thus, it contributes to infertility in women with PCOS [27].

Dyslipidemia may occur in women with PCOS. Lipid abnormalities such as increased triglyceride, bad cholesterol (LDL-C), and very low-density lipoprotein (VLDL-C) values and decreased good cholesterol (HDL-C) values are observed [28]. Dyslipidemia in women with PCOS is caused by insulin resistance, obesity and hyperandrogenism [29].

Inflammation is a cause of hyperandrogenism [30,31]. Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory chemical that worsens insulin resistance. This occurs by decreasing the expression of glucose transporter type 4 (GLUT-4) and the interaction of pro-inflammatory molecules with the insulin signaling pathway [32–34]. Additionally, TNF-α promotes the proliferation of theca cells in vitro and inhibits interleukin 1 (IL-1), FSH, LH receptors; This leads to inhibition of follicular development and ovulation [35,36]. The increase in C reactive protein (CRP) levels is a factor in the formation of insulin resistance in insulin-sensitive tissues. It achieves this by increasing pro-inflammatory factors secreted by the liver and monocytes [25].

Increased oxidative stress level activates nuclear factor kappa B. Nuclear factor kappa B is involved in the inflammatory process and affects the production of pro-inflammatory cytokines such as TNF-α and IL-6 [25,37,38]. Additionally, oxidative stress plays a role in obesity. It provides pre-adipocyte proliferation and adipocyte differentiation by increasing the size of mature adipocytes [36]. High levels of oxidative stress activate certain protein kinases that trigger serine/threonine phosphorylation instead of the normal tyrosine phosphorylation of the insulin resistance system.

Dyslipidemia can be seen in women with PCOS. Lipid abnormalities such as an increase in triglycerides, bad cholesterol (LDL-C), very low density lipoprotein (VLDL-C) and a decrease in good cholesterol (HDL-C) are observed [28]. Dyslipidemia in women with PCOS is caused by insulin resistance, obesity and hyperandrogenism [29].

Inflammation is a cause of hyperandrogenism [30,31]. Tumor necrosis factor alpha (TNF-α) is a proinflammatory chemical that worsens insulin resistance. This occurs through decreased expression of glucose transporter type 4 (GLUT-4) and interaction of proinflammatory molecules with the insulin signaling pathway [32,39]. In addition, TNF-α induces proliferation of teka cells in vitro and inhibits interleukin 1 (IL-1), FSH, LH receptors, which leads to inhibition of follicular development and ovulation [26,36]. Increased levels of C reactive protein (CRP) are a factor in the development of insulin resistance in insulin-sensitive tissues. It does this by increasing proinflammatory factors secreted by the liver and monocytes [25].

Increased levels of oxidative stress activate nuclear factor kappa B. Nuclear factor kappa B is involved in the inflammatory process and affects the production of proinflammatory cytokines such as TNF-α and IL-6 [25,37,38]. Oxidative stress also plays a role in obesity. Increases mature adipocyte size and promotes pre-adipocyte proliferation and adipocyte differentiation [36]. High levels of oxidative stress activate certain protein kinases that trigger serine/threonine phosphorylation instead of the normal tyrosine phosphorylation of the insulin resistance system. Thus, the insulin signaling pathway is inhibited, which causes insulin resistance [32]. High oxidative stress levels have been detected in PCOS patients [26,40,41].

Environmental toxins such as heavy metals, pesticides, and endocrine disrupting chemicals have been found to contribute to the development of PCOS. The serum levels of endocrine disrupting chemicals are higher in women with PCOS [42,43]. Endocrine disrupting chemicals contributes to insulin resistance, obesity and infertility, and is also linked to oxidative stress and inflammation [44]. They cause epigenetic changes in female reproductive DNA, which can affect subsequent generations and enable the transmission of PCOS features [43]. Polycyclic aromatic hydrocarbons formed in burnt coal and wood, cigarette smoke, garbage, and meat cooked at high temperatures are effective in the formation of PCOS [45].

2.3. Clinical Symptoms of PCOS

It has been found that high levels of LH and gonadotropin-releasing hormones (GnRH) are among the clinical symptoms of PCOS [46]. FSH levels decreased or did not change. Low but constant values of FSH ensure the continuous production of new follicles. The follicles produced cannot reach full maturity. Ovulation does not occur. These atretic follicles continue to enrich the androgen-secreting ovarian stromal portion with increased LH secretion. The typical pattern of GnRH secretion (LH/FSH ratio > 2.5) is a result of either altered hypothalamic GnRH secretion or increased sensitivity of the pituitary gland to hypothalamic GnRH. Pulsatile secretion of GnRH regulates the decrease and increase of gonadotropin synthesis. While high pulsatile secretion can stimulate LH synthesis, low pulsatile secretion can stimulate FSH synthesis [47,48]. Stimulation of ovarian theca cells as a result of the increase in GnRH produces more androgens [46]. The arrest of follicular development can be corrected by increasing endogenous FSH levels or by providing exogenous FSH [49]. Prolactin levels are increased in approximately 25% of patients with PCOS [50]. It has also been found that theca cells in PCOS patients produce higher amounts of testosterone, 17-hydroprogesterone and progesterone than in normal patients [51]. Additionally, estrone (E1) levels are increased in women with PCOS [52]. The sex hormone binding globulin (SHBG) value of a woman with PCOS decreases by 50% compared to the normal value. Accordingly, the amount of free androgens increases [53].

Serum levels of advanced glycation end products are increased in patients with PCOS. This causes ovarian dysfunction, insulin resistance and obesity [54]. Reducing dietary advanced glycation end-products (AGE) intake in patients with PCOS helps prevent PCOS-related diseases [55].

2.4. Treatment of PCOS

Recommendations from the international evidence-based guideline for the evaluation and management of PCOS are given in Table 1.

Table 1 Recommendations from the international evidence-based guideline for the evaluation and management of PCOS [10]

PCOS and Cardiovascular disease (CVD) risk recommendations (Clinical consensus recommendations)	Weight monitoring (every visit or every 6-12 months) Weight, height, waist circumference, ideally body mass index (BMI) should be calculated. 1. PCOS; cardiovascular risk factors should be investigated and CVD risk should be calculated 2. In the evaluation of risk factors; obesity, smoking, dyslipidemia, hypertension; If IGT, physical activity (-) is detected, CVD risk should be considered high. 3. Overweight and obese PCOS; Fasting lipid profile (LDL cholesterol, HDL-cholesterol, triglyceride) should be checked regardless of age, and the frequency of follow-up should be determined according to the presence of hyperlipidemia and CVD risk. 4. PCOS; blood pressure should be checked annually or more frequently depending on CVD risk The frequency of risk assessments should be determined by taking ethnic characteristics into consideration.
PCOS-Gestational DM, impaired glucose tolerance (IGT), Type 2 DM (Clinical consensus recommendations)	1. Glycemic status should be determined at the beginning (follow-up should be done every 1-3 years) (According to DM risk factors: if BMI > 25 kg/m2)

Individuals with CVD risk factors such as a history of IGT, family history of diabetes, hypertension, gestational diabetes, or obesity should undergo oral glucose testing. Lipid profile, weight monitoring and blood pressure should be checked annually [56]. If there are problems in determining CVD risk, coronary calcium score can be evaluated in women older than 40 years of age to help assess risk [57]. Additional tests are useful in risk stratification in older women with PCOS. A coronary calcium score greater than 0 indicates the presence of subclinical atherosclerosis. It supports the initiation of statin group drugs [57].

2.4.1. Non-pharmacological Treatment

Since the actual cause of PCOS is unknown, treatment is symptomatic. There are few treatment approaches that cure all aspects of the syndrome [58].

Weight loss: Increased androgen levels cause women with PCOS to gain abdominal fat and gain weight. This is why women with PCOS have a pear-shaped body instead of an apple-shaped body [59]. The first step in the management of PCOS is to restrict calorie intake and lose weight [60]. Losing 2-5% of body weight improves ovulation and menstrual irregularity [61–64]. Losing more than 5% of body weight increases a person's chances of getting pregnant, giving a live birth, and decreasing ovarian volume and follicle number [65–71]. With weight loss, the incidence of metabolic syndrome decreases and free testosterone levels decrease [72]. Obese PCOS patients should achieve normal BMI.

Improving sleep patterns: Estrogen, progesterone and melatonin levels decrease in women with PCOS. This fall increases the risk of non-clinical sleep disorders [73].

Quitting smoking: Among women with PCOS, it has been found that smokers have a 38% higher risk of developing PCOS than never smokers[74]. Smoking causes an increase in the miscarriage rate and a decrease in the live birth rate in women with PCOS [75,76].

Psychological treatment: Psychological problems such as psychosexual dysfunction, depression and anxiety, eating disorders, and negative body image negatively affect PCOS symptoms. Appropriate evaluation and management are required [10]. Cognitive behavioral interventions are performed to increase participation and adherence to a healthy lifestyle in women with PCOS. Different psychological interventions such as mindfulness meditation and counseling can be performed [77,78]. In the randomized controlled study, it was determined that the quality of life of women with PCOS improved and their psychological fatigue decreased in 8-week group sessions [79]. Mindfulness meditation programs are another non-pharmacological treatment to improve psychological health and reduce stress [80].

Exercise: It is important in losing weight. It is useful in improving insulin sensitivity [81]. The American Heart Association recommends approximately 150 minutes of moderate or 75 minutes of vigorous and intense exercise per week [72]. It is recommended to prevent weight gain, minimize sedentary time, and include strength training two days a week in the exercise program [10]. Exercise has been observed to improve fasting insulin test (FINS), homeostatic model assessment (HOMA-IR), total cholesterol (TC), LDL-C, TAG (radioisotope bound to a pharmaceutical or natural chemical substance used to monitor any metabolic process), body composition (body fat percentage) and aerobic fitness [82]. Weight loss through exercise improves symptoms in women with PCOS [61]. Doing regular exercise can restart ovulation in women with PCOS through modulation of the hypothalamic pituitary gonadal axis [81].

Diet: Healthy nutrition and reaching or maintaining adequate body weight are very important for PCOS patients. Proper nutrition improves insulin resistance, metabolic and reproductive functions [59]. Decrease in fiber consumption and increase in saturated fat intake in women with PCOS increases the clinical symptoms of the disease and the risk of chronic disease [83]. Ideal nutrition should be rich in fiber and low in saturated fat and carbohydrates [59]. Diets that will provide weight loss should be recommended for overweight and obese women with PCOS [84]. A low glycemic index diet reduces insulin sensitivity and improves reproductive hormones. It contributes to regular menstruation. It improves type 2 diabetes and CVD risk factors [85–88]. It has been observed that high protein intake reduces insulin and dehydroepiandrosterone stimulation more than glucose-rich food intake in women with PCOS [89].

Considering the relationship between PCOS and obesity, insulin resistance, and low-grade chronic inflammation, the Mediterranean diet is one of the most appropriate non-drug strategies for PCOS patients. This diet is based on eating plant-based foods, including fruits, vegetables, whole grains, seeds and nuts. Healthy lipids from olives, hazelnuts and fish such as sardine and salmon are important for this diet. A moderate amount of dairy products and a lower amount of red meat should be consumed. Spices and herbs are used to flavor foods to prevent excess salt. Polyphenols obtained from red wine and olive oil have therapeutic potential in patients with PCOS. It reduces the progression of inflammation and improves both hyperinsulinemia and insulin sensitivity [90,91].

Complementary and alternative medicine treatments: It has been observed that only 60% of pharmacological treatments are effective in PCOS patients [92]. The most important advantage of these treatments is that people tend to accept these methods due to the influence of their beliefs and culture. This increases the patient's compliance with treatment. Based on studies, various methods such as immunotherapy, psychotherapy, dietary therapy (herbal and medicinal foods, probiotics, and vitamin or supplement therapy), yoga, spa, Tai Chi, oxygen therapy, and traditional Chinese medicine have been recognized as effective strategies to reduce the severity and complication of PCOS. [93–98].

It has been observed that some supplements are effective in women with PCOS. These products include vitamin D supplements, resveratrol, alpha-lipoic acid, berberine, folic acid, omega-3, myoinositol, d-chiro-inositol [99].

Laparoscopic ovarian puncture is an outpatient surgical intervention in which multiple perforations are created on the ovarian surface and stroma. This surgical intervention destroys androgen-producing tissue. In this way, androgen levels decrease. It is as effective as medical interventions in increasing multiple pregnancies [100].

Bariatric surgery is especially important in weight loss, which is closely related to improvement in insulin resistance, hyperandrogenism, menstruation and ovulation dysfunction. It takes part in the regression of PCOS and increases fertility. Bariatric surgery is performed in obese patients with PCOS, especially in patients with metabolic syndrome [101].

Probiotics, prebiotics and synbiotics: Women with PCOS have greater intestinal permeability and the gut microbiome is less diverse than women without PCOS. This may cause hyperandrogenism and increased systemic inflammation levels [102,103]. Bifidobacterium, Enterococcus, Streptococcus and Bacillus species are the bacteria most commonly used as probiotic supplements [104]. Probiotic supplementation improves the metabolic profile in women with PCOS [105]. Prebiotics cause specific changes in the composition and activity of a person's intestinal microbiota. The most well-known are lactulose, inulin, galactooligosaccharides and fructooligosaccharides [106], which promote the growth of Lactobacillus and Bifidobacterium. Thus, glucose, triglyceride, LDL and total cholesterol levels decrease [107]. A study found that regular consumption of dextrin, a prebiotic supplement, helps regulate metabolic parameters. It reduces menstrual cycle abnormalities and hyperandrogenism in women with PCOS [108]. In a study conducted in women with PCOS, it was observed that the use of probiotics/symbiotics could improve metabolic, hormonal and systemic inflammatory factors [109].

2.4.2. Pharmacological Treatment

Oral contraceptives: With the use of oral contraceptives, the susceptibility to cancer is reduced in women with PCOS. In particular, the risk of ovarian cancer decreases [110]. They are the first drugs used for the treatment of hirsutism, menstrual abnormalities and acne in women with PCOS [111]. Oral contraceptives reduce androgen production in the ovaries. Thus, hyperandrogenism decreases. It reduces the levels of free androgens in the blood. It increases the SHBG value produced by the liver. It prevents the peripheral conversion of testosterone to dihydrotestosterone and binds dihydrotestosterone to androgen receptors, thus reducing androgen release [112]. Due to the increased risk of teratogenicity for the male fetus, PCOS patients should also use oral contraceptives while using antiandrogens [113].

Antiandrogens: Antiandrogens are used in the treatment of problems such as menstrual disorders, acne, hirsutism, androgenic alopecia due to PCOS, and hyperandrogenism. Antiandrogens block the function of testosterone [114]. As a result of the use of oral contraceptives containing antiandrogenic compounds in PCOS patients, it has been observed that the adipokine and lipid profiles and metabolic phenotypes of the patients improve. It has been observed that ovulation and menstrual cycles improve in PCOS patients using flutamide [115–119]. Use of flutamide alone causes hepatotoxicity, so it is used with metformin [120]. Steroidal antiandrogens such as spironolactone and cyproterone acetate significantly reduce hirsutism and acne [121]. Finasteride, a 5α reductase inhibitor that prevents the conversion of testosterone to dihydrotestosterone, is the first drug used to relieve hyperandrogenic symptoms and effectively treat hirsutism in PCOS patients [122,123]. However, the teratogenic effects of finasteride are risky. Therefore, its use in women is limited. It is used in women who do not want to ovulate or in postmenopausal women [124,125].

In PCOS patients, excessive insulin levels cause deterioration of the ovaries. Theca cells greatly increase androgen secretion. As a result, follicular maturation stops. Thus, polycystic eggs are formed [126]. Drugs in this group

reduce insulin resistance. It normalizes insulin level. It reduces androgen levels. Thus, the menstrual cycle improves [127].

It has been observed that the use of the combination of metformin, an antidiabetic with a biguanide structure, and clomiphene citrate in infertile PCOS patients increases the ovulation and pregnancy rate [128]. Metformin also has a preventive role in long-term diseases related to PCOS patients, including type 2 diabetes, cardiovascular diseases, hypertension, and endometrial cancer [129,130]. The use of high doses of metformin has been found to be more effective in PCOS patients. However, metformin causes many side effects such as vomiting, nausea, diarrhea, bloating, anorexia and abdominal pain [131]. Additionally, studies have shown vitamin B12 deficiency in PCOS patients using metformin for a long time [132]. In a randomized controlled study, using the combination of thiazolidinedione and metformin in PCOS patients reduced total testosterone levels, and it was observed that this combination was much more effective in improving insulin and lipid metabolism than using metformin alone [133].

Thiazolidine group drugs are the second group of drugs chosen for the treatment of insulin resistance in women with PCOS (Stout and Fugate, 2005). These drugs stimulate peroxisome proliferator-activated receptor-gamma (PPAR ɣ). PPAR ɣ increases insulin sensitivity in adipose tissue [134]. These drugs are preferred in women with PCOS who are resistant to clomiphene. Its positive effects have been observed in increasing ovulation and pregnancy rates [135–137]. They increase SHBG levels and reduce excess androgens [138]. Thiazolidine group drugs are in category C in pregnant experimental animals, so their use in pregnant women should be carefully monitored [137].

Drugs used to prevent anovulation: These are drugs that stimulate ovulation. It is an effective treatment for PCOS patients with fertility needs. In PCOS, anovulation, low FSH levels cause antral follicle growth arrest in the final stages of maturation [139].

Clomiphene is the first drug used to induce ovulation in PCOS patients. Clomiphene citrate inhibits negative feedback in the estrogen signaling pathway. Thus, the amount of FSH increases. As a result of the increase in FSH, follicles grow. The amount of LH increases and ovulation occurs [140]. Pregnancy occurs in 30% of PCOS patients using clomiphene. However, 20% of these pregnancies result in miscarriage or stillbirth. Side effects such as ovarian hyperstimulation syndrome, hot flashes, multiple pregnancies, and gastrointestinal bloating may occur as a result of clomiphene use [141,142].

Tamoxifen is a drug that acts similarly to clomiphene, which is used when clomiphene citrate does not work [143,144]. Tamoxifen has positive effects on cervical and endometrial mucus [143]. Due to its favourable effect on the uterus, the combined use of clomiphene and tamoxifen in women with PCOS has led to an increased pregnancy rate [144].

Aromatase inhibitors block the conversion of androgens to estrogens in peripheral tissues, ovarian follicles and the brain. A positive feedback occurs with estrogen in the hypothalamic-pituitary-ovarian axis and induces ovulation. In women with PCOS, aromatase is reduced and, as an effect, the follicles responsible for ovulation are reduced. Letrozole and anastrozole have been recommended as primary and secondary treatments to induce ovulation [121,145,146]. When anastrozole was compared with letrozole, it was observed that letrozole use significantly increased pregnancy rates [147]. Letrozole stimulates monofollicular growth and does not lead to peripheral antiestrogenic effects on the endometrium [148]. Letrozole, unlike clomifene, can maintain its antiestrogenic effect on the endometrium by suppressing estrogen receptors more effectively, which makes it more advantageous [145].

Recombinant FSH is a second-line treatment option for anovulatory infertile PCOS women compared with other gonadotropins such as human menopausal gonadotropin (HMG) [149]. Low-dose FSH treatment can be considered as a suitable option to increase ovulation induction and pregnancy rates in PCOS patients [139,150]. Gonadotropin treatments can be costly so, alternative reproductive techniques such as intrauterine insemination or *in vitro* fertilization may be preferred instead of this method [149,151].

Statins: Dyslipidemia is common in individuals with PCOS disease. Increasing LDL-C and triglyceride levels and decreasing HDL levels create CVD risk [152]. The drugs in this group have an effect by reducing sex steroid production, correcting dyslipidemia, alleviating inflammation, and reducing ovarian androgen production by preventing androgen production of theca cells [153]. They also reduce triglycerides, LDL-C and total cholesterol [154]. In a study conducted in PCOS patients using atorvastatin, it was observed that total testosterone levels decreased by 17.1% [155]. In one study, in addition to atorvastatin and placebo groups, when both were given metformin for 12 weeks, the atorvastatin-treated group performed significantly better than the placebo-treated group in terms of HOMA-IR, free androgen index, total testosterone and SHBG; at the end of the study, it was observed that atorvastatin enhanced the effect of metformin [156]. In this study, atorvastatin was observed to significantly reduce acylation-stimulating protein, IL-6, and monocyte chemoattractant protein-1, which are markers of inflammation and adipose tissue dysfunction. Following this decrease, a significant improvement was observed in HOMA-IR and testosterone levels [157].

Other studies have shown that hyperandrogenism, dehydroepiandrosterone sulphate (DHEAS), inflammatory markers and insulin resistance significantly decreased and serum vitamin D levels increased in PCOS women using atorvastatin. It has been observed that serum malondialdehyde levels, a measure of oxidative stress, are significantly reduced in obese people with PCOS [156,158–161].

Medroxyprogesterone acetate: In a dosage regimen of 5 to 10 mg/day for 10 to 14 days each month, it may be used to treat amenorrhea or dysfunctional uterine bleeding in PCOS patients who are unwilling or unable to become pregnant. Monthly progestin treatment eliminates abnormal endometrial proliferation but does not suppress ovarian androgen production [12]. The use of medroxyprogesterone acetate in PCOS patients also improves the lipid profile and insulin sensitivity [162–164].

Glucagon-like peptide-1 (GLP-1) receptor agonists: Considering that insulin resistance is among the main causes of metabolic and endocrine dysfunction in PCOS, the effect of GLP-1 receptor agonist treatment for PCOS patients is undeniable. The drugs in this group are formulated to mimic the effects of the GLP-1 hormone secreted by L cells in the distal part of the small intestine. These agonists lead to the suppression of the hypothalamic hunger center and a decrease in glucagon release [165]. At the same time, these agonists affect the amount of insulin and increase postprandial glucose levels, which leads to early satiety [166]. Drugs in this group also regulate homeostatic feeding, which involves adjusting calorie intake to maintain energy balance. This regulation is achieved by increasing the functional connectivity between the nucleus tractus solitarius and the arcuate nucleus in the hypothalamus [167]. In PCOS patients, GLP-1 agonists may indirectly increase insulin sensitivity due to weight loss [168]. Semaglutide, dulaglutide, liraglutide and exenatide are GLP-1 agonist drugs. A study comparing the efficacy of GLP-1 agonists and metformin in women with PCOS showed that GLP-1 agonists provided a significant improvement in insulin sensitivity, BMI and abdominal circumference compared to metformin [169]. Another study revealed that the use of GLP-1 receptor agonists alone was effective in reducing hepatic fat content, regulating adiposity, correcting lipid profiles and improving metabolic parameters, in addition to promoting glycemic control and weight loss [8].

Micro RNA (miRNA) therapy: MiRNAs participate in many physiological activities, including apoptosis, proliferation, differentiation, stress and metabolism responses [170]. Considering the data obtained in recent years, it has been suggested that abnormal miRNA expression is observed in theca cells, follicular fluid, granulosa cells, adipose tissue, cumulus cells, peripheral blood leukocytes and serum affected by PCOS [170–174]. MiRNAs participate in many physiological activities including apoptosis, proliferation, differentiation, stress and metabolic responses [170]. Using modern technology and accessible databases, miRNAs can enable us for precise analysis, prevention and management of reproductive disorders such as PCOS. The main goal is to perform large-scale replication experiments to find specific miRNAs with significant modulatory effects on PCOS. The functional significance of individual miRNAs in PCOS pathology can be examined and their functionality can be confirmed both *in vivo* and *in vitro*. Potential miRNA-based therapeutic options will offer new horizons and convincing alternatives for the treatment of PCOS and related metabolic complications. Small interfering RNA therapies, anti-miRNA oligonucleotides, and miRNA mimics are currently being extensively investigated. Currently, there are no drugs that specifically target miRNAs associated with PCOS. Several clinical trials are underway to evaluate the potential therapeutic effects of miRNA targeting to obesity and associated metabolic disorders, which may also benefit women with PCOS [8].

Treatment with IL-22: A study showed that IL-22 levels decreased in the serum and follicular fluid of PCOS patients. It has been observed that administering IL-22 to mice can help improve insulin resistance, ovarian dysfunction, and infertility in intestinal bacteria and regulate prenatal Anti Müllerian Hormone (AMH) [175].

3. Conclusion

PCOS is a complex metabolic, endocrine disease that affects 8.7%-17.8% of women of reproductive age and is characterized by hyperandrogenism and menstrual abnormalities. Research shows that the prevalence of PCOS is increasing over the years. Although its etiology is unknown, it is said to occur as a result of the interaction of environmental and genetic factors. It has many symptoms such as depression, acne, weight gain, hirsutism, lack of sexual desire, and male pattern baldness.

To determine whether a person has PCOS, a complete medical history, physical examination, blood tests and pelvic ultrasound are required. Physical examination and medical history are useful in understanding the cause of symptoms such as unexplained weight gain, male pattern hair loss, menstrual cycle abnormalities, skin changes and high blood pressure. In the blood test, hormone, glucose and lipid levels are evaluated. Pelvic ultrasound is performed to screen for ovarian cysts.

There are many risk factors for the development of PCOS, such as oligoamenorrhea, hyperandrogenism, insulin resistance, weight, dyslipidemia, inflammation, oxidative stress, and endocrine disrupting chemicals. Oligoamenorrhea means at least 45 days between menstruations or six or fewer menstruations in a year. In hyperandrogenism, excessive LH production stimulates androgen production in the ovaries. FSH deficiency impairs the growth of follicles. The resulting imbalance between LH and FSH causes the theca cells in the ovaries to be stimulated to proliferate. This leads to increased steroidogenesis and, as a result, hyperandrogenism in women with PCOS. Insulin resistance is characterized by increased circulating insulin levels both at baseline and after glycemic load. It can cause various metabolic and reproductive abnormalities. Women with PCOS experience an increase in weight. Obesity causes and exacerbates insulin resistance. It may cause infertility in women with PCOS. Oxidative stress occurs as a result of the imbalance between antioxidants and pro-oxidants. Endocrine disrupting chemicals contribute to insulin resistance, obesity and infertility; these chemicals are also linked to oxidative stress and inflammation. They lead to epigenetic changes in female reproductive DNA that can affect subsequent generations and transmit PCOS traits.

In PCOS, while LH, GnRH, prolactin, estrone, AMH, AGE levels increase, FSH and SHBG values decrease.

Recommendations for PCOS include the following: blood pressure measurement should be performed annually; oral glucose testing should be performed in individuals with CVD risk factors such as family history, family history of diabetes, hypertension, gestational diabetes or obesity; fasting lipid profile should be performed annually in all women with PCOS; weight monitoring should be checked annually, and screening for diabetes mellitus in pregnancy should be performed. Most treatments for PCOS address existing symptoms, such as ovulation dysfunction and infertility.

Non-pharmacological treatment includes weight loss, improvement of sleep patterns, quitting smoking, exercise, psychological treatment, healthy nutrition, alternative medicine treatments (phytotherapy, mesotherapy, etc.), food

supplements (vitamin D, resveratrol, berberine, myoinositol, D chiro inositol, etc.) and the use of probiotics. Women with PCOS have a pear-shaped body. While losing 2-5% of body weight improves ovulation and menstrual irregularity, losing more than 5% increases a person's chances of becoming pregnant, giving birth to a live birth, and decreasing ovarian volume and follicle number. Estrogen, progesterone and melatonin levels decrease in women with PCOS. This increases the risk of non-clinical sleep disorders. Interventions that improve mental health can be made by increasing diet and physical activity. Doing regular exercise; may restart ovulation in women with PCOS through modulation of the hypothalamic pituitary gonadal axis. Nutrition is also of great importance in women with PCOS. Mediterranean diet reduces oxidative stress markers. It has antiatherosclerotic and antithrombotic properties. It improves insulin sensitivity. The use of food supplements is also important in the non-pharmacological treatment of PCOS.

There are many pharmacological treatment options for symptoms. With the use of oral contraceptives, the susceptibility to cancer decreases in women with PCOS. It reduces androgen production in the ovaries. Thus, hyperandrogenism decreases. Women with hirsutism usually use oral contraceptives for 6 months to achieve clinical improvement. Antiandrogen drugs (spironolactone, finasteride, etc.) are used in the treatment of problems such as menstrual disorders, acne, hirsutism, androgenic alopecia due to PCOS, and hyperandrogenism. These drugs block the function of testosterone. Drugs that increase insulin sensitivity (thiazolidinediones, metformin) reduce insulin resistance. It normalizes insulin level and reduces androgen levels. Thus, the menstrual cycle also improves. Drugs used to prevent anovulation (clomiphene, tamoxifen, etc.) are drugs that stimulate ovulation. It is an effective treatment for PCOS patients with fertility needs. Statin group drugs (atorvastatin, rosuvastatin, etc.) have an effect by reducing sex steroid production, correcting dyslipidemia, alleviating inflammation, and reducing ovarian androgen production by preventing androgen production of theca cells. They reduce triglycerides, LDL-C and total cholesterol. Medroxyprogesterone acetate can be used to treat amenorrhea or dysfunctional uterine bleeding in PCOS patients who are unwilling or unable to become pregnant. The use of medroxyprogesterone acetate in PCOS patients also improves the lipid profile and insulin sensitivity. GLP-1 receptor agonists lead to suppression of the hypothalamic hunger center and reduction in glucagon release. At the same time, these agonists affect the amount of insulin and increase postprandial glucose levels, which leads to early satiety. Drugs in this group also regulate homeostatic nutrition, which involves adjusting calorie intake to maintain energy balance.

In addition to these treatments, laparoscopic ovarian puncture and bariatric surgery can be performed. Laparoscopic ovarian puncture is as effective as medical interventions in increasing multiple pregnancies. Bariatric surgery is effective in losing weight. Bariatric surgery is important in weight loss, which is closely associated with improvement in insulin resistance, hyperandrogenism, menstrual and ovulatory dysfunction. It takes part in the regression of PCOS and increases fertility.

Although there is no definitive treatment for PCOS disease, it is predicted that health management is very important in this disease; PCOS disease can be managed better with proper nutrition, exercise and plenty of water consumption.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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