Review Article

Polycystic Ovary Syndrome: pathogenesis, management, and treatment with metals and organic compounds



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1. Introduction

<u>ABSTRACT</u>

Polycystic ovary syndrome (PCOS) is a popular illness in women after puberty age. It's described via overdone androgen production, and ovulation unrest while elevating metabolic syndrome. PCOS was usually diagnosed by Ultrasound or blood test to check the androgens and other hormone levels. There are many causes of having pathogenesis of POCS which was related to abnormalities in hormone levels, insulin resistance, obesity, and others. The symptoms of PCOS could include irregular periods, excess body hair, weight gain, oily skin, and infertility. Due to the variety of symptoms, the POCS has many different types of treatment options, for instant use of medications or lifestyle changes such as weight loss. Many medications are used to treat PCOS like organic compounds and have proven effective in treating PCOS as well as many metallic elements will aid medicinal chemists in planning, organizing, and implementing new approaches toward the discovery of novel drugs. One of the most important medications which were used to treat PCOS is clomiphene citrate and that is commonly used for the treatment of infertility. This review highlights to the causes and treatments of PCOS and gives many examples of recent research that uses drugs and metallic elements as a medication.

Polycystic ovary syndrome (PCOS) is a common illness that affects between 5 to 10% of women [1]. The cysts aren't dangerous but to irregular hormones, lead causing abnormalities from periods that make it challenging to obtain pregnant [2]. It characterizes a status when at most ovary is greater than 10 mL with diameters ranging from 2 to 9 mm[3]. The ovaries while the adrenal gland and peripheral adipose tissue both participate to make a usually irregular [4]. It's as well-known as Stein-Leventhal syndrome or hyperandrogenic anovulation (HA). It is a well-called syndrome "O" that be more nourishment, excess production from ovarian confusion, ovulatory uncertainty, and insulin[5]. It's connected with the expansion

from Diabetes Mellitus (DM) and frequent miscarriage [<u>6</u>].

Such as the whole syndrome, HA is a group of issues discovered together. Not whole females together with PCOS have whole the same signs. A female must have two of three signs to be diagnosed with PCOS: chronic absence of ovulation, and ovaries with many fluid-filled sacs. Obesity is popular among females, while they're predisposed to DM, hypertension, lipid unnatural, sleep disturbances, depression, while metabolic syndrome. Endometrial cancer be as well increased *via* persistent anovulation [7]. The signs from HA maybe have an adult influence on psychological well-being, menstrual cycle disruption, hyperandrogenism, as well as reproductive concerns, obesity. and

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psychiatric disorders. The high levels of testosterone, androstenedione, prolactin, while Luteinizing Hormone (LH), as well as normal, high, or low estrogen levels, are utilized to diagnose hyperandrogenemia (HA). Females with HA are more likely to have hyperinsulinemia, and insulin resistance (IR), while poor glucose tolerance and insulin resistance can develop in lean females with PCOS [8]. Young females together with HAinduced endometrial hyperplasia be more probable to develop endometrial cancer than PCOS females. The exact etiology and pathophysiology of PCOS are unknown [9].

therapy includes lifestyle Its recommendations as well as a variety of therapy, according to the nature of an adult's difficulties. PCOS seems to be ignored, and as a result, individuals may be mismanaged [10]. In addition, PCOS management may necessitate the participation of a number of healthcare providers, including physicians care. gynecologists, endocrinologists, dermatologists. dialectologists. and psychiatrists. Important components of the condition may be overlooked in some clinics, such as gynecological disorders [10]. A of situation variables. varietv including location, diet, pollution, and socioeconomic position, may all have to improve PCOS [11].

2. Pathogenesis Poly Cystic Ovary Syndrome

The etiology of PCOS is unknown. Illness is occasionally inherited. If any of your family members be impacted with PCOS, your hazer from improving Poly Cystic Ovary Syndrome may be increased.

2.1. Abnormalities hormone levels

other variables Manv mav also contribute to Polycystic Ovary Syndrome called syndrome "O" while influencing various bodily systems. Insulin stimulates glucose uptake in adipocytes, and skeletal and cardiac muscle while suppressing glucose synthesis hepatic cell while lipolysis. Insulin Resistance (IR) is defined as insulin's diminished capacity to exert those physiologic actions, which results in higher circulating insulin levels in response to a glucose load [12]. IR causes

hyperinsulinemia, which stimulates androgen synthesis in ovarian theca cells in conjunction together with LH. This elevated androgen interacts together with insulin to reduce sex hormones, resulting in a rise in free androgens while hirsutism [12, 13].

2.2. Insulin Resistance (IR)

IR is important in the pathophysiology of PCOS and related disorders including cardiovascular disease (CV) and metabolic syndrome. The pathophysiology of IR in is unknown, however, illness Diamanti-Kandarakis and Dunaif18 indicate a postbinding impairment in insulin receptor signaling in their 2012 update on PCOS the reasons. IR prevalence rates have been observed to range between 44% and 85%.19 The euglycemic insulin clamp test is the goldstandard test for IR, but its clinical application is limited due to cost and logistics [14]. Females with PCOS exhibit postprandial dysglycemia rather than fasting dysglycemia, which lends itself to the oral glucose challenge test as an additional method to identify irregular [12].

2.3. Obesity

Obesity is popular in females with syndrome "O", but not whole PCOS patients be obese. Obesity has been found to contribute to PCOS signs, with visceral fat, in particular, plaving major role. Adipokines, а involving adiponectin, are released by visceral adipose tissue. Adiponectin expression is reduced in obesitandle and was related to insulin resistance. Adiponectin is an antiinflammatory, insulin-sensitizing molecule [15]. A meta-analysis published in 2014 found reduced total adiponectin levels in PCOS females regardless of Body Mass Index (BMI) [16].

2.4. Dyslipidemia

It's more frequent in PCOS females than in weight-matched controls. Females especially had greater triglyceride levels while lower high-density lipoprotein values. Although such a relationship is independent of BMI, obesity was demonstrated to worsen lipid. IR appears to have a role in hyperlipidemia as well, possibly through lipolysis activation while changing the expression of hepatic lipase and lipoprotein lipase $[\underline{17}]$.

2.5. Sleep Disturbances

The consequences of PCOS extend beyond insulin and lipid abnormalities to metabolic processes and psychological effects. New research suggesting a relationship between PCOS and sleep disturbances has been disseminated in the last few years [18]. Obstructive sleep apnea and severe daytime sleepiness are more common in females with female with PCOS had a greater PCOS. happening after controlling for BMI. involving females of normal weight [19]. Because the endocrine system regulates the sleep-wake cycle, PCOS is probable to alter sleep mechanisms and natural arousal. Many found studies have а relationship between sleep disruption and sleep restriction exacerbating insulin resistance [<u>20</u>].

2.6. Metabolic Syndrome

Metabolic syndrome is a metabolic illness that elevated the hazer of Diabetes Mellitus (DM). coronary artery disease and cardiovascular disease. In females, three of the five problematic criteria are present, according to the International Diabetes Federation: such as high-density lipoprotein, hypertension, waist circumference, triglycerides, and fasting glucose. One of the diagnostic criteria is pharmacologic treatment for abnormal hyperglycemia, hypertension, or dyslipidemia. Females with PCOS are more likely to develop metabolic syndrome. A recent study found that the risk of metabolic syndrome in females who have HA is 11 times higher than in age-matched controls [21].

2.7. Cardiovascular Risk

Females with PCOS have an independent hazer from CV. in addition to an elevated happening of DM, obesity, and obstructive sleep apnea. Females with HA have elevated inflammation, oxidative stress, and decreased fibrinolysis [22]. Glintborg and partners studied CV hazer in a population study of Danish females with PCOS compared to controls without PCOS in a 2018 study. In females with HA, the risk ratio for evolution CV was 1.7. Obesity, diabetes, infertility, and usage of oral contraceptives in the past were all linked to an elevated hazer of CV. Hypertension and dyslipidemia were among the outcomes [23].

3. Treatment and Management of PCOS

Treatments of PCOS Therapy must be adjusted to each patient's particular helps; treatment aims may involve alleviating hyperandrogenic signs, promoting ovulation, organizing and menstruation while preventing cardiometabolic problems. The most troubling signs for females with HA include hirsutism, infertility, and irregular menstruation. Because of the complicated etiology of PCOS, treatment is rarely nanotherapeutic, but rather tailored to the patient's specific indications and signs. Several complementary therapies for the administration, while therapy for HA has been proposed, include [24].

3.1. Diet and lifestyle changes

Diet while lifestyle modifications are recognized as the foundation of HA therapy. To alleviate the most apparent signs of PCOS, like monthly abnormalities, infertility-causing anovulation, and, androgen-related symptoms, as well as many pharmaceutical and non-pharmacological therapies can be utilized. There are several therapeutic options with benefits for metabolic comorbidities in PCOS; nevertheless, it is equally important to recognize that no single medication may entirely address the variety of metabolic abnormalities in HA-diagnosed females [25].

3.1.1. Hirsutism

For most females, the Endocrine Society Clinical Practice Guidelines 2018 on Hirsutism recommends а COC as first-line pharmacologic therapy [26]. Furthermore, the Endocrine Society Clinical Practice recommendations for the Diagnosis while Treatment from HA [5] and international recommendations diagnosing for while managing PCOS [27] both recommend COCs as first-line therapy for hirsutism [27]. If there is no clinical response to COC monotherapy after six months, so there is usually add spironolactone from 50-100 mg twice a day [28].

3.1.2. Metabolic abnormalities

females' Most first-line therapy is ovulatory cycle restoration, which can improve metabolic risk. The strategy for obesity therapy is similar in that it's for people without HA, beginning with lifestyle adjustments [29] followed bv pharmacotherapy and, when necessary, bariatric surgery.

Weight reduction recommends calorierestricted diets paired with exercise to help female who have PCOS while obese loses weight. Although no major randomized trials of exercise-specific therapies have been conducted, a comprehensive evaluation of exercise therapy in PCOS indicated that it may result in moderate weight reduction while benefits in ovulation and insulin sensitivity [<u>30</u>].

3.1.3. Insulin resistance/type 2 diabetes

Svndrome "O" pathogenesis includes impaired insulin secretion while functioning [26]. Androgen levels in syndrome "0" be known regulated to be via hyperinsulinemia while IR. Insulin regulates ovarian function, while high insulin levels can be detrimental to ovarian function [<u>26</u>].

Biguanides (metformin) and thiazolidinediones (pioglitazone, rosiglitazone) are two medicines that can lower insulin levels in females together with HA. Those medications may also lower ovarian androgen production while restoring normal menstrual cycle [31].

3.1.4. Obstructive sleep apnea

For example, it's a prevalent condition hyperandrogenism (HA) females. among essential IR, glucose intolerance. and DM be whole factors to consider [26]. A similar benefit was reported in a metaanalysis of eight studies [32]. Steatohepatitis that is not caused by alcohol Nonalcoholic steatohepatitis (NASH) appears to be more common in females together with HA. In these females, both weight loss and metformin therapy are back to enhance metabolic and hepatic function [26, 32].

3.1.5. Depression/anxiety

Females who have HA have a worse quality of life while having an increased incidence of sadness and anxiety when compared to the female of the same BMI who don't have HA [<u>33</u>]. However, the efficacy and safety of antidepressant therapy have not yet been established in women with PCOS and anxiety or depression [<u>33</u>].

3.1.6. Anovulation and Infertility

Weight loss The approach to obesity management is the same as that for patients without PCOS, starting with lifestyle changes (diet and exercise) and bariatric surgery if necessary Ovulation induction [34]. medications [28]: For oligo-ovulatory women with PCOS undergoing ovulation induction, letrozole is the first-line therapy over clomiphene citrate, regardless of the patient's BMI. The drug is not approved by the US Food and Drug Administration (FDA) for this purpose; Therefore, Clomiphene citrate had been the first-line drug for this population for many years, with metformin as an alternative. However, clomiphene and metformin appear less effective for live birth rates than letrozole [35]. Gonadotropin therapy is the administration of exogenous gonadotropins [<u>36</u>].

In vitro fertilization (IVF)If the over mentioned strategies fail, the next step is IVF, however, the risk of OHSS is an elevation in females together with PCOS passes controlled ovarian hyperstimulation for IVF, while metformin administration before or through IVF cycles maybe minimizes this hazer [<u>37</u>].

4. Drugs Used for PCOS

4.1. Clomiphene citrate:

A derivative of triphenyl ethylene stilbene was an estrogen agonist. In HA patients, it's utilized as the first medication for the inducement of ovulation. The estrogen receptor antagonist interferes with the negative feedback of the estrogen signaling system, leading to elevated FSH levels. Follicular growth is stimulated by elevated FSH [<u>38</u>]. It includes the early phase of the menstrual cycle. It's the primary medication for ovulation induction in HA patients figure 1. It's the estrogen receptor antagonist which interferes with the negative feedback of the estrogen signaling pathway, leading to raised FSH. Elevated FSH promotes follicular growth [39]. It includes the first half of the menstrual cycle [38, 39]. It's the reason the pituitary gland in the brain frees additional FSH while LH.

Depending upon the target tissue the clomiphene citrate acts as a selective estrogen receptor modulator (SERM), similar to raloxifene and tamoxifen. the three drugs inhibit estrogen binding to estrogen receptors (ERs)[<u>38</u>].



Fig. 1. Structure of Clomiphene citrate

4.2. Metformin

Metformin is a type of guanidine that is biguanide carrying two methyl substituents. It has a role as a PCOS, geroprotector, environmental contaminant, xenobiotic, and hypoglycemic agent. It is functionally related to a biguanide. It is a conjugate base of metformin. Insulin sensitivity medications like metformin and troglitazone counteract certain hyperandrogenic symptoms via lowering total and free testosterone concentrations [40]. It promotes ovulation, alleviates IR, and lowers overlv elevated testosterone levels. It improves menstruation. and ovulation. while fertility figure 2 [41].

In HA, 3-6 months of metformin therapy to increase ovulatory function while circulating testosterone is effective [40, 41]. Metformin inhibits the mitochondrial respiratory chain in the liver, activating AMPK, and increasing insulin sensitivity, while decreasing cyclic adenosine monophosphate (cAMP), hence reducing the production of gluconeogenic enzymes. The mechanism action of metformin triggers the pituitary gland to increase the amount of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This process stimulates the growth of the ovarian follicle and initiates ovulation [40].



Fig. 2. Structure of Metformin

4.3. Glucocorticoids

To stimulate ovulation, prednisone, and dexamethasone have been utilized. Low dosage dexamethasone (0.25-0.5 mg) at night may be administered in HA individuals with high adrenal androgen figure 3 [42].



Fig. 3. Structure of Glucocorticoids

4.4. Gonadotropins (Gonadotropin - releasing hormone agonist)

It's utilized as a second-line treatment following clomiphene citrate resistance. It initiates ovulation, maintains while stimulating optimal follicle development with the regulated injection of FSH₄, and therapy begins in small amounts figure 4 [<u>43</u>]. Receptors while effects of Gonadotropin-Releasing Hormone

It works on gonadotropes in the anterior pituitary through GnRH receptors (GnRHRs), promoting the production while the release of LH and FSH, consequently influencing gametogenesis and steroidogenesis.



Fig. 4. Structure of Gonadotropin-releasing hormone agonist

4.5. N-acetyl-cysteine (NAC)

It contains antioxidants necessary for the body's glutathione formation, inhibiting oxidative while preventing stress hyperinsulinemia (figure 5) **[44]**. In syndrome " O " patients, NAC is shown to reduce insulin and testosterone levels while improving blood homocysteine and lipid profile. In addition, NAC administration was shown to enhance the average number of >18mm ovulatory follicles and peak endometrial thickness in PCOS patients.



Fig. 5. Structure of N-acetyl-cysteine (NAC)

5. Relationship of metals with PCOS

Metal is an element that forms positive ions and has metallic bonds. Iron be wanted via practically whole living creatures because it participates in several metabolic processes including oxygen transport, DNA synthesis, and electron transport. Iron deficiency anemia is a major issue for mothers and children in developing nation's figure 6. Iron levels in signs "O" patients' serum while bodies are increased are increasing a potential cause of coronary artery diseases [45].



Copper is required for the production of red blood cells, bones, and connective tissue. The enzyme superoxide dismutase binds to around 80% of the copper in erythrocytes. Syndrome "O" be thought to be implicated in the disruption of systemic copper homeostasis [46].

It's discovered a trend to elevate copper content in females with PCOS, however, the changes were not statistically verified. Copper ions behave as a catalyst to form reactive oxygen species (ROS), resulting in oxidative stress[<u>47</u>]. Long-term Cu²⁺ exposure has also been demonstrated to impair the general function of the ovaries. Copper coupled with homocysteine to form Cu-Hcy complexes raises the hazer of early vascular illness in HA females [<u>48</u>].

Manganese, an essential element, induces oxidative stress by interfering with glucose metabolism [49]. Manganese has been linked to a glucose metabolism issue in females with PCOS. Kurdoglu and Co. According to those scientists, the elevated manganese exposure can be attributable to PCOS causes [25]. Magnesium is linked to DM and other metabolic disorders.

Zinc is the most critical needful element for prominent public health ramifications. It's a diversity of biological functions that be considered a multifunctional minor element because of its capacity to connect to over 300 enzymes and over 2000 transcriptional factors. RNA is essential for converting genetic information into proteins in the body [50]. Zinc is a gatekeeper of Immune Function. Nutrients, Zinc has critical functions in immunological function. A lack of zinc causes enhanced systemic inflammation while thymus atrophy. It balances immune cell numbers and activities at the optimum concentration. In excessive amounts, it causes the adaptive and innate immune systems to malfunction [50].

HA appears that a rich diet or mineral supplementation is essential. It's worthwhile to deem including goods high in these nutrients for the diet. The elevated levels of macroelements (Mg and K) observed in HA females because of impaired Na, and the Ca seemed to be a preventive impact. A higher Na content in RBC is too discovered, which has a detrimental impact on the body, including Mg while Zn water retention. greater concentrations supported greater HDL levels in the PCOS-NIR group, but greater Na while Ni contents favored decreased HDL levels [25]. Nickel is capable of causing free oxidation cell membranes radical in while may have an impact in disrupting folliculogenesis and ovulation in PCOS patients [25]. Nickel levels in the blood of females together with HA demonstrated an elevated amount of this element [25, 51]. The high amount of Ni in blood serum might be a reason or a contributing factor to HA [50].

6. Conclusion

PCOS is caused when the ovaries release a high amount of androgens, hormones of sex males that be normally present in tiny levels in females. Illness and etiology are unsure. There is a certificate that genetics be included. Some additional variables, especially obesity, also have a function in the evolution from HA: Increased quantities from male hormones known as androgens: Rise quantities of androgen prevent your ovaries from creating eggs, as a result of which period is irregular.

Therapies for signs related to irregular periods, reproductive issues, excess hair, acne, and obesity involve the oral contraceptive pill. Metformin is an insulin-sensitizing medication. Hormones are known as gonadotropins. Many medications are used to treat certain cases of breast cancer, as well as many metal complexes that have been proven in the treatment of breast cancer.

There is a relationship between metallic elements with PCOS it seems. In the syndrome "O" group, a wealthy diet or mineral supplementation is essential. It's worthwhile to deem including goods high in those nutrients in the diet. Elevated levels of macroelements (Mg and K) detected in PCOS females caused by Na, and the Ca be impairment seemed to have a shielding impact. Regrettably, a higher Na consist in RBC was also discovered, which has a detrimental impact on the body, including water retention. Greater Mg and Zn concentrations favored greater HDL levels in the HA, while higher Na while Ni consists preferred lower HDL levels.

Conflict of Interest

The authors hereby declare that they have no conflict of interest.

Author's contributions

All authors equally participated in designing experiment analysis and interpretation of data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

No human or animals were used in the present research.

Consent for publications

All authors have read and approved the final manuscript for publication.

Availability of data and material

The authors have embedded all data in the manuscript.

Informed Consent

The authors declare not used any patients in this research.

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