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The current possible treatment approaches of Polycystic Ovary Syndrome (PCOS)

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Abstract:

Introduction

Polycystic ovary syndrome (PCOS), first described by Stein and Leventhal in 1935, is one of the most prevalent endocrine system conditions affecting women of reproductive age. It affects between 6% and 13% of women and the majority of cases are identified between the ages of 20 and 30. Unfortunately, the disease is usually diagnosed only when bothersome symptoms such as hair loss, alopecia, acne, and infertility-related problems occur. Based on the Rotterdam criteria, four phenotypes of PCOS are distinguished.

Aim of the study

This review aims to present the current state of knowledge about possible treatment approaches, both non-pharmacological and pharmacological.

Materials and methods

The paper was created based on the Pubmed database. The literature was reviewed using the keywords: ”PCOS”, ”PCOS treatment” and “ PCOS medications “.

The current state of knowledge

Treatments for PCOS must be tailored to the specific needs of each patient. In the management of PCOS, special attention is paid to diet, physical activity, and restoration of the Gut Microbiome. Medications used in therapy are oral contraceptives and anti-androgens, insulin sensitizers, ovulation inducers, calcium and vitamin D supplements, statins, Glucagon-like-peptide-1 (GLP-1) agonists, inositols and interleukin 22 (IL-22) therapy.

Summary

Treatment options for menstrual irregularities and hirsutism are based on the clinical goals and preferences of the patient. The ideal would be causal treatment, but due to the ongoing lack of full understanding of the pathogenesis of the syndrome, is not entirely feasible. The ideal would be causal treatment, but due to the ongoing lack of full understanding of the pathogenesis of the syndrome, is not entirely feasible. The most important is a multimodal approach to treat comorbid conditions such as diabetes mellitus type 2, obesity, hyperlipidemia, depression, and infertility.

Keywords: PCOS; PCOS treatment; PCOS medications

Introduction

Polycystic ovary syndrome (PCOS), also known as hyperandrogenic anovulation (HA) or Stein–Leventhal syndrome is one of the most prevalent endocrine system conditions affecting women of reproductive age [1]. First described in 1935 by Stein and Leventhal

remains a diagnostic and therapeutic challenge for doctors to this day [2]. The prevalence of PCOS varies between 6% and 13% based on which diagnostic criteria are used: the National Institutes of Health, Rotterdam, or Androgen Excess-PCOS Society [3]. The World Health Organization (WHO) estimates that in 2012 PCOS affected 116 million women (3.4%) globally [4]. The most widely accepted criteria to diagnose PCOS is the Rotterdam criteria, which identify 4 phenotypes. Phenotype A is the most classic and it is characterized by hyperandrogenism and abnormal uterine bleeding with polycystic ovarian morphology on ultrasonography. Phenotype B does not have abnormal ovaries on ultrasonography, but it has other features from phenotype A. The “ovulatory phenotype” or phenotype C has features of

hyperandrogenism and polycystic ovarian morphology. The nonhyperandrogenic phenotype" or phenotype D has abnormal uterine bleeding and polycystic ovarian morphology [5]. The presentation of the different phenotypes is shown in Table 1.

Table 1. PCOS phenotypes.

Phenotype	Clinical Presentation		
	Androgen excess (a)	Ovulatory dysfunction	Polycystic ovarian morphology (b)
A	+	+	+
B	+	+	
C	+		+
D		+	+

(a) Androgen excess can be diagnosed by:

1. Calculated free testosterone or free androgen index OR.
2. Calculated bioavailable testosterone OR.
3. Consider androstenedione or DHEAS if testosterone is normal and high index of suspicion for hyperandrogenism

(b) Ultrasound criteria: Ultrasonography should be transvaginal and use high resolution. Follicle count per ovary should be greater than or equal to 25 (2–9 mm) or ovarian volume greater than or equal to 10 mL.

PCOS is usually only diagnosed when complications develop that significantly reduce a patient's quality of life (e.g., hair loss, alopecia, acne, and infertility-related problems) [6]. It can occur at any age, beginning with menarche, the majority of instances are identified between the ages of 20 and 30 [7]. While the exact cause of this multifactorial disorder is unknown, a combination of inherited and environmental factors is thought to play a primary role [8]. The pathophysiology of this condition is influenced by alterations in steroidogenesis, ovarian folliculogenesis, neuroendocrine function, metabolism, insulin production, insulin sensitivity, adipose cell activity, inflammatory factors, and sympathetic nerve function [9]. Barrea et al. point out 4 key contributors to pathophysiological alterations in PCOS and these

are the high consumption of carbohydrates, hyperinsulinemia, hyperandrogenemia, and persistent low-grade inflammation [10].

This review summarizes the possible treatment approaches, both non-pharmacological interventions and pharmacological treatment options.

Diet

Numerous factors like imbalanced dietary patterns, poor lifestyle activities, improper care and medication, late diagnosis, and ignorance are involved in the prevalence of this disease in women. Hence, an early diagnosis and improved dietary and lifestyle management may improve the life quality and timely recovery of the patient from this disease. It has been recommended that a balanced diet with 40% energy from carbohydrates, 30% from fats, and 30% from protein with optimum physical activity could reduce severe PCOS symptoms and improve metabolic balance [11].

Restoration of the Gut Microbiome

Giampaolino et al. point out that dysbiosis of gut microbiota may be a potential driver in the development of PCOS symptoms. The novel management strategies for this disorder are probiotics (living microorganisms), prebiotics (sources of food for beneficial gut bacteria), synbiotics, and more recent therapies including Fecal Microbiota Transplantation (FMT) [12]. Probiotic supplements have been demonstrated to improve the metabolic profile of PCOS [13, 14, 15]. In the study by Ahmadi et al., it was shown that the supplementation of probiotics (L. acidophilus, L. casei, and B. bifidum) for 12 weeks led to a statistically significant reduction in weight and body mass index (BMI) in PCOS patients compared to the placebo, with positive effects on glycemia, triglycerides, and cholesterol [13]. Furthermore, many studies point out that probiotic supplementation plays a significant role in the regulation of hormonal and inflammatory indicators. There was a significant reduction of the free androgen index (FAI) and malondialdehyde (MDA) observed and an increase in SHBG and nitric oxide (NO). In addition, probiotics have a positive influence on improvement in the weight, BMI, insulin, HOMA-IR, TGs, VLDL-cholesterol, hirsutism, and total testosterone of PCOS patients [16, 17, 18]. Prebiotics by stimulation of the growth of Bifidobacterium and Lactobacillus, have similar positive effects on metabolic markers [19]. According to Gholizadeh Shamasbi et al., the regular supplementation of prebiotics can help with the reduction of hyperandrogenism as well as menstrual cycle abnormalities in PCOS women [20]. The effect of FMT on the treatment of PCOS has only been studied in vivo. In Quaranta et al. study, PCOS rat models

treated with FMTs had improved menstrual cycles and decreased androgen biosynthesis as compared to the untreated group [21]. Positive results of many researchers should motivate the development of this method of treating PCOS in the future.

Oral contraceptives and anti-androgens

Anti-androgens and combined oral contraceptive pills (COCPs) may mitigate hyperandrogenism-related symptoms of polycystic ovary syndrome (PCOS) [22]. Anti-androgen medications such as spironolactone, flutamide, finasteride, and cyproterone acetate (CPA) have been used to decrease hyperandrogenism-related symptoms. Anti-androgen medications act in one of three ways; either by competitively inhibiting the androgen-binding receptors; decreasing androgen production (although the manner in which this occurs is not well understood); or inhibiting 5-α-reductase in the skin, which is an enzyme that converts testosterone into its active form, 5-α-dihydrotestosterone (DHT) [23]. Through these mechanisms, anti-androgen medications could eliminate the hyperandrogenic state of PCOS and improve the various hyperandrogenism-related symptoms associated with the condition.

A study by Forslund M et al., proved that ethinyl estradiol (EE)/cyproterone acetate (CPA) was better in reducing hirsutism as well as biochemical hyperandrogenism (testosterone [MD 0.38 nmol/L {95% CI 0.33-0.43}]) and BMI (MD 0.62 kg/m2 [95% CI 0.05-1.20]) compared with conventional COCPs. There was no difference in hirsutism between high and low EE doses [24].

While in the Zhe Tang et al. study, oral contraceptives performed exceptionally well in improving menstruation (Emax: 149%; T50: 7.44 weeks), hirsutism score (Emax: 66.2%; T50: 26.2 weeks), and FAI (Emax: 75.7%; T50: 0.51 weeks). Antiandrogens were less potent in reducing hirsutism scores (Emax: 40.2% versus 66.2%) and FAI (Emax: 34.5% versus 75.7%) compared to oral contraceptives [25].

Insulin sensitizers

Among all of the insulin sensitizers, metformin is the most widely used in PCOS, due to its efficacy and safety. It is indicated in combination with combined oral contraceptive pills (COCs), especially for overweight or obese patients, or when COCs are contraindicated [26]. However, the beneficial effects of metformin are increasingly evident, especially when combined with lifestyle modifications, improving the pathogenetic mechanisms underlying PCOS, restoring ovarian function, and improving metabolic profile, especially insulin sensitivity and, unlike COCs, lipoprotein pattern [27]. Recent studies have shown that

metformin can improve the inflammatory state both indirectly by improving metabolic parameters, and directly through its anti-inflammatory effect. This mechanism can regulate T-cell balance as reported in mice, where metformin reduces CD4 +/IL-17 + (TH17) and increases CD4 +/Foxp3 + (TREG) [28]. In addition, metformin performs its beneficial anti-inflammatory and health-promoting actions by influencing other structures, such as mitochondrial function, modulation of immunity through mechanisms not yet fully understood, and independently of its role in glycemic control. Another often-forgotten aspect concerns depression and other psychiatric disorders, which affect PCOS patients. Metformin has been demonstrated to improve several mental health disorders, indirectly through the improvement of some hormonal and metabolic aspects [29].

Obesity significantly affects both natural and assisted conception, as well as the possibility of a healthy pregnancy. Metformin appears to have direct effects on ovarian function in addition to inhibiting the production of hepatic glucose and improving cellular insulin sensitivity. Therefore, it makes sense to think that medications like metformin that lower insulin and make the body more sensitive to insulin would help with the symptoms and the results of pregnancy for PCOS women [30].

Ovulation inducers

Polycystic ovary syndrome (PCOS) is characterized by menstrual irregularities, high androgen levels, and ovarian cysts. Clomiphene citrate (Clomid) and letrozole have both been investigated as ovulation induction therapies for PCOS. A total of 100 women diagnosed with PCOS and infertility participated in the study, which took place from March 2021 to July 2022 at the Maternity and Children Teaching Hospital in Adiwaniyah Province, Iraq. Participants were randomly assigned to one of two groups (each with 50 women): the first group received clomiphene citrate in a stair step pattern (single dose of 50 mg, 100 mg, and 150 mg) for five days, for a maximum of three cycles; the second group received letrozole in a stair step pattern (single dose of 2.5, 5, and 7.5 mg) for five days, for a maximum of three cycles. Follicle size was monitored using ultrasound to achieve a follicle size >18 mm. The ovulation rate was higher in the letrozole group (86.0%) compared to the clomiphene citrate group (72.0%), although the difference was not statistically significant (p=0.086). The pregnancy rate was slightly higher in the letrozole group (22.0% vs 18.0%), but also not statistically significant (p=0.617). However, the mean time from menstruation to ovulation was significantly shorter in the letrozole group (17.20±1.32 days) compared to the

clomiphene citrate group (24.08 ± 1.56 days, p<0.001). There were no significant differences in common side effects between the two groups [31].

In a Zhuo Liu et al. study, pooled analysis indicated that letrozole treatment prevailed against clomiphene citrate in ovulation rate (RR 1.14, 95% CI 1.06-1.21, P <.001), clinical pregnancy rate (RR 1.48, 95% CI 1.34-1.63, P <.001), and live-birth rate (RR 1.49, 95% CI 1.27-1.74, P <.001) [32].

Calcium and vitamin D supplements

Vitamin D plays a role in ovarian follicular development and luteinization, via altering AMH signaling, FSH sensitivity, and progesterone production in human granulosa cells. It also has a positive impact on glucose homeostasis and hyperinsulinemia is one of the potential pathogenetic factors of PCOS [33]. Low 25(OH)D levels may aggravate PCOS symptoms, such as insulin resistance, ovulatory and menstrual irregularities, infertility, hyperandrogenism, and obesity. Shojaeian et al. study revealed that calcium and vitamin D supplementation reduces menstrual disturbances and improves metabolic factors in PCOS over a long-term period [34].

Statins

Dyslipidemia is one of the comorbid conditions that women with PCOS are suffering from. High levels of triglycerides and LDL-cholesterol and low HDL-cholesterol levels are significant predictors of cardiovascular risk [35]. Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, that help improve the lipid profile and subsequently reduce cardiovascular disease morbidity. Moreover, they are useful in PCOS treatment, because they lower sex steroid production, reduce dyslipidemia, reduce inflammation, and lower ovarian androgen production by preventing thecal cells from producing androgen [36]. Sathyapalan et al. reported that the women who were taking atorvastatin had considerably lower levels of androstenedione and dehydroepiandrosterone sulfate (DHEAS) [37]. Furthermore, in another study, a 12-week course of atorvastatin significantly increased the levels of serum vitamin D (25OH-D) in PCOS women [38]. Miao et al. meta-analysis revealed that statins induce a significant decrease in metabolic parameters such as total testosterone, free testosterone, androstenedione, DHEAS, LH, the LH-to-FSH ratio, and prolactin [39].

Glukagon-like-peptide 1 (GLP-1) agonists

Among incretin mimetics, glucagon-like peptide-1 receptor agonists (GLP-1 RA) offer a great opportunity to simultaneously treat different conditions of PCOS, improving body weight, insulin resistance, and cardiovascular risk. In the last years, several studies demonstrated the safety and efficacy of exenatide and liraglutide use, alone or in combination with metformin, in PCOS women [40]. The combination of GLP-1 RA and metformin seems to be superior to each single agent alone, for improving not only BMI, central adiposity, and insulin resistance, but also menstrual cycles and hyperandrogenism, especially in obese PCOS patients [41, 42]. GLP-1 receptor agonists cause insulin release in a glucose-dependent manner, yielding clinical benefits such as heightened satiety, reduced appetite, and appetite regulation. GLP-1RAs have demonstrated efficacy in reducing glycated hemoglobin levels and promoting weight loss while ameliorating hyperlipidemia [43].

Inositol

Inositol acts as a second messenger with insulin-like functions and is safe and well-tolerated [44]. The two most common isomers of inositol are MI, which has been shown to significantly improve ovulatory function, and DCI, which is able to reduce peripheral insulin resistance in patients with PCOS [45, 46]. Some studies have proposed that a combination of both MI and DCI, at a plasma ratio of 40:1, can restore normal hormonal function quicker than MI or DCI alone [47]. No side effects have been described in clinical studies examining the effect of inositol [48, 49]. Several studies have confirmed the role of MYO and DCI as insulin sensitizers, improving both metabolic and oxidative imbalance [50]. In addition, in the ovary, MYO also acts as a second messenger of FSH signaling: its supplementation can restore regular menses and ovulation, improve oocyte and embryo quality, and reduce the amount of recombinant FSH administered during ovarian stimulation protocols. On the contrary, the supplementation of DCI alone may worsen insulin-mediated androgen synthesis and fertility in PCOS women [51].

Interleukin (IL-22) therapy

IL-22 is a cytokine produced by intestinal immune cells and exerts an important role in eliciting antimicrobial immunity and maintaining mucosal barrier integrity within the intestine [52]. De Leo et al. point out a variety of metabolic benefits, as it improves insulin sensitivity, preserves the gut mucosal barrier and endocrine functions, decreases endotoxemia and chronic inflammation, and regulates lipid metabolism in the liver and adipose tissues [53]. A

Qi et al. study reported reduced levels of IL-22 in the serum and follicular fluid of PCOS patients [54]. Clinical trials have shown that the administration of exogenous IL-22 could provide therapeutic benefits in PCOS treatment, among others IL-22 could reverse insulin resistance, aberrant ovarian morphology, and decrease the embryo number.

Conclusions

Treatment options for menstrual irregularities and hirsutism are based on the clinical goals and preferences of the patient. The ideal would be causal treatment, but due to the ongoing lack of full understanding of the pathogenesis of the syndrome, is not entirely feasible. The ideal would be causal treatment, but due to the ongoing lack of full understanding of the pathogenesis of the syndrome, is not entirely feasible. The most important is a multimodal approach to treat comorbid conditions such as diabetes mellitus type 2, obesity, hyperlipidemia, depression, and infertility.

Author contributions

Conceptualization: LJ, KJ, LL; methodology: LJ, LŁ, KK, NM; software: LŁ, KJ, KS, NM; check: LŁ, LJ, KK, LL, KK; formal analysis: KI, KK, LL, KK; investigation: KI, KM, NM, KS; resources: KI,; data storage: L£, LJ, KI; writing - rough preparation: LŁ, LJ, KM, KI; writing - review and editing: KI, LŁ; visualization: LJ, KK, KJ, NM, KS; supervision: LJ; project administration: LJ ; All authors have read and agreed with the published version of the manuscript.

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