POLYCYSTIC OVARY SYNDROME: PATHOPHYSIOLOGY, PRESENTATION AND TREATMENT A MINI-REVIEW ARTICLE

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SINDROM POLICISTIČNIH JAJNIKA: PATOFIZIOLOGIJA, PREZENTACIJA I LEČENJE MINI REVIJSKI PRIKAZ

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common heterogeneous disorder which is known as syndrome. The term 'syndrome' refers to a collection of clinical features or a phenotype. The specific features of the PCOS phenotype include clinical signs of androgen excess, elevated serum androgen concentrations, irregular menses, and infertility. It is common heterogeneous disorder which affects women with different clinical presentations. In the basis of this disease is hormonal imbalance, such as insulin resistance and hyperinsulinemia. This review was based on searching all the available literature in the next databases: Pubmed, ClinicalTrials, Embase, Medline Complete, Web of Science, Cochrane Library, the Chinese Science and Technology Periodical Database (VIP), WanFang Database (Chinese Ministry of Science & Technology). The search terms included hormonal and metabolic aspects, therapy of PCOS, polycystic ovary syndrome, PCOS. We included only randomized clinical intervention trials in young women published in last five years and included 12 articles in our review analysis. More research is needed to clarify the complex pathophysiology of PCOS. No single test is currently available for its diagnosis. Additionally, once diagnosis is established, the options for treatment are of limited number and effectiveness because they target only the symptoms of PCOS. Finally, patients with PCOS have higher rates of metabolic complications, such as cardiovascular disease, but their impact on mortality is not clear. Therefore, more prospective epidemiologic studies on the topic are necessary.

Keywords: women, diagnosis, hyperandrogenism, polycystic ovary syndrome, treatment.

SAŽETAK

Sindrom policističnih jajnika (SPJ) je čest heterogeni poremećaj koji je poznat kao sindrom. Termin „sindrom“ odnosi se na kolekciju kliničkih karakteristika ili fenotipa. Specifične osobine fenotipa SPJ uključuju kliničke znake viška androgena, povišene koncentracije androgena u serumu, neredovne menstruacije i neplodnost. Čest je heterogeni poremećaj koji pogađa žene sa različitim kliničkim prikazima. U osnovi ove bolesti je hormonska neravnoteža, poput insulinske rezistencije i hiperinsulinemije. Ovaj pregledni rad zasnovan je na pretraživanju sve dostupne literature u sledećim bazama podataka: Pubmed, ClinicalTrials, Embase, Medline Complete, Web of Science, Cochrane Library, kineska naučna i tehnološka baza podataka (VIP), WanFang baza (Chinese Ministry of Science & Technology). Pojmovi za pretragu su uključivali hormonalne i metaboličke aspekte, terapiju SPJ-a, sindrom policističnih jajnika, SPJ-a. Uključili smo samo randomizirana ispitivanja kliničkih intervencija kod mladih žena objavljenih u poslednjih pet godina i 12 članaka u uključeno u završni pregled. Potrebno je više istraživanja kako bi se razjasnila složena patofiziologija SPJ. Trenutno nije dostupan nijedan test za brzu i tačnu dijagnozu. Pored toga, nakon uspostavljanja dijagnoze, mogućnosti lečenja su ograničene i i slabo efikasne jer ciljaju samo simptome SPJ-a. Na kraju, pacijenti sa SPJ-a imaju veći rizik od metaboličkih komplikacija, poput kardiovaskularnih bolesti, ali njihov uticaj na smrtnost nije jasan. Stoga su neophodne prospektivne epidemiološke studije na tu temu koje bi razjasnile ovu problematiku.

Ključne reči: žene, dijagnoza, hiperandrogenizam, sindrom policističnih jajnika, lečenje.

BACKGROUND

Polycystic ovary syndrome (PCOS) is a common heterogeneous disorder which is known as syndrome. The term 'syndrome' refers to a collection of clinical features or a phenotype (1, 2). The specific features of the PCOS phenotype include clinical signs of androgen excess, elevated serum androgen concentrations, irregular menses, and infertility. It is common heterogeneous disorder which affects women with different clinical presentations. In the basis of this disease is hormonal imbalance, such as insulin resistance and hyperinsulinemia. Thus, PCOS adversely affects endocrine, metabolic, and cardiovascular health. More than 80% of women presenting with symptoms of androgen excess have PCOS (1, 2). Also, over 90% of normally menstruating women with hirsutism are identified with polycystic ovaries. Prevalence estimates for PCOS, as defined by the NIH/NICHD criteria, indicate that PCOS is a common endocrinopathy affecting 4%–8% of women of reproductive age (1, 2).

This review was based on searching all the available literature in the next databases: Pubmed, ClinicalTrials, Embase, Medline Complete, Web of Science, Cochrane Library, the Chinese Science and Technology Periodical Database (VIP), WanFang Database (Chinese Ministry of Science & Technology). The search terms included hormonal and metabolic aspects, therapy of PCOS, polycystic ovary syndrome, PCOS.

Pathophysiology and clinical presentation of PCOS

PCOS is the most common endocrinopathy among reproductive-aged women in the United States, affecting approximately 7% of female patients (3, 4). Although its exact etiology is unclear, PCOS is currently thought to emerge from a complex interaction of genetic and environmental traits. Evidence from one twin-family study indicates that there is a strong correlation between familial factors and the presence of PCOS (3, 4).

The female hypothalamic–pituitary–ovarian (HPO) axis is a meticulously synchronized and tightly regulated network ultimately responsible for reproductive competence and survival of the species. The HPO axis responds to internal signals (i.e., hormonal and neuronal) and external factors (i.e., environment influences). Beginning during gestation, these factors impact future generations through epigenetic factors affecting the brain and the developing germ cells (5–7).

Polycystic ovary syndrome (PCOS), a disorder primarily characterized by signs and symptoms of androgen excess and ovulatory dysfunction, disrupts HPO axis function (8–11).

The pathogenesis of PCOS has been linked to altered luteinizing hormone (LH) action, insulin resistance, and a possible predisposition to hyperandrogenism. One theory maintains that underlying insulin resistance exacerbates hyperandrogenism by suppressing synthesis of sex hormone-binding globulin and increasing adrenal and ovarian synthesis of androgens, thereby increasing androgen levels. These

androgens then lead to irregular menses and physical manifestations of hyperandrogenism (9, 12–15).

The primary pathophysiologic defect in PCOS remains unknown. Key features of the syndrome include altered gonadotropin secretion, hyperandrogenism, and insulin resistance. Women with PCOS have an increased pulse frequency of the gonadotropin luteinizing hormone (LH) (11–15). It is uncertain whether increased LH release is due to an inherent defect in the pulsatile release of gonadotropin-releasing hormone (Gn-RH) from the hypothalamus or to low levels of circulating progesterone, as lower levels of progesterone may be associated with accelerated Gn-RH pulsatility. Regardless of the source, increased pulsatility of Gn-RH favors the production of LH over follicle-stimulating hormone (FSH) and results in relatively higher circulating levels of LH. The effect of higher concentrations of LH is increased production of androgens by ovarian theca cells (15, 16).

The most common androgen-related symptoms associated with PCOS are acne, hirsutism, and alopecia. The symptoms vary for each patient; some patients present with only one or two symptoms, while a few patients complain of all three (17).

Diagnostic criteria of PCOS

Diagnosis of PCOS was based on defined criteria and exclusion criteria (Table 1) (18, 19). Each issuing group considers PCOS a diagnosis of exclusion, and other diagnoses, such as congenital adrenal hyperplasia, non-classic adrenal hyperplasia, Cushing syndrome, androgen-secreting tumor, idiopathic hyperandrogenism, idiopathic hirsutism, hyperprolactinemia, and thyroid disorders must be excluded.

Diagnosis can generally be accomplished with a careful history, physical examination, and basic laboratory testing, without the need for ultrasonography or other imaging. Hyperandrogenism can be diagnosed clinically by the presence of excessive acne, androgenic alopecia, or hirsutism (terminal hair in a male-pattern distribution); or chemically, by elevated serum levels of total, bioavailable, or free testosterone or dehydroepiandrosterone sulfate. Measurement of androgen levels is helpful in the rare occasion that an androgen-secreting tumor is suspected (e.g., when a patient has marked virilization or rapid onset of symptoms associated with PCOS) (18–22).

Ovulatory dysfunction refers to oligomenorrhea (cycles more than 35 days apart but less than six months apart) or amenorrhea (absence of menstruation for six to 12 months after a cyclic pattern has been established).

The inclusion of ultrasound morphology of the ovaries as a further potential criterion to define PCOS was proposed by the Rotterdam consensus conference (18), which established that at least two of the following criteria – oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries (PCO) at ultrasound – are sufficient for the diagnosis (18, 19).

Table 1. Defined criteria for the diagnosis of PCOS (18, 19)

European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) criteria	National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD)	Androgen Excess Society
Present two criteria: Clinical and/or biochemical hyperandrogenism Polycystic ovaries Oligo-ovulation or anovulation	Includes all the next criteria: Clinical and/or biochemical hyperandrogenism Menstrual dysfunction	Includes all the next criteria: Clinical and/or biochemical hyperandrogenism Ovarian dysfunction and/or polycystic ovaries

Extraovarian factors for PCOS

The factors causing PCOS are multiple. Genetic, or lifestyle mistakes, and their combinations can cause PCOS (23, 24). Thyroid dysfunction, hyperprolactinemia, androgen-secreting tumors, Cushing's syndrome (a syndrome associated with excess cortisol levels), and congenital adrenal hyperplasia can drive PCOS. Chemical exposure has been held responsible for the development of PCOS. The exposure to a number of chemicals, by accidental (pesticide, vehicle exhausts, industrial pollutants etc.) or deliberate (cosmetics, household cleaning agents, chemotherapeutics etc.), means are common in current times. Personal care products such as perfume, sunscreen, deodorant, hair dye etc., which have become the quintessential grooming ingredients, are a major culprit for the rising instances of PCOS (23, 24). A majority of consumers are unaware of the fact that these innocuous-seeming hygiene substances are endocrine disruptors. These chemical products contain phthalates, parabens, isopropanol, glutaraldehyde, benzophenones, oil of turpentine, metals (nickel sulfate, cobalt chloride), benzophenones etc. Chemicals such as bisphenol A (BPA), present in packaged and canned foods, which when exposed to for a long period, can lead to reproductive issues, including PCOS (25-28).

Intraovarian factors for PCOS

The main intraovarian reason for PCOS is caused by hormonal disbalance (29). It is known that the ovary remains sensitive to the effects of insulin, as it is immune to insulin resistance. This is known as the DCI paradox (30). Hyperinsulinemia alters the FSH to luteinizing hormone (LH) shift, preventing the selection of a dominant follicle. Insulin increases granulosa cell sensitivity to LH, thus increasing ovarian androgen production as well (31). This is mediated by a stimulation of cytochrome P450c17 α . Ovarian theca cells in women with PCOS are also more efficient at testosterone production. High-insulin levels impede ovulation, too, probably through the inositol pathway (32, 33).

Potential preventive and therapeutic strategies in women with diagnosed PCOS

In Table 2 are presented the most common pharmacological treatments in clinical practice. PCOS treatment focuses

on managing of patients individual concerns, such as infertility, hirsutism, acne or obesity (34). Specific treatment might involve lifestyle changes or medication. Well, non-pharmacological treatment is based on Lifestyle modification as a critical to prevent or delay serious health consequences associated with PCOS, and it should be initiated in all overweight women with the syndrome. In overweight women, the symptoms and overall risk of developing long-term health problems from PCOS can be greatly improved by losing excess weight. Weight loss of just 5% can lead to a significant improvement in PCOS (34, 35).

Pharmacological treatments are based on various options (37-40). Typically, oral contraceptive pills (OCPs) are first-line for pharmacologic management of hirsutism in premenopausal women (36). Women often use laser hair removal and other mechanical hair removal options because pharmacologic treatments do not produce the results they desire. It generally takes at least 6 months of treatment to see a response due to the growth cycle of hair (37). Antiandrogens can be added if there has been no improvement after 6 months of treatment. OCPs and antiandrogens have both been effective in the treatment of acne (38). In severe acne, isotretinoin may offer benefits for some patients. There is limited data for treatment of alopecia, but OCPs and androgen blockers are used (37-40). The research world demands a rationale for the necessary justification to carry out any scientific study, and the therapeutic rationale underlying the use of inositols in PCOS derives from their activities as insulin sensitizing molecules and their beneficial effects on metabolism.

Previous studies had highlighted the pivotal role of MI administration for enhancing the success of in vitro human fertilization (IVF) (41, 42).

Various authors have studied the effect of DCI on endocrine, metabolic, and reproductive parameters in PCOS (39-43). Administration of 600 mg DCI/day for 6-8 weeks to lean women with PCOS (BMI 20.0–24.4 kg/m²) reduces insulin and free testosterone levels, while decreasing systolic blood pressure, diastolic blood pressure, and serum triglycerides. A higher rate of ovulation is noted with DCI, though the difference is not statistically significant. In a randomized controlled trial conducted in fifty obese PCOS women, a

combination of 550 mg MI and 13.6 mg DCI, in capsule formulation, was found better than 2 g powdered MI, at improving metabolic, endocrine, and ovulation parameters, when administered twice daily over 6 months (39-43). Another study showed a significant improvement in insulin sensitivity as well as lipid profile in such patients.

A recent meta-analysis (39-43) evaluated the efficacy of treatments with MI, alone or combined with DCI (40 : 1 ratio of MI : DCI) for 12–24 weeks, in nine RCTs comprising 247 cases and 249 controls (44).

Table 2. Pharmacological options for PCOS (44)

Drug	Characteristics of treatment		
	The effects	Dosage regime	Adverse effects
Oral contraceptives	Androgen excess, contraception, regulation cycle, protection of endometrium	1 tbl per day	Breast tenderness, weight gain, fluid retention, increased risk of thromboembolism
Clomiphene	Ovulation stimulation	50-150 mg	Hot flashes, nausea, headaches, blurred vision, multiple gestation
Gonadotropins	Ovulation stimulation	Dosage and duration dependent on product and patient's response	Abdominal pain, nausea, breast tenderness, injection site reaction, multiple pregnancy, ovarian hyperstimulation
Metformin	Hyperinsulinemia, anovulation, androgen excess	500 mg- 850 mg	Nausea and vomiting, diarrhea, anorexia, metallic taste, lactic acidosis
Spironolactone	Hirsutism, acne	100-200 mg/day	Intermenstrual bleeding, hyperkalemia, hypotension
Pioglitazone/Rosiglitazone	Hyperinsulinemia, anovulation, androgen excess	30 -45 mg/day	Weight gain, edema, increased LDL cholesterol with rosiglitazone

Analysis of Literature Data

Our initial search identified and screened 2023 articles. We excluded 1600 articles based on the title and abstract and retrieved 423 articles for more detailed evaluation. We included only randomized clinical intervention trials in young women published in last five years and included 12 articles in our review analysis. All studies were reviewed by all

authors independently, and the which did not fit the eligibility criteria were excluded. The search results are presented in Table 3. From all studies we observed duration of follow-up, sample size, types of pharmacological and non-pharmacological treatment and final results of investigation (Table 3).

Table 3. The characteristics of the included studies (45-56)

Clinical trials	Sample size	Duration of treatment	Pharmacological treatment of PCOS	Non-Pharmacological treatment of PCOS	Significant results
<i>Jamilian M et al., 2018 (45)</i>	60 women	6 weeks	None	Probiotic, Selenium	Reduced hs-CRP (β - 0.58 mg/L; 95% CI, - 0.97, - 0.19; P = 0.004)
<i>Dastorani M et al., 2018 (46)</i>	40 women	12 weeks	None	Vitamin D	Decreased TCHOL and LDL (p=0.04)
<i>Kazemi M et al., 2018 (47)</i>	95 women	16 weeks		Low-glycemic index pulse-based diet	Decreased TC/HDL-C (p = 0.02)

Clinical trials	Sample size	Duration of treatment	Pharmacological treatment of PCOS	Non-Pharmacological treatment of PCOS	Significant results
<i>Arentz S et al., 2017 (48)</i>	122 women	3 months	None	Cinnamomum verum, Glycyrrhiza glabra, Hypericum perforatum and Paeonia lactiflora.	Decreased insulin levels, BMI and LH ($p < 0.05$)
<i>Borzoei A et al., 2018 (49)</i>	84 women	8 weeks	None	Cinnamon	Serum triglyceride and body mass index significantly decreased ($p = 0.001$; $p = 0.002$)
<i>Pedersen AJT et al., 2018 (50)</i>	40 women	12 months	Metformin; oral contraceptive pills (150 µg desogestrel + 30 µg ethinylestradiol)	None	Reduced weight (median weight change -2.4 kg, 25th-75th percentile -5.2 to 0.3 kg, $p < 0.001$) and increased triglycerides (0.2 mmol/L (0.0-0.6 mmol/L), $p < 0.01$) without significant changes in other lipid parameters or insulin sensitivity
<i>Nordio M et al., 2019 (51)</i>	56 women	3 months	None	myo-inositol (MI) and D-chiro-inositol (DCI)	Restoring ovulation
<i>Ostadmohammadi V et al., 2019 (52)</i>	60 women	12 weeks	None	50,000 IU vitamin plus 8×10^9 CFU/day probiotic	Reduction in total testosterone (β - 0.19 ng/mL; 95% CI, - 0.28, - 0.10; $P < 0.001$), hirsutism (β - 0.95; 95% CI, - 1.39, - 0.51; $P < 0.001$), high-sensitivity C-reactive protein (hs-CRP)
<i>Javed Z et al., 2019 (53)</i>	40 women	3 months	None	Vitamin D	Reduced: ALT ($p = 0.042$), HOMA-IR
<i>Wang QY et al., 2016 (54)</i>	99 women	6 months	oral contraceptives with drospirenone or cyproterone acetate	None	Blood pressure, Fasting glucose, fasting insulin, and homeostasis model assessment-insulin resistance decreased significantly
<i>Jensterle M et al., 2017 (55)</i>	30 women	12 weeks	Liraglutide 3 mg, Metformin	None	BMI and waist circumference reduction, OGTT glucose levels
<i>Liang R et al., 2019 (56)</i>	100 women	6 months	None	Heyan Kuntai (6 kinds of plants)	Decreased LH, FSH and E2

CONCLUSION

Polycystic ovary syndrome (PCOS) is a complex condition that is most often diagnosed by the presence of two of the three following criteria: hyperandrogenism, ovulatory

dysfunction, and polycystic ovaries. Because these findings may have multiple causes other than PCOS, a careful, targeted history and physical examination are required to ensure appropriate diagnosis and treatment. More research is needed to clarify the complex pathophysiology of PCOS. No

single test is currently available for its diagnosis. Additionally, once diagnosis is established, the options for treatment are of limited number and effectiveness because they target only the symptoms of PCOS. Finally, patients with PCOS have higher rates of metabolic complications, such as cardiovascular disease, but their impact on mortality is not clear. Therefore, more prospective epidemiologic studies on the topic are necessary.

CONFLICT OF INTERESTS

None.

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