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Polycystic Ovary Syndrome- treatment update

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1. Abstract

Introduction:

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders. It gets its name from the characteristic appearance of the ovaries observed in ultrasound imaging. Statistically, PCOS affects about 4-12% of women of reproductive age. PCOS can have a variety of symptoms and courses, and its causes have not been fully understood. Women with PCOS are at a higher risk of developing diabetes, hypertension, hyperlipidemia, and endometrial cancer compared to their healthy peers. The purpose of our work is to discuss the available methods used in the treatment of this syndrome.

Research Objective:

The primary aim of this literature review is to show available methods of treating PCOS based on the latest scientific research.

Materials and methods:

The review was based on the analysis of materials collected in the "Pubmed" database, books and other scientific articles.

Conclusions:

Polycystic Ovary Syndrome (PCOS) remains an important issue that affects women's functioning and their hormonal balance. A review of the literature has shown that the use of medications and supplements in the form of herbs and plants has a positive impact on women's hormonal health, contributing to the regulation of the menstrual cycle and the stimulation of ovulation. Further research on the use of herbs is necessary, as based on the current sources, no definitive conclusions can be drawn.

Keywords: Endocrine disorder; Polycystic Ovary Syndrome; Hyperandrogenism; Treatment; Infertility; Ovulation

2. Introduction

Between 4 and 12 percent of women of reproductive age suffer from PCOS. Studies have shown an increased risk of developing PCOS in daughters of mothers diagnosed with PCOS, as well as in sisters who have the condition.[1] Polycystic ovary syndrome (PCOS) is a condition that leads to the absence of ovulation. It was first described by I.F. Stein and M.L. Leventhal in 1935. Today, PCOS is diagnosed based on the diagnostic criteria established by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), known as the Rotterdam criteria, published in 2003. A diagnosis of PCOS can be made if two out of the following three criteria are met:

1. Clinical/biochemical hyperandrogenism
2. Polycystic ovaries on ultrasound
3. Oligo/anovulation.

A diagnosis of PCOS can be made after excluding other conditions that present with similar symptoms, such as hyperprolactinemia, acromegaly, androgen-secreting tumors, congenital adrenal hyperplasia, Cushing's syndrome, and thyroid disorders (both hyperthyroidism and hypothyroidism).[1]

2.1 Pathomechanism

The pathomechanism of PCOS development has not been fully understood. The primary cause of these disorders is attributed to increased secretion of LH and the excessive response of the thecal cells to LH stimulation, which results in the production of excessive amounts of androgens (testosterone, androstenedione) by the thecal cells. These androgens then disrupt the hypothalamic-pituitary axis, leading to an increase in LH secretion. Increased androgen levels contribute to obesity and fat tissue redistribution, which raise the risk of insulin resistance. Elevated androgen levels, obesity, and insulin resistance result in decreased production of sex hormone-binding globulin, which further exacerbates hyperandrogenism due to the increased amount of free active androgens. To assess hyperandrogenism, it is recommended to measure androgens such as: free testosterone, androstenedione, DHEA-S, and DHEA. Hyperandrogenemia contributes to the production of an increased number of ovarian follicles and promotes their developmental arrest in the follicular phase, resulting in a characteristic appearance of polycystic ovaries. A polycystic ovary contains two to three times more follicles than in healthy women. The polycystic ovary is characterized by stromal hypertrophy, occupying at least 25% of the ovarian medulla, with antral follicles located at the peripheral part of the ovary. Currently, the appearance of the ovaries is assessed using ultrasound.
A polycystic ovary is diagnosed when the ovarian volume is at least 10 cm^3 or when at least 12 follicles of 2-9mm in diameter are present in the ovary. The diagnosis of polycystic ovary syndrome requires the presence of at least 25 follicles and clinical symptoms. The diagnosis should be based on the clinical context, as similar morphology may be observed in ovaries during hypogonadotropic hypogonadism.[1]

2.2 Diagnosis of PCOS

The diagnosis of polycystic ovary syndrome in a woman is based on the presence of at least 2 out of 3 criteria:

1. Clinical/biochemical hyperandrogenism
2. Polycystic ovaries on ultrasound
3. Oligo/anovulation. [1]

There are 4 subtypes of PCOS.

- **Phenotype A**: characterized by oligomenorrhea/anovulation and polycystic ovaries.
- **Phenotype B**: characterized by hyperandrogenemia/hyperandrogenism and anovulation/oligomenorrhea.
- **Phenotype C**: characterized by hyperandrogenemia/hyperandrogenism and polycystic ovarian morphology.
- **Phenotype D:** characterized by oligomenorrhea/anovulation and polycystic ovarian morphology coexist without the presence of hyperandrogenemia/hyperandrogenism. [2]

Clinical symptoms of polycystic ovary syndrome include infrequent menstruation (oligomenorrhea), which occurs in about 70% of patients, while secondary amenorrhea is observed in about 20% of patients. The presence of eumenorrhea in patients does not indicate regular ovulation. It is believed that in 30% of patients with PCOS who have regular menstrual cycles, irregular ovulation occurs. PCOS with regular ovulations is present in 5-10% of patients. Infertility in PCOS is mainly caused by ovulation disorders. Statistically, 60 to 80% of women with PCOS suffer from moderate to severe hirsutism.

Stimulation of sebaceous glands by androgens results in oily hair, acne, and seborrheic changes. Alopecia occurs in 5-10% of women with PCOS. Insulin resistance in women with PCOS occurs in about 70% of overweight women and in 30% of women with normal body weight. PCOS increases the risk of endometrial cancer, cardiovascular diseases, and type 2 diabetes.
The main goals of PCOS treatment are: induction of ovulation, reduction of the risk of cardiovascular diseases, endometrial cancer, type 2 diabetes, infertility treatment, and reduction of hyperandrogenism severity. Important factors in PCOS treatment include lifestyle modification, proper nutrition, weight normalization, and regular physical exercise. Pharmacological treatment is conducted depending on the patient's reproductive plans and expectations regarding symptom relief.[1]

2.3 Pharmacological Treatment

In pharmacological treatment, the use of combined oral contraceptives results in alleviation of hyperandrogenism symptoms through the reduction of thecal cell stimulation and the direct anti-androgenic effect exerted by progestins. Additionally, menstrual cycle regulation is achieved, which reduces the risk of endometrial cancer and hyperplasia. Combined oral contraceptives also provide effective contraception. In cases where estrogen use is contraindicated, progestin therapy can be considered. Progestin therapy prevents endometrial hyperplasia but has minimal anti-androgenic effects. As an alternative to progestins to prevent endometrial hyperplasia, the use of a levonorgestrel-containing intrauterine device can be considered.
The use of metformin reduces insulin resistance. Between 30% and 50% of patients taking metformin regain regular menstrual cycles, which are ovulatory. Taking metformin increases the number of ovulations and pregnancies in women with PCOS. Additionally, it lowers androgen levels and hyperandrogenism. Furthermore, it prevents the development of type 2 diabetes, but there is no evidence regarding the impact of metformin on the endometrium.
Women who do not plan pregnancy may take anti-androgen medications in addition to contraception. The most commonly used medication is spironolactone. [1]

2.4 Infertility Treatment

The most commonly used medication for infertility treatment is clomiphene citrate. This medication induces ovulation. The advantages of this medication include: rare occurrence of side effects, low treatment cost, simple dosing regimen, and few contraindications. Ovulation is achieved in about 75-80% of patients. In the case of failure to induce ovulation with clomiphene citrate, a stimulation protocol with GnRH analogs and gonadotropins is used.[1]

2.5 Laparoscopic Treatment

Laparoscopic treatment is used when pharmacological ovulation induction is unsuccessful, when there is a need to assess the pelvic cavity, or when control is not possible with gonadotropin use. 50% of patients still require ovulation stimulation treatment.
If these methods are not effective, in vitro fertilization (IVF) can be used. Women with PCOS are at a higher risk of ovarian hyperstimulation syndrome and multiple pregnancies. [1]

3. Traditional methods of treating PCOS

3.1 Clomiphene Citrate

Clomiphene is a pharmacotherapeutic substance used to induce ovulation. It is a selective estrogen receptor modulator. The use of clomiphene citrate can result in a live birth rate of up to 40%.[3] Clomiphene citrate is the first-line drug for ovulation induction in women with PCOS. The action of clomiphene citrate involves blocking estrogen receptors in the hypothalamus, and through a negative feedback mechanism, it leads to an increase in the levels of endogenous gonadotropins, resulting in the development of a dominant follicle.[3] Indications for the use of clomiphene include the treatment of infertility in women caused by the absence of ovulation. Treatment typically begins on the 5th day of the cycle when regular menstrual bleeding occurs. In the absence of menstruation, treatment can begin on any day. There are two treatment regimens. The first involves administering 50 mg of clomiphene citrate daily for 5 days, followed by an evaluation of the ovaries. Ovulation should occur between days 11 and 15 of the cycle. The second regimen is used when the first regimen is ineffective. It involves administering 100 mg of the drug for 5 days starting on the 5th day of the next cycle. If ineffective, the second regimen can be repeated, and if ovulation does not occur, an additional 3-month treatment cycle may be conducted after a 3-month break. If this is still unsuccessful, further use of the drug is not recommended. Due to the risk of ovarian hyperstimulation, it is advised that the initial dose for women with PCOS be 25 mg. Clomiphene citrate should not be used in women diagnosed with ovarian cysts, hormone-dependent tumors, gonadal dysgenesis, thyroid or adrenal dysfunction, or primary pituitary insufficiency. Clinical studies have shown that the incidence of multiple pregnancies with clomiphene use was 7.9%. Moreover, it has been observed that the use of Clostilbegyt (a brand of clomiphene) increases the risk of ectopic pregnancy, and in patients with uterine fibroids, clomiphene use may cause the fibroids to enlarge.[4]

3.2 LOD (Laparoscopic Ovarian Drilling)

Between 2015 and 2018, a randomized study was conducted on women with PCOS. The study focused on the effectiveness of LOD. The study included women aged 18 to 39, with a BMI below 30, no contraindications for laparoscopy, who had undergone at least two unsuccessful in vitro fertilization (IVF) attempts, and whose partners had normal semen analysis results. Women with endocrinological diseases, diabetes, or previous ovarian surgeries were excluded from the study. At the beginning of the study, levels of FSH and LH in blood serum were measured, and the number of antral follicles was assessed. In the experimental group, LOD was performed using 40W bipolar energy applied to 4 to 6 sites on the ovary. Following this, women underwent ART therapy with GnRH antagonists after one month. In the control group, patients underwent ART therapy with GnRH antagonists without the LOD procedure. Both groups were given daily FSH at a dose of 150 IU starting on day 2 of the cycle. GnRH antagonist (0.25 mg daily) was administered when the mean diameter of the dominant follicle reached at least 13 mm. To trigger ovulation, hCG (10,000 IU) was administered when at least two dominant follicles, each with a diameter of at least 18 mm, were visible on ultrasound. Oocytes were retrieved 34-36 hours after hCG administration, followed by ICSI. In both groups, a maximum of two embryos at the blastocyst stage were transferred.

The primary outcomes were biochemical and clinical pregnancy. Pregnancy was confirmed by the presence of a fetal heartbeat at 6-7 weeks or a positive B-hCG test 14 days after ICSI. [5]

Results:

Initially, 70 women participated in the study, 16 were excluded, and 20 withdrew. The remaining 34 patients were randomly assigned to one of the two groups. No significant differences were found between the two groups regarding BMI, age, the number of antral follicles, FSH and LH levels, pregnancy rate, and the number of previous unsuccessful IVF cycles. The study showed no significant differences between the two groups in terms of the total dose of gonadotropins used, estradiol levels on the day of hCG administration, the number of antagonist ampoules used, stimulation duration, the number of high-quality embryos, or the total number of oocytes retrieved. No issues with the development of oocytes and embryos were observed in the study. In the experimental group, the ovarian hyperstimulation syndrome (OHSS) rate was significantly lower than in the control group. A spontaneous pregnancy was recorded in one case in the LOD group. No statistically significant differences were found regarding live births, clinical pregnancies, or miscarriages. The rates of pregnancy complications (preeclampsia, gestational diabetes, preterm birth, intrauterine growth restriction) were similar in both groups. LOD performed prior to IVF in PCOS patients who had undergone at least two unsuccessful IVF cycles did not improve pregnancy outcomes but reduced the OHSS rate. [5]

3.3 Metformin

Metformin is a chemical compound used in the treatment of type 2 diabetes, particularly in patients who cannot achieve appropriate blood glucose levels. Metformin can be used with insulin, other oral antidiabetic medications, or as monotherapy. Indications for the use of metformin also include impaired glucose tolerance and polycystic ovary syndrome (PCOS).[6] The action of metformin involves increasing tissue sensitivity to insulin. Furthermore, it stimulates the ovaries to secrete larger amounts of estrogen and SHBG (sex hormone-binding globulin) and reduces androgen production. Metformin may also help lower testosterone and insulin levels in women with PCOS.[7] A study was conducted to examine the impact of metformin, a low-carbohydrate, and high-protein diet on the menstrual cycle in girls with PCOS. The study included women whose menstrual cycle occurred no more than six times in the previous year or those who did not have a menstrual cycle during the previous year. Metformin was administered in doses of 1.5-2.55g per day along with a high-protein, low-carbohydrate diet. Follow-up visits took place every 8-10 weeks for six months. The results of the study showed that all women who participated achieved normal hemoglobin A1c levels and normal fasting glucose levels. Ten out of eleven women experienced regular menstrual cycles after using metformin. Of the regular cycles, 39% were also ovulatory with normal progesterone levels in the luteal phase. Nine women managed to lose weight. Additionally, there was an increase in estradiol and progesterone levels, while total cholesterol levels decreased.[8]

3.4 Spironolactone

Spironolactone is a medication that belongs to the group of mineralocorticoid receptor antagonists. It is registered for the treatment of hypertension and heart failure. The use of 100 mg of spironolactone for a period of 6 to 9 months leads to a reduction in hair loss, improves hirsutism, and decreases the severity of acne and seborrhea.[9] Using larger amounts of the drug may be associated with side effects, mainly irregular menstrual cycles. [10] The effects of treatment persist even after the treatment is completed. Spironolactone partially inhibits adrenal and ovarian steroidogenesis by blocking 5α-reductase and 17-hydroxysteroid dehydrogenase. Additionally, it increases SHBG levels and activates aromatase. The use of spironolactone is considered the most effective treatment for hirsutism, hair loss, and acne caused by elevated androgen levels. Spironolactone may also help prevent complications arising from inflammation associated with PCOS.[9] However, spironolactone is currently not approved for the treatment of acne. [10]

3.5 Inositol

Inositols belong to the B-vitamin group. There are nine stereoisomers of inositol. Inositols are synthesized in the body. The actions of inositol include increasing tissue sensitivity to insulin, influencing the regularity of the menstrual cycle, and alleviating symptoms of hyperandrogenism, both laboratory and clinical.[11] Treatment for women with PCOS aims to achieve a Myo-inositol/D-chiro-inositol ratio similar to those found in healthy women in follicular fluid and plasma.[12] Inositol is effective in the treatment of polycystic ovary syndrome (PCOS), and its use is considered safe. However, inositol is not currently considered standard therapy in guidelines due to insufficient evidence of its effectiveness. A randomized study with a placebo control group included 1,691 patients. Of these, 806 women took inositol, 311 received placebo, and 509 used metformin. Among the patients taking inositol, the likelihood of experiencing a regular menstrual cycle was 1.79 times higher than in the placebo group. The results for inositol and metformin were comparable. Inositol led to a greater reduction in free and total testosterone, BMI, glucose, insulin, and androstenedione levels compared to placebo. A significant increase in SHBG was observed in the inositol group compared to the placebo group.[11] Despite these findings, the evidence regarding the use of inositol remains inconclusive. Therefore, doctors should consider the lack of clear evidence supporting the effectiveness of inositol when deciding whether to use it in treatment.[13]

4. Alternative Treatment Methods for PCOS Based on Herbal Use

4.1 Curcumin

Curcumin is a biologically active compound found in turmeric.[14] It was discovered in 1815 from *Curcuma longa*. [15] Currently, it is considered a substance with potential use in women suffering from PCOS. For patients with PCOS. [14] Curcumin has shown supportive effects in lowering blood glucose levels, hyperandrogenism, and insulin resistance.[16] In a double-blind study, patients were randomly divided into two groups. One group took curcumin (500 mg three times a day) and was observed for twelve weeks. The placebo group was also monitored for twelve weeks. The study results included an analysis of sex hormone levels, fasting blood glucose (FPG), hirsutism, and fasting insulin levels (FI). Secondary outcomes were anthropometric measurements. The study involved 72 participants, and 67 completed it.[17]

In the curcumin group, a reduction in fasting blood glucose levels and DHEA levels was observed at the end of the treatment compared to the control and placebo groups. In the women treated with curcumin, an insignificant increase in estradiol levels was noted compared to the control group, without any adverse effects. Women with PCOS who experience hyperglycemia and elevated androgen levels may benefit from the use of curcumin. However, the results of the study should be further verified through additional research focusing on a wider range of doses and longer monitoring periods.[14]

4.2 Green Mint and Peppermint

Green mint and peppermint are among the most commonly studied species from the *Lamiaceae* family for the treatment of PCOS.[18] They have been evaluated for disorders such as dysmenorrhea, amenorrhea, and polycystic ovary syndrome (PCOS). These mints contain two main components: phenols and essential oils.[19] Studies have shown that green mint extract alleviates the symptoms of PCOS and affects the histological structure of the ovaries in models induced by letrozole and estradiol.[20] Peppermint oil, when used in rats with PCOS at doses of 150 and 300 mg/kg, reduced the number of atretic follicles, ovarian cysts, and lowered testosterone levels.[21] Peppermint tea (40g/L) alleviated ovarian fibrosis induced by letrozole and contributed to a decrease in estradiol levels.[20] Clinical studies have shown that drinking green mint tea (5 grams per 250 milliliters of water) twice a day for 30 days resulted in reduced total and free testosterone levels and increased FSH and LH levels. Green mint is considered a useful substance in the treatment of hyperandrogenism in women diagnosed with PCOS. *Mentha spicata* not only lowers total and free testosterone levels but also reduces the number of ovarian cysts.[22]

4.3 Pomegranate Juice

Pomegranate contains mostly polyphenols.[23] A parallel, randomized, triple-blind trial was conducted with 92 women suffering from polycystic ovary syndrome (PCOS). The participants were divided into three groups, each consisting of 23 women. Each group received two liters of pomegranate juice per week: pomegranate juice, symbiotic pomegranate juice (SPJ), or a symbiotic beverage (SB). The control group consisted of women who received two liters of placebo beverage per week. At the end of the study, 86 participants were examined. In the experimental groups, significant reductions in BMI, waist circumference, weight, and insulin resistance were observed. In the two groups of women consuming symbiotic pomegranate juice (SPJ) and the symbiotic beverage (SB), significant decreases in testosterone levels were noted. However, no significant differences were observed in FSH, LH, or FPG levels between any of the groups.[24]

4.4 Cinnamon

Cinnamon leaves and bark are used to create cinnamon oil. Cinnamaldehyde and polyphenols are the main active compounds. [25] Cinnamon has reproductive and metabolic benefits in the treatment of PCOS.[26] Cinnamaldehyde is believed to lower blood glucose levels by regulating the expression of the GLUT4 gene. It also protects pancreatic beta cells by enhancing the antioxidant response to reactive oxygen species produced during hyperglycemia.[27] In a study, increased insulin sensitivity was observed in women with PCOS who took cinnamon extract three times a day for eight weeks.[28] The improved insulin sensitivity and reduced insulin resistance occurred through enhanced glucose utilization and strengthening of the PI kinase signaling pathway. Based on clinical studies, it is suggested that women with PCOS who suffer from menstrual irregularities may take cinnamon as a supplement at a dose of 1500 mg/kg body weight for six months. This supplementation helps regulate menstrual cycles and contributes to lowering insulin resistance.[26]

4.5 Chinese Cinnamon

The main chemical components present in Chinese cinnamon include glycosides, terpenoids, and phenylpropanoids.[29] A randomized, placebo-controlled study was conducted lasting eight weeks. The study involved 15 overweight women who were dealing with amenorrhea or oligomenorrhea. The participants took 333 mg of Chinese cinnamon extract or placebo tablets three times a day for eight weeks. In the experimental group, increased insulin sensitivity was observed, but no differences were found between the two groups regarding testosterone, estradiol levels, or BMI.[30]

4.6 Berberine

Berberine is a compound extracted from Chinese herbs, such as *Coptis chinensis*. Its effects have been studied in an animal model using rats. PCOS was induced in the rats through an injection of testosterone propionate. The rats were divided into four groups: a model group, a high-dose berberine group, a low-dose berberine group, a control group, and a metformin group. The study assessed ovarian morphology, lipid profile, glucose metabolism, and hormone levels. mRNA sequencing of the ovaries was performed to evaluate the impact of berberine on ovulation. Biomarkers responsible for endometrial receptivity were studied in the endometrium using immunohistochemistry. In the model group, a decrease in corpora lutea and an increase in cystic follicles were observed. It is believed that high-dose berberine intervention could reverse these changes. Berberine contributed to a decrease in total cholesterol and LH levels in the serum of the PCOS rats. However, it did not affect fasting insulin levels or the HOMA-IR index but improved impaired glucose tolerance. mRNA sequencing of the ovaries was based on receptors *LHCGR* and *CYP19A1*. In the model group, the expression of mRNA in granulosa cells of *CYP19A1* and *LHCGR*, as well as protein expression in the ovaries, were reduced. After administering berberine, an increase in protein and mRNA expression in the ovaries was observed. The increased endometrial thickness and reduced protein expression of integrin αvβ3 and LPAR3 in the model group could be reversed by berberine treatment. The study indicated that berberine may have a positive effect on ovulation in PCOS by promoting increased expression of *CYP19A1* and *LHCGR*. Additionally, it may influence endometrial thickness through its effect on αvβ3 and LPAR3.[31]

5. Conclusion

Traditional methods of treating PCOS are still commonly used, and their application should depend on the individual needs of the patient and her symptoms

Clomiphene citrate is the first-line medication for ovulation stimulation. **LOD (laparoscopic ovarian drilling),** by damaging a portion of the ovary, reduces the number of cysts and increases the chance of ovulation. **Metformin** reduces insulin resistance by affecting glucose metabolism, which may support ovulation in women undergoing infertility treatment. **Spironolactone** inhibits steroidogenesis of both ovarian and adrenal origin. It is used to treat hair loss, hirsutism, and acne caused by hyperandrogenism. **Inositol** increases tissue sensitivity to insulin, influences cycle regularity, and alleviates symptoms of hyperandrogenism.

Research indicates that Alternative Treatment Methods for PCOS Based on Herbal Use may have a positive effect on alleviating the symptoms associated with this endocrinological disorder.

Despite the growing number of studies on the impact of using herbs on treating PCOS long-term, randomized, and controlled analyses are still needed to obtain more reliable results.

6. Discloure

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