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## A Comprehensive Review on Treatments for Polycystic Ovarian Syndrome (PCOS)

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## ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a prevalent hormonal disorder-affecting woman of reproductive age, marked by imbalances in hormones, insulin resistance, and metabolic irregularities. It manifests with symptoms such as irregular menstrual cycles, ovarian cysts, hirsutism, acne, and infertility. PCOS not only poses challenges to reproductive health but also elevates the risk of conditions like infertility, type 2 diabetes, and cardiovascular disease. Diagnoses encompass evaluating symptoms, hormonal profiles, and ovarian ultrasound results. The management of PCOS is designed to alleviate symptoms, restore hormonal equilibrium, and reduce associated health risks. PCOS is addressed through various systems of medicine, including lifestyle modifications, Allopathic or Western Medicine, Ayurvedic Medicine, Traditional Chinese Medicine (TCM), Persian Herbal Medicine, and Complementary and Alternative Medicine (CAM). Tailored to individual symptoms and health needs, these approaches aim to enhance the overall well-being of individuals with PCOS. Aspects of the mentioned systems of medicine can be combined to create personalized treatment plans that are the most effective in treating PCOS for unique patients.

### Keywords

Polycystic Ovary Syndrome, Reproductive health, Hormonal imbalance.

## What is Polycystic Ovarian Syndrome?

Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder primarily affecting women of reproductive age. It is characterized by irregular menstrual cycles, elevated levels of androgens (male hormones), and the presence of small cysts on the ovaries. While the exact cause remains unclear, both genetic and environmental factors are believed to contribute to PCOS.

Beyond its impact on reproductive health, PCOS is associated with metabolic abnormalities, including insulin resistance, which heightens the risk of developing type 2 diabetes and cardiovascular disease. PCOS is recognized as a multifaceted disorder with diverse manifestations, encompassing not only reproductive challenges but also affecting metabolic and cardiovascular well-being. Recent studies have delved into the molecular mechanisms of insulin resistance in PCOS, exploring potential therapeutic interventions to manage the syndrome and its associated complications [1,2]. Furthermore, research highlights the importance of personalized treatment approaches, considering the heterogeneity of PCOS

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presentations [3]. The evolving understanding of PCOS emphasizes the necessity for comprehensive and individualized care to address its complex nature and mitigate associated health risks.

## **Pathophysiology of PCOS**

The endocrine system is made up of numerous glands that secrete hormones that work together to aid in the maintenance of normal bodily functions, such as metabolism, reproduction, and growth and development, to name a few [4]. A certain disorder that results in dysregulation of the endocrine system is Polycystic Ovary Syndrome, commonly known as PCOS, which is a hormonal imbalance among women of reproductive age [5]. The endocrine glands specifically involved in the regulation of normal female reproductive health are the hypothalamus, pituitary gland, and ovaries [4]. The hypothalamus secretes a hormone known as gonadotropin releasing hormone (GnRH), which stimulates the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland [4]. Secretion of GnRH is crucial in determining the primary female sex characteristics, sexual development, and menstruation in females. FSH aids in the production of eggs by the ovaries while LH stimulates the release of the egg from the ovary [6,7]. In PCOS patients, the abnormal FSH and LH levels result in ovulatory dysfunction, which can lead to hyperandrogenism and insulin resistance [5].

Ovulatory dysfunction is characterized by a disruption in normal ovulation. Women diagnosed with PCOS were found to have decreased FSH levels and increased LH levels [5]. This means there are not enough eggs produced to be released, resulting in anovulation or irregular ovulation, which may lead to the formation of multiple ovarian cysts and enlarged ovaries [5]. This results in the body being in a chronic inflammatory state, ultimately causing women to experience hormonal imbalances, irregular menses or amenorrhea, and fertility issues [5]. As mentioned above, due to the imbalance of hormone levels, there is an increased secretion of androgens, male sex hormones, which leads to hyperandrogenism. In a healthy female, the theca cells, which are found in ovarian follicles, produce a small amount of androgen. However, in PCOS patients, whose ovaries have become cystic, these theca cells are highly sensitive to abnormal hormone levels, which leads to the over secretion of androgens [8]. In females, this results in the development of secondary male sex characteristics such as male pattern baldness (alopecia), excessive facial and body hair (hirsutism), central obesity, acne, and oily skin [5]. Lastly, insulin resistance was also observed in PCOS patients. Insulin is a hormone that helps regulate glucose in the body. Insulin resistance occurs when the body does not respond to insulin, resulting in hyperinsulinemia, which is high levels of insulin in the blood [8]. Insulin reacts with LH in polycystic ovaries leading to the activation of an enzyme called P450c17 $\alpha$ , which regulates androgen synthesis, causing an increase in androgens [9]. It is still unclear as to whether PCOS results in insulin resistance or if being resistant to insulin puts you at a higher risk of acquiring PCOS.

## **Diagnosis and Symptoms of PCOS**

Polycystic ovary syndrome (PCOS) is a complex condition affecting

4-18% of reproductive-age women, with its prevalence depending on diagnostic criteria. It involves hormonal imbalances, insulin resistance, and metabolic abnormalities, increasing the risk of infertility, type 2 diabetes, and cardiovascular disease (CVD), impacting quality of life. PCOS is underdiagnosed due to its diverse phenotypes. In terms of reproductive health, PCOS is the leading cause of anovulatory infertility, with about 90-95% of anovulatory women seeking infertility treatment having PCOS. The condition is characterized by elevated luteinizing hormone, reduced folliclestimulating hormone, and increased levels of androgens and insulin. Clinical features include oligomenorrhea or amenorrhea, ovarian cysts, and hair and skin symptoms. Pregnant women with PCOS face a higher risk of gestational diabetes and first-trimester spontaneous abortion. While the exact cause is unknown, PCOS is considered multifactorial with both environmental and genetic components, as evidenced by a higher prevalence (20-40%) among first-degree female relatives compared to the general population (4-6%) [10].

Polycystic Ovary Syndrome (PCOS) manifests with a range of signs and symptoms that impact various aspects of reproductive and metabolic health. One notable characteristic is the enlargement of ovaries, containing multiple small cysts known as follicles. Unfortunately, these follicles often fail to mature and release eggs regularly, contributing to irregular menstrual cycles or even the absence of periods. Hirsutism, marked by the excessive growth of coarse hair, particularly on the face and around the mouth, is a distinctive physical manifestation resulting from elevated levels of androgens. PCOS also poses challenges to fertility, as hormonal imbalances can disrupt the growth and release of eggs from the ovaries. This interference with the reproductive process leads to infertility. Irregular menstrual cycles, characterized by anovulation, further contribute to difficulties in achieving fertility, emphasizing the syndrome's impact on reproductive health. Weight gain, especially concentrated around the abdominal region, is a prevalent symptom intricately linked to the metabolic aspects of PCOS. Elevated androgen levels associated with the syndrome induce skin-related manifestations, including acne and increased skin oiliness. Understanding these varied symptoms is crucial for the accurate diagnosis and management of PCOS, facilitating a comprehensive approach to address both reproductive and metabolic aspects of the syndrome [11-13].

Functional Ovarian Hyperandrogenism (FOH) accounts for nearly all cases of PCOS, with two-thirds presenting as typical FOH, characterized by androgen dysregulation and an over-response of 17-hydroxyprogesterone (17-OHP) to gonadotropin stimulation. The remaining PCOS cases with atypical FOH lack an over response of 17-OHP but exhibit elevated testosterone levels after suppressing adrenal androgen production. FOH-associated PCOS is marked by hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology. The multifactorial nature of FOH involves hereditary and environmental factors, including insulin excess, which sensitizes the ovary to luteinizing hormone (LH) [14].

Currently there are three diagnostic criteria sets that are commonly used for diagnosing PCOS in adults: the National Institutes of Health

(NIH), Rotterdam, and Androgen Excess-PCOS Society (AE-PCOS) criteria. The NIH criteria define PCOS as oligomenorrhea/ anovulation and clinical or biochemical hyperandrogenism. The Rotterdam criteria require any 2 of the following 3 criteria: oligomenorrhea/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries on ultrasound. AE-PCOS criteria include oligomenorrhea/oligo-ovulation or polycystic ovaries on ultrasound and clinical or biochemical hyperandrogenism. Exclusion of conditions mimicking PCOS, such as hypothyroidism and adrenal disorders, is essential. During adolescence, symptoms resembling PCOS often occur, including irregular menses, clinical hyperandrogenism, and polycystic ovaries. However, diagnosing PCOS during the first 2 years after menarche is discouraged. Clinical hyperandrogenism evaluation in adolescence lacks a standardized grading system. Proposed PCOS risk factors lack robust evidence. Some adolescents diagnosed with PCOS may not meet criteria upon further adult evaluation due to these limitations [15].

#### Table 1: PCOS Diagnostic Criteria.

| National Institutes of<br>Health (NIH), 1990           | ESHRE/ASRM<br>Rotterdam, 2003 | Androgen Excess–<br>PCOS Society (AE-<br>PCOS), 2006 |  |
|--|-------------------------------|--|--|
| Both criteria needed: -                                | 2 of 3 criteria needed: -     | Both criteria needed:                                |  |
| Chronic anovulation                                    | Oligomenorrhea and/or         | - Ovarian dysfunction                                |  |
| - Clinical and/or                                      | anovulation                   | and/or polycystic                                    |  |
| biochemical signs of                                   | - Clinical and/or             | ovaries - Clinical and/                              |  |
| hyperandrogenism                                       | biochemical signs of          | or biochemical signs                                 |  |
| *exclusion of other                                    | hyperandrogenism              | of hyperandrogenism                                  |  |
| endocrinopathies                                       | - Polycystic ovaries          | *exclusion of other                                  |  |
| and androgen excess                                    | *exclusion of other           | endocrinopathies                                     |  |
| disorders needed                                       | endocrinopathies              | and androgen excess                                  |  |
|  | and androgen excess           | disorders needed                                     |  |
|  | disorders needed              |  |  |
| ESHRE/ASRM: European Society of Human Reproduction and |                               |  |  |
| Embryology/American Society for Reproductive Medicine  |                               |  |  |

Diagnosing PCOS is challenging due to variations in symptoms based on age, race, weight, and medications. In adolescents, the overlap of normal puberty characteristics with PCOS signs complicates diagnosis. Some authors propose alternative diagnostic criteria for adolescent PCOS. Sultan and Paris recommend four of the following five criteria: oligomenorrhea or amenorrhea 2 years after menarche, clinical hyperandrogenism, biochemical hyperandrogenism, insulin resistance or hyperinsulinemia, and polycystic ovaries on ultrasound. Carmina and colleagues suggest applying Rotterdam criteria but limiting a definitive diagnosis to adolescents meeting all three criteria, considering those with two may develop PCOS in adulthood. While these proposed criteria are stricter, they lack endorsement from expert panels or societies in the field [16].

Adolescent PCOS diagnosis is intricate due to overlapping features with normal puberty, like acne, irregular menstruation, and hyperinsulinemia. Anovulatory cycles, typical during the first 2-3 post-menarche years, can lead to persistent oligomenorrhea,

indicating potential ovarian or adrenal issues. Ultrasound efficacy is limited as adolescents commonly have large, multicystic ovaries [14].

## **Chronic Anovulation**

Cycles beyond 35 days suggest chronic anovulation; however, those between 32 to 35-36 days need ovulatory dysfunction assessment. Adolescents with cycles shorter than 35 days can be evaluated through mid-luteal phase progesterone levels (days 20 to 21), with implications including infertility, endometrial hyperplasia, and cancer [14].

## Hyperandrogenism

Clinical hyperandrogenism, diagnosed in adults with hirsutism, alopecia, and acne, is a substitute for biochemical hyperandrogenism. Adolescent-only hirsutism warrants consideration. Hair loss varies, and severe cases may indicate a 40% likelihood of developing PCOS. Signs of virilization, such as increased muscle mass and clitoromegaly, suggest further investigation, raising suspicion for tumors [14].

## **Free Testosterone**

Free testosterone (FT) denotes the unbound fraction of testosterone, typically constituting 2-3% of total testosterone in men. It is considered a more accurate indicator of the actual androgenic status of an individual [17]. Free testosterone levels, more sensitive than total testosterone, are pivotal for diagnosing androgen excess. Methodological issues in commercial assays emphasize the need for awareness, with equilibrium dialysis techniques preferred when available. Calculated free testosterone is an alternative when equilibrium dialysis is not an option, ensuring accurate results [14].

Improved diagnosis and treatment of women's health issues are among the many reasons why women's participation in medicine is so important. In the United States, women make up approximately half of the population, but the field of women's healthcare is still relatively new. The medical community has only recently come to recognize the need to address the unique requirements of women, throughout the past century. There are many ways that sex affects health results like disease risk, progression, and results. There is no one-size-fits-all approach to healthcare [15].

Women's health is a critical area of focus since it tackles previous disparities and guarantees equitable access to high-quality healthcare. The influence of society on health disparities between genders and there is a need for international action to attain gender parity and women's equal rights. Women frequently have delayed diagnosis and unique health problems; treating these problems immediately improves women's health outcomes at all stages of life. By 2050, the number of women over 50 is expected to rise significantly, according to UN forecasts. Women's health problems affect several medical specialties as well as general well-being, going beyond reproductive problems. The Lancet Women's Commission emphasizes how urgently the health sector must act to eliminate gender disparities in workforce distribution and healthcare delivery. This comprehensive review aims to contribute

to the unique health challenges faced by women worldwide by emphasizing the need to properly treat complex reproductive health conditions such as polycystic ovarian syndrome [16].

### **Comorbidities of PCOS**

Conditions that typically occur at the same time as polycystic ovarian syndrome with potential to worsen symptoms, or the comorbidities of PCOS, can be divided into reproductive comorbidities, metabolic comorbidities, and psychological comorbidities [18,19].

## **Reproductive Comorbidities** Subfertility

Subfertility is the term used to describe reduced fertility with prolonged time of unwanted non-conception. With PCOS, patients will have elevated levels of luteinizing hormone, androgens and insulin coupled with reduced follicle stimulating hormone levels. Such imbalances can cause oligomenorrhea (infrequent menstruation) or amenorrhea (lack of menstruation) and if left untreated, may lead to fertility issues with ovarian insufficiency or impaired endometrium [20].

## **Pregnancy Complications**

PCOS can be characterized by various cysts on the surface of ovaries, which can cause further pregnancy complications such as preeclampsia (dangerous levels of high blood pressure leading to possible organ damage), cardiac dysfunction, or even venous thromboembolism (blood clots) [21]. PCOS patients also have a higher risk of first-trimester spontaneous abortion [22]. The role of polycystic ovary syndrome in reproductive and metabolic health: overview and approaches for treatment.

## Metabolic Comorbidities Dyslipidemia

Deposits of lipids on the skin or on subcutaneous tissue, known as xanthomas, are characteristic of dyslipidemia. Dyslipidemia can be diagnosed after measuring serum lipids such as cholesterols, triglycerides, high-density lipoproteins (HDL), and low-density lipoprotein cholesterol (LDL-C). A recent meta-analysis shows that in PCOS patients, triglyceride levels are typically 26 mg/dL and LDL levels are 12 mg/dL higher compared to controls. On the other hand, the high-density lipoprotein levels cholesterol concentration was 6 mg/dL lower in PCOS patients [23].

## Impaired Glucose Tolerance and/or Type 2 Diabetes Mellitus

According to a study, 29.6% of PCOS patients have impaired glucose tolerance [24]. Impaired glucose tolerance which can be defined as "two-hour glucose levels of 140 to 199 mg per dL (7.8 to 11.9 mmol) on the 75-g oral glucose tolerance test" [25]. Having such elevated glucose levels increases the risk for developing diabetes, specifically, Type 2 diabetes mellitus.

Type 2 diabetes has been found in women who are diagnosed as being overweight or obese. Research has found that women with PCOS were four times more likely to develop type 2 diabetes compared to women without the disorder [26]. PCOS patients with insulin resistance have an increased risk of type 2 diabetes, which causes higher levels of androgens, which will further affect ovulation, period cycles, and hair growth. In general, Asians have been found to have more central fat depots and visceral fat accumulation than Caucasians in both children and adults regardless of body composition measurement methods. South Asians including those from Bangladesh, Nepal, Pakistan, India, and Sri Lanka have more fat mass than European counterparts at the same BMI, putting them at a higher risk for developing type 2 diabetes that can worsen PCOS symptoms [27]. PCOS patients with insulin resistance have an increased risk of type 2 diabetes, which causes higher levels of androgens, which will further affect ovulation, period cycles, and hair growth.

## Hypertension

It has been shown that higher androgen levels can impact blood pressure in women with PCOS who are not obese but the mechanisms through which this happens is still being researched. A study had shown that women with PCOS were 40% more likely to have elevated blood pressure than in women without PCOS regardless of age, BMI, diabetes or dyslipidemia [28,29]. In general, the increased hypertension seen in most PCOS patients can be attributed to obesity. Ethnic background may also need to be considered when analyzing hypertension as Asians and Hispanics have a lower prevalence of elevated blood pressure. BMI was also found to be a predictor of both systolic and diastolic blood pressures among PCOS patients.

## **Cardiovascular Disease**

Cardiovascular diseases include coronary artery disease or coronary heart disease (CAD or CHD), cerebrovascular disease, peripheral artery disease (PAD) and aortic atherosclerosis [30]. It has been found that women with PCOS have increased carotid intima media thickness (CIMT) which may contribute to the development of carotid artery disease. Carotid artery disease involves the clogging of the carotid arteries, with fatty deposits also known as plaques. The narrowed arteries may eventually lead to serious deprivation of oxygen to the brain resulting in sudden headache, dizziness, trouble communicating and/or numbness or weakness [31]. Research has found that PCOS diagnosis was the strongest predictor of CIMT even after adjusting for age, BMI, and smoking status [32].

#### Psychological comorbidities Low Self esteem

Symptoms experienced by PCOS patients including weight gain, difficulty losing that weight, excessive hair growth on face, and loss of hair are often considered to be far from societal beauty standards which cause most women with PCOS to have low self-esteem. In Iran, it was found infertile women had lower levels of self-esteem, especially those with hirsutism [33]. A similar trend has been seen in women all around the world as PCOS symptoms such as hirsutism often makes women feel that they do not meet societal beauty standards. Low self-esteem for prolonged periods of time may cause individuals to develop symptoms of depression and/or anxiety.

#### Anxiety

Increased anxiety levels are due to the significantly greater physiological reaction to stress. PCOS patients may develop symptoms such as feeling restless or having sleep issues. These symptoms can be due to the hormonal imbalances' characteristic of PCOS as well, but the combination of these conditions may exacerbate the symptoms. Individuals struggling with body image issues may develop social anxiety disorder. It has been found that women with PCOS are around three times more likely to report anxiety symptoms compared to women without PCOS [34]. Likewise, PCOS patients were more likely to develop symptoms of depression as well [34]. Two studies showed that the prevalence of anxiety amongst PCOS patients was between 28%-39% while the prevalence of depression was anywhere between 11%-25% of PCOS patients [35,36].

| Table 4: Preva | lence of differ | ent psychia | tric morbidities |
|----------------|-----------------|-------------|------------------|
|----------------|-----------------|-------------|------------------|

| Psychiatric diagnosis            | Group      |               | Total (%)  |  |
|----------------------------------|------------|---------------|------------|--|
|                                  | PCOS n (%) | Control n (%) |            |  |
| No diagnosis                     | 52 (47.3)  | 36 (90.0)     | 88 (58.7)  |  |
| BPAD                             | 3 (2.72)   | 0 (0.00)      | 3 (2)      |  |
| Suicidality                      | 9 (8.18)   | 0 (0.00)      | 9 (6)      |  |
| Dysthymia                        | 2 (1.81)   | 0 (0.00)      | 2 (1.33)   |  |
| Generalized anxiety<br>disorder  | 17 (15.45) | 0 (0.00)      | 17 (11.33) |  |
| Major depressive disorder        | 26 (23.64) | 3 (7.5)       | 29 (19.33) |  |
| Agoraphobia                      | 1 (0.9)    | 0 (0.00)      | 1 (0.7)    |  |
| Obsessive compulsive<br>disorder | 7 (6.36)   | 1 (2.5)       | 8 (2)      |  |
| Panic disorder                   | 17 (15.45) | 2 (5)         | 19 (5.33)  |  |
| PTSD                             | 1 (0.9)    | 0 (0.00)      | 1 (0.7)    |  |

BPAD – Bipolar affective disorder; PTSD – Posttraumatic stress disorder; PCOS – Polycystic ovary syndrome

Table 4 in Hussain A, Chandel RK, Ganie MA, Dar MA, Rather YH, Wani ZA, et al. Prevalence of psychiatric disorders in patients with a diagnosis of polycystic ovary syndrome in Kashmir. Indian J Psychol Med. 2015; 37: 66–70.

## Depression

Hirsutism and difficulty losing weight has also contributed to low self-confidence and increased desire to stay away from social settings, furthering negative thoughts and symptoms of depression. Through the patient health questionnaire 9, 64.1% of women with PCOS were diagnosed with depressive disorders, which was significantly higher than those in a non-PCOS group [37]. It was also found that there was a notably higher prevalence of depression in PCOS in those considered overweight and obese categories which could be due to the link between abnormal metabolism typical of PCOS and its relation to the dysfunction of the Hypothalamic-Pituitary-Adrenal axis [38]. Dysfunction of the Hypothalamic-Pituitary adrenal axis can lead to the development of depression as the axis is essential to balancing hormones released in response to chronic stress [38]. It has been clear that hyperandrogenism and infertility both would contribute to the severity of the symptoms. Hirsutism is caused by hyperandrogenism, which may cause individuals to continuously have low self-esteem which may

develop into depression [39]. Infertility for those who wish to have children may take a greater toll on mental health. PCOS patients with infertility issues are most likely already experiencing low self-esteem, then they will pursue fertility treatments in hopes of becoming pregnant. Unfortunately, a study found an increased prevalence of Major Depressive Disorder (MDD) amongst women and their partners through going through fertility treatment over an 18-month period [40].

#### **Eating Disorder**

Eating disorders involve a series of lifestyle choices that often cause severe disturbances and illness in people's lives by affecting physical and mental health. In a study involving 318 women including those with PCOS and those with hyperandrogenic conditions, it was found that there was an increased prevalence of clinical and subclinical bulimia nervosa among women with PCOS compared to healthy women [41].

Bulimia nervosa may be characterized by binge eating and then also forced vomiting, excessive use of laxatives or diuretics, fasting, excessive exercise or a combination of these behaviors. Ways of reducing the amount of food that the body processes may also be due to the belief that weight must be lost to better PCOS symptoms. Further symptoms include chronically inflamed and sore throat, acid reflux disorder, and other gastrointestinal problems as well as electrolyte imbalance [42].

Having bulimia nervosa may also cause patients to get rid of foods and nutrients that could have been essential to the body functioning properly. Research has found that a majority of PCOS patients already consume imbalanced diets with deficiencies in fiber, omega 3, calcium, magnesium, zinc, and various vitamins [43]. The use of excessive laxatives may hinder the absorption of these nutrients and thus further conditions such as insulin resistance (reduced through fiber consumption) or hair loss (reduced through magnesium consumption) [44].

## **Psychosexual Dysfunction**

Psychosexual dysfunction is an emotional or mental condition characterized by difficulty becoming sexually aroused or experiencing sexual satisfaction [45]. Unfortunately, women with PCOS may experience psychosexual dysfunction when experiencing obesity, hyperandrogenism or hirsutism. In a cross-sectional study done with 130 married women with PCOS, it was found that a significant proportion of PCOS patients suffer from sexual dysfunction [46]. This is why PCOS patients should be screened so that interventions may be put into place to improve their quality of life.

## **Environmental Toxicity**

Plasticizers are one of the toxins that can further the development of PCOS. Phthalates and Bisphenol A (BPA) are plasticizers that can function as endocrine-disrupting chemicals that affect fetuses, infants, and/or young children the most. Prenatal exposure in prolonged periods may then alter fetal programming, which may increase the risk of developing PCOS even trans generationally. Plasticizers also have the capability of interfering with weight gain, insulin resistance, and resulting hyperinsulinemia, which will further type 2 diabetes and cardiovascular disease which would worsen polycystic ovarian syndrome symptoms and make it even more complicated to develop a proper treatment plan [47].

## **Demographic Overview** Familial History + PCOS

Various studies have found a correlation between genetic predisposition and environmental factors in the causation of PCOS. However, the specific genes involved in this disorder have yet to be identified. A study conducted by Kahser-Miller and colleagues attempted to determine if there was a possible familial connection in the development of PCOS. When interviewed, it was discovered that 67% of their PCOS patients had a family history of PCOS in their first- or second-degree female relatives [48]. This indicates that having a familial predisposition of PCOS may increase the risk of developing the disorder.

## **Obesity + PCOS**

In addition to genetic components, certain factors such as unhealthy eating habits and a sedentary lifestyle could result in obesity, which may ultimately lead to the progression of PCOS. The development of obesity may amplify other characteristics of PCOS such as irregular menses and amenorrhea. In a study referenced by Barbara and colleagues, women with PCOS were encouraged to go through a weight reduction plan and the results showed significant improvement in the regularity of their menstrual cycles [9]. This suggests that obesity is a notable contributor that may exacerbate the symptoms of PCOS.

## **Countries with the Highest and Lowest Prevalence of PCOS**

As of 2017, countries with the lowest prevalence of PCOS are North Africa and Middle Eastern countries [49]. However, this may be a "false negative" because cases in these countries may be underreported due to low socio-economic backgrounds, decreased population, and decreased resources. On the other hand, countries with the highest prevalence of PCOS were found to be Ecuador, Peru, Bolivia, Japan, and Bermuda [49]. Though the exact etiology behind this is unknown, what can be concluded is that a multitude of factors influenced by certain cultural and societal norms such as dietary habits, physical inactivity, low socioeconomic status, and a lack of access to healthcare, education, and health awareness may contribute towards the progression of PCOS [49].

## **PCOS Prevalence in the United States**

Regarding the prevalence of PCOS in women of the United States, the amount of research material available was very limited. In a study conducted by Okoroh and colleagues, women diagnosed with PCOS in the US were most likely either living in the Southern US, between 25-34 years old, infertile, or have a history of metabolic syndrome or taking oral contraceptives [50]. Of the women diagnosed with PCOS in the US, 47.5% were from the South [50].

## **PCOS Characteristics in Different Ethnicities**

In a systematic review conducted by Sendur and Yildiz, women

from various racial and ethnic backgrounds with a diagnosis of PCOS were compared. It was found that Middle Eastern, Hispanic, and South Asian women were more hirsute, when compared to White and East Asian women [51]. It was also concluded that these ethnicities presented with the most severe phenotype of PCOS due to the presence of higher androgen levels, central adiposity, and an increased prevalence of insulin resistance [51]. This suggests that ethnic and racial components can significantly impact how PCOS presents itself in various women.

## Systems of Medicine Related to PCOS Allopathic/ Western Treatments for PCOS

Allopathic or Western medicine has been characterized using drugs, treatments and surgical procedures. Maintenance of health along with acute care and prevention is essential to allopathic practice. Within allopathic medicine, obstetrician-gynecologists are physicians with an MD and specialization in OB-GYN, focusing on female reproductive health typically treating polycystic ovary syndrome. Treatment plans may consist of pharmaceuticals, nutraceuticals (dietary supplements) and lifestyle changes.

## **Allopathic Pharmaceuticals for PCOS**

Various pharmaceuticals or medications may be prescribed for PCOS patients when they exhibit characterizing symptoms such as hirsutism, menstrual irregularities or insulin resistance [52].

## **Insulin Sensitizing Agents**

Insulin sensitizing agents are prescribed to better the metabolism and hormone levels of PCOS patients. These medications treat hyperinsulinemia, which is the presence of elevated levels of insulin in the blood. This state can be due to insulin resistance, resulting in higher blood sugar levels causing even more insulin to be produced [53]. Such a condition of having both insulin resistance and hyperinsulinemia can worsen symptoms of hyperglycemia, and prediabetes and eventually perpetuate the development of Type 2 diabetes [54]. Metformin, a commonly prescribed insulin sensitizer, has been prescribed with hopes that it may restore evolution in PCOS patients along with lifestyles changes. It is also believed to reduce the risk of ovarian hyperstimulation syndrome which involves enlargement of the ovaries and causes fluid to shift to other parts of the body [55]. Additionally, metformin has been found to treat various types of cancer, specifically reducing DNA damage and mutation rates which may help with reducing the development of cysts on the ovaries which can be characteristics of PCOS [56]. Myonositols are also a type of insulin sensitizer commonly used for PCOS treatment, but they are typically established as a nutraceutical and will be discussed further later in the paper.

## Clomiphene

Clomiphene is typically prescribed for PCOS patients who are experiencing amenorrhea and/or anovulatory or oligo-ovulatory infertility. The drug is a selective estrogen receptor modulator that aims to induce ovulation, typically used by patients who wish to conceive. A shorter treatment period or a lower dosage may be preferred to prevent ovarian hyperstimulation syndrome, or fluid leakage into the body from the ovaries, in patients with PCOS [57,58].

### **Rosiglitazone and Pioglitazone**

Both Rosiglitazone and Pioglitazone are classified as thiazolidinediones which are typically used to treat metabolic conditions. This class of drugs may act as insulin-sensitizing agents and decrease the expression of enzymes that convert cortisone to active cortisol. This function is important as some women with PCOS experience hormone imbalances due to the adrenal cortex producing excess cortisol and androgens [59]. Though the results are promising, such medication does have side effects such as fluid retention, weight gain, and increased bone fractures in women, which should be monitored [60].

#### **Oral Contraceptives**

Oral contraceptives or birth control pills, either a combination of estrogen and progesterone or just progesterone, are typically prescribed as a way of preventing pregnancy [11]. Birth control pills may be prescribed in combination with antiandrogens to improve their clinical effect. Pregnancy prevention is important when undergoing hirsutism treatment as accidental exposure of a male fetus to antiandrogens may harm fetal development. Though oral contraceptives are taken for pregnancy prevention, they may also be used to treat menstrual pain, endometriosis related pain and irregular menstruation which can be seen amongst PCOS patients [61].

## Antiandrogens

Antiandrogens can decrease androgen production or competitively inhibit androgen-binding receptors [11]. These medications are prescribed when a patient is experiencing hyperandrogenism and menstrual irregularities.

An example of an antiandrogen commonly used for PCOS treatment is Spironolactone. Spironolactone, an aldosterone antagonist, is typically used to lower levels or block actions of androgen on hair follicles which will reduce excessive hair growth with hirsutism [62]. In combination with Metformin, it has also been found that it can reduce one's Homeostatic Model Assessment (HOMA)-IR which means a reduced resistance to insulin [62]. Despite its supposed benefits, there is the possibility of experiencing side effects such as fatigue, postural hypotension and dizziness [63].

## **Topical Eflornithine**

In order to combat excessive hair growth, topical effornithine may be prescribed. Effornithine is used for slowing hair growth by inhibiting the enzyme ornithine decarboxylase in hair follicles to get rid of excessive, unwanted facial hair [64]. Usage of this topical medication is recommended for 4-8 weeks (about 2 months) but there is the possibility that the hair growth will return to the initial state if stopped after 8 weeks [64].

## Lifestyles Changes Recommended in Allopathic Medicine

In overweight and obese individuals, the symptoms of PCOS tend to be exacerbated due to underlying metabolic conditions and likely metabolic syndrome itself [65,66]. Hormonal imbalances – particularly increased blood insulin and androgen levels – can become worse [65,66]. A higher ratio between Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) is also characteristic of PCOS, affecting ovulation and androgen production [65,67]. Insulin resistance can impair the primary purpose of insulin itself, which is to stimulate glucose uptake for metabolism [66]. Reduced glucose uptake in skeletal muscles can result in fatigue and decreased muscular efficiency when exercising [66]. Obese individuals tend to exhibit greater insulin resistance, menstrual irregularity, and hirsutism, which is excessive hair growth in the mouth and chin areas due to elevated androgen levels [66,68].

Thus, exercise, dietary restrictions, and lifestyle modifications are highly recommended to obese or overweight patients with PCOS [69-71]. Weight loss is often considered as one of the primary steps taken to treat PCOS effectively [71]. It was found that 5-10% weight loss can even improve menstrual irregularity, ovulation, glucose tolerance, hyperinsulinemia, and insulin resistance [66,71-74]. Weight loss can also improve – and possibly even reverse – insulin resistance in skeletal muscles [66]. If medications are taken to achieve weight loss, safety must be considered since many patients wish to conceive [70,71]. Weight loss may also reduce LH levels and the LH/FSH ratio, decreasing androgen production and hyperandrogenemia [66,73]. Decreased abdominal fat volume was also demonstrated to decrease lipid levels in the blood [73].

Due to exercise, improvements in insulin sensitivity and lipid metabolism (from increased lipid uptake and oxidation in skeletal muscles) can result [66]. In a similar manner, exercise can also ameliorate metabolic syndrome [66]. Physical activity for 30-45 minutes demonstrated improvements in insulin resistance, lipid profile, waist circumference, and BMI [72]. A reduced waist to hip ratio is indicative of better health [72]. Additionally, about 50% of the women in a particular study demonstrated improvements in menstrual irregularities and ovulation following regular exercise training [66]. Specifically, endurance exercise was shown to improve mitochondrial density and proliferation, capillary density, blood flow to skeletal muscles, and the stability of proteins involved in the signal transduction pathway of insulin [66]. Regular exercise improved the quality of life of women living with PCOS and reduced PCOS-related risk factors [66].

In adolescent girls with PCOS aged 15-18, yoga was found to be more effective than conventional exercise at improving insulin resistance and glucose and lipid levels in the blood [72,73]. In a prior study, yoga demonstrated improvements in blood glucose and lipid levels in obese individuals with diabetes; in another study, increased insulin sensitivity was demonstrated in men who regularly practiced yoga for at least one year [73]. Asanas (specific postures) – specifically those involving back bending postures – were found to be beneficial for PCOS patients, such as surya namaskar (sun salutation postures), sarvangasana (shoulder stand pose), paschimottanasana (forward bending pose that stretches the back), ardha matsyendrasana (twisting pose), matsyasana (back bending pose), and ustrasana (kneeling and back bending pose) [75,73]. Kapalabhati pranayama, a breathing practice that clears the lungs, may also be beneficial for PCOS patients [69,72,73]. Pranayama can improve muscles' insulin receptor expression and blood supply; over time, it may result in a reduced waist to hip ratio [72]. Perhaps, a combination of traditional and modern management methods may produce the best results. A balanced and controlled diet, along with exercise, is essential to prevent weight gain [69]. A healthy diet can greatly benefit overall health. PCOS patients are advised to consume vegetables regularly; onion and garlic may be beneficial. Certain foods, especially spicy, oily, and sweet foods, may aggravate PCOS symptoms [75]. Meditation and the pursuit of a stress-free lifestyle may also prove effective in the treatment of PCOS [69].

#### Nutraceuticals Recommended by Allopathic Medicine

Nutraceuticals, also known as dietary supplements, may also be recommended to treat PCOS symptoms. The DSHEA of 1994 specifies that the definition of "dietary supplement" is a product that supplements the diet and contains one or more dietary ingredients. Dietary supplements may include a vitamin, a mineral, an herb or other botanical, an amino acid, or a dietary substance [76]. In the Western world, there is a large variety of dietary supplements that have been incorporated from other cultures and countries but there are four that are used more commonly than others. These nutraceuticals include Curcumin, Inositol and derivatives, Vitamin D and Coenzyme Q10 (CoQ10) [77].

#### Curcumin

Curcumin derived from Curcuma longa known as turmeric has been used in many Asian countries as a part of their diet, but it also acts as an antioxidant, having the ability to help induce ovulation and better the biochemical state of PCOS patients [78,79]. Present findings have found that curcumin affects serum markers of inflammation, weight loss and glucose and lipid metabolism in patients with PCOS. The studies' results highlighted that an intake of curcumin has aided in the decreased level of BMI in patients that were overweight or obese. Curcumin is also known for its hypoglycemic properties, meaning that it can aid in lowering blood glucose levels [80]. Though further research needs to be conducted, current data points towards curcumin potentially having the ability to lower androgen levels in PCOS patients.

#### Inositols

Inositols are precursors to substances that may serve as second messengers for hormones such as follicle-stimulating hormone and insulin. Defects in the processing of inositols lead to insulin resistance which is characteristic of PCOS [81]. It has been found that Myoinositols can function as insulin-sensitizing agents affecting pathways at both the ovarian and nonovarian levels. Replacing myoinositols may also be essential to replenishing the intracellular depletion that may occur when a patient experiences hyperglycemia and insulin resistance which are notable in diabetes mellitus [82]. D-Chiro-inositol (DCI) treatment has also been found to reduce blood pressure, harmful lipid levels and reduce insulin levels in PCOS patients [81].

### Vitamin D

Though vitamin D deficiency is not a cause of PCOS symptoms it can worsen conditions such as insulin resistance and metabolic syndrome. Physicians may promote Vitamin D supplementation to better insulin synthesis and release expression of insulin receptors and suppress pro-inflammatory cytokines. Research has also found that vitamin D supplementation taken with myoinositol and melatonin increases pregnancy rate for PCOS patients desiring to increase their fertility and have children in the future [77].

### **Coenzyme Q10**

Coenzyme Q10 (CoQ10) is a lipid-soluble antioxidant that is already synthesized by human cells and is required for cell growth. PCOS patients typically have an inflammatory state characterized by higher plasma concentrations of inflammatory cytokines. These high concentrations push for macrophage recruitment and adhesion molecule production. CoQ10 supplements have greatly reduced these serum concentrations in overweight patients with PCOS. Such supplementation has also been found to help with reducing overall testosterone levels, which promotes follicle development and normal ovulation [83]. As dieticians become more involved in the treatment of PCOS, more supplements are being recommended such as Berberine, L-Carnitine, and Resveratrol.

#### Berberine

Berberine may be derived from the roots or stems of Berberis aristata, B.Chitria, and B. Lycium (Indian Berberis species) and are typically used for asthma, eye sores or for the general elimination of inflammation and swelling [84,85]. Berberine has been prescribed by clinicians in hopes of improving the insulin resistance that may be experienced by PCOS patients. Berberine supplements have been found to improve carbohydrate metabolic parameters, hormonal and lipid profiles and clinical characteristics overall when taken by itself or with an oral contraceptive pill. Berberine helped with improving reproductive hormones (TT, SHBG, LH, LH/FSH ratio), lowering fasting blood glucose and improved lipid profile when compared to a placebo or no treatment at all. [86]

## **L-Carnitine**

L-carnitine is the derivative from an amino acid which is present in foods of animal origin but is also available as a dietary supplement since it is considered a conditionally essential nutrient [87]. L-Carnitine has been prescribed with the hopes that it may decrease the risk of cardiovascular events by normalizing metabolic profiles which may vary due to PCOS. It has also been reported that prescribing L-carnitine to clomiphene-resistant patients with PCOS has improved the quality of ovulation, lipid profiles, BMI and pregnancy rates [88].

## Resveratrol

Resveratrol is a natural polyphenol found in a variety of plant species including grapes' skin and seeds that is now available as a supplement. Several studies have shown that resveratrol has a high antioxidant and anti-inflammatory potential [89]. However, in relation to PCOS Resveratrol has been found to be beneficial for reducing ovarian and adrenal androgen levels which may be higher in PCOS patients [90]. A prospective randomized trial showed that Resveratrol had the ability to reduce serum testosterone levels by more than 20% within 3 months of treatment for PCOS patients, making it a promising option [91].

## **Ayurvedic Perspective on PCOS**

Ayurvedic medicine, an ancient holistic system originating from India, boasts a rich tradition spanning thousands of years. The term "Ayurveda," rooted in Sanskrit, translates to "knowledge of life." At its core, Ayurveda emphasizes the delicate equilibrium between the mind, body, and spirit as the foundation for health and wellbeing. This traditional medical system incorporates a diverse range of practices, such as herbal medicine, dietary guidance, yoga, meditation, and detoxification techniques. Research indicates that Ayurvedic interventions hold promise in addressing various health conditions, spanning chronic diseases, mental health concerns, and lifestyle-related disorders [92,93].

Polycystic Ovary Syndrome (PCOS) stands out as a significant health challenge due to its pervasive impact on reproductive, metabolic, and psychological facets. Ayurvedic approaches, often encompassing herbal remedies, dietary adjustments, and lifestyle modifications, emerge as potential contributors to managing specific aspects of PCOS, as suggested by recent studies [92,93].

Polycystic Ovarian Syndrome (PCOS) stands out as the most prevalent endocrine condition affecting women in their reproductive years. This complex syndrome presents with a variety of symptoms, including amenorrhea, hirsutism, obesity, enlarged polycystic ovaries, acne, and elevated levels of androstenedione and testosterone. The primary contributors to PCOS involve heightened insulin levels, excess androgen (male hormone), and increased luteinizing hormone (LH), though the precise origin remains unknown [94].

In the realm of Ayurveda, an ancient holistic system of medicine, PCOS finds its classification under Yonivyapad and Artavadushti, emphasizing imbalances in doshas—specifically vata and kapha. Ayurveda identifies the root cause of PCOS in "Mithyaachar," representing inappropriate eating habits and an aberrant way of living, including irregular sleep patterns and stress. Both Mithyaahara (improper dietary habits) and Mithyavihar (unhealthy lifestyle) significantly contribute to obesity, a critical factor in PCOS development [94].

Ayurvedic treatment for PCOS is individualized based on symptoms, categorizing PCOS into three groups: infertility, symptoms associated with hyperandrogenism, and irregular menstrual cycles. Ayurveda offers a personalized approach to alleviate and eliminate PCOS symptoms through dietary adjustments, herbal remedies, and lifestyle modifications [94]. Treatment strategies are tailored based on the specific nature, size, and underlying causes of symptoms, utilizing the Tridosha theory to address Vata, Pitta, and Kapha imbalances [95].

According to Ayurveda's Tridosha theory, human physiology is governed by three fundamental forces known as doshas, each with distinct characteristics and functions. Vata facilitates internal transfers in the body, contributing to processes like cell division, waste elimination, and nerve impulse transmission. Pitta regulates digestion, metabolic activities, energy balance, and various physiological functions. Kapha oversees the body's structure and cohesion, including storage, stability, and development. The individual's constitution, or Prakriti, is a unique combination of these doshas. While all doshas consist of the five Mahabhutas (Air (Vayu), Water (Jal), Fire (Agni), Earth (bhumi), and Space (Aakash)), one of them typically dominates, with the others exerting a smaller influence [95].

For Vata vitiation causing irregular menstruation and pain, Ayurvedic herbs like Shatavari and Satapushpa are recommended, often administered through formulations like Satapushpa Shatavari powder (SSP) or Satapushpa–Shatavari Grita (SSG) Matravasti (therapeutic enema). Pitta vitiation leading to hirsutism, acne, and cardiovascular issues is managed with herbs like Manjistha and Ashoka for hirsutism, and Neem and Kutki for acne. Kapha vitiation resulting in weight gain, cyst growth, and depression is addressed with treatments like enemas prepared with Triphala for obesity [96].

Aartava-kshaya, correlating with PCOS, is characterized by a deficiency or loss of menstrual blood, with Ayurvedic interventions focusing on regulating metabolism, clearing obstructions in the pelvic cavity, and normalizing the menstrual system (Aartava Dhatu). The treatment principles aim to restore balance among Dosha, Dhatu, and Upadhatu, considering specific manifestations associated with Kapha, Pitta, and Vata predominance [96].

The management of PCOS should prioritize normalizing the menstrual cycle, achieving ovulation, and addressing associated issues such as hirsutism, acne, and weight concerns, along with managing hyperglycemia and hyperlipidemia to reduce cardiovascular disease risk. Tailoring the treatment approach based on individual symptoms is crucial, incorporating Nidana Parivarjana (avoidance of disease-causing factors). Women are advised to follow principles like Swasthaya Rakshana, including Dincharya (daily regimen), Ritucharya (seasonal regimen), Sadvritta, Achara Rasayana, Hitahara, Samyaka Nidra (adequate sleep), and Vyayama (physical activity) to prevent the onset of the disease [72].

Ayurvedic medications play a key role in PCOS management, addressing specific symptoms:

| Ayurvedic Medication | Symptoms addressed   |  |
|----------------------|--|--|
| Yashtimadhu          | Reduces serum testosterone, beneficial for hirsutism and PCOS  |  |
| Meshshringi          | Reduces glucose absorption, stimulates pancreatic growth, and enhances insulin release                           |  |
| Shatavari            | Stimulates folliculogenesis, aids ovulation,<br>prepares the uterus for conception, and<br>prevents miscarriages |  |

| Methika | Reduces ovarian volume and cyst size, increases LH and FSH                                 |  |
|---------|--|--|
| Kumari  | Decreases testosterone and insulin levels, improves progesterone and estradiol levels      |  |
| Lodhra  | Reduces testosterone levels, restores<br>estrogen, progesterone, and cholesterol<br>levels |  |

Panchakarma, a comprehensive Ayurvedic therapy, is applied in PCOS management. Vamana Karma elevates metabolism and contributes to weight reduction, influencing liver metabolism crucial for hormone synthesis. Uttara Basti is beneficial for gynecological disorders by clearing menstrual blood-carrying channels, pacifying vitiated Apana Vayu, and promoting follicular maturity. Incorporating yoga asanas further aids in improving lipid profiles, glucose levels, and insulin resistance in adolescent girls with PCOS [72].

The selection of medications considers factors like Prakruti (body type), Vikruti (current imbalance), Dosha (energies), Dushya (bodily tissues), Agni (digestive fire), and Ama (toxins). Meshshringi is studied for reducing glucose absorption, stimulating pancreatic growth, and enhancing insulin release. Shatavari is supported for infertility, stimulating folliculogenesis and aiding ovulation. Methika demonstrates a reduction in ovarian volume and cyst size. Kumari has experimental evidence for regulating hormonal levels and improving insulin resistance. Jatamamshi offers antiandrogenic effects, and Lodhra, prescribed for female reproductive dysfunctions, significantly reduces testosterone levels and supports ovarian tissue health [97].

## **Persian Herbal Medicine Treatment for PCOS**

Many women with PCOS seek traditional treatment in adjunct [98]. Traditional Persian medicine can be employed to treat PCOS holistically, using centuries-old remedies found in medieval medicinal Persian manuscripts [99]. The herbal treatments used to alleviate a condition called Ehtebās-e-Tams may be applicable to PCOS as they have similar symptoms [99]. Traditional medicine seems to focus more on holistic treatment compared to modern medicine with a greater focus on treating the causes compared to the symptoms; ancient Persian physicians likely aimed to treat both menstrual irregularities and the underlying metabolic conditions associated with the condition. In Iran, it seems that there is a renewed interest in these traditional herbs, even among pharmaceutical companies. Some of the treatments include single herbs while others include combinations of several herbs [99]. In the remainder of this section, a few medicinal herbs along with their benefits in relation to PCOS will be presented.

*Heracleum persicum* (also known as Persian hogweed or Golpar plant) proved to decrease testosterone levels and body weight in male mice [100]. High testosterone levels tend to be exhibited by women with PCOS. In another study, *Heracleum persicum* was found to decrease levels of LH, estradiol, and testosterone and increase FSH levels in PCOS rats [101]. Additionally, *Heracleum persicum* extract proved beneficial for diabetic rats: improving the function of  $\beta$ -cells in the pancreas and decreasing blood glucose levels [102].

*Cinnamomum verum* was shown to improve insulin sensitivity, menstrual regularity, and digestive flatulence (which is essentially the accumulation of gas) [98]. In one study, cinnamon proved to improve the frequency of menstrual cycles [103]. Cinnamon extract also proved to reduce insulin resistance in PCOS women by increasing the activity of a protein in insulin's signal transduction pathway: phosphatidylinositol 3-kinase [104]. In diabetic rats, reduced levels in fasting blood glucose, HDL, LDL, total cholesterol, and triglycerides were observed following treatment with *Cinnamomum verum* [105].

Treatment using *Origanum majorana* (which is the marjoram herb used to make marjoram tea) demonstrated improvements in insulin sensitivity and reduced adrenal androgen levels [106]. *Glycyrrhiza glabra* was shown to reduce androgen levels, improve digestive flatulence and drug metabolism, and serve anti-inflammatory purposes [98]. *Hypericum perforatum* was also shown to improve drug metabolism, reduce depression, and boost mood – in addition to other cognition effects [98]. *Paeonia lactiflora* proved to reduce androgen levels and improve mood [98]. Depression is quite common in women with PCOS, so *hypericum perforatum* and *paeonia lactiflora* can benefit such patients [98].

 Table 2: Traditional Persian Medicine: A Few Herbal Remedies.

| Scientific<br>Name      | Anti-<br>hyperglycemic | Anti-<br>dyslipidemic | Anti-<br>obesity | Ovulation-<br>inducing |
|-------------------------|------------------------|-----------------------|------------------|------------------------|
| Cinnamomum<br>verum     | $\checkmark$           | $\checkmark$          |                  |                        |
| Glycyrrhiza<br>glabra   |                        | $\checkmark$          | $\checkmark$     |                        |
| Hypericum<br>perforatum | $\checkmark$           | $\checkmark$          | $\checkmark$     |                        |
| Origanum<br>majorana    | $\checkmark$           |                       |                  | $\checkmark$           |

Adapted from [99]: Table 1 in Hosseinkhani, A., Asadi, N., Pasalar, M., & Zarshenas, M. M. (2018). Traditional Persian Medicine and management of metabolic dysfunction in polycystic ovary syndrome. *Journal of Traditional and Complementary Medicine*, 8(1), 17–23. https://doi.org/10.1016/j.jtcme.2017.04.006

## Traditional Chinese Medicine Outlook on PCOS

Traditional Chinese Medicine (TCM) stands as an extensive and time-honored healthcare system with roots tracing back thousands of years in China. Its holistic approach integrates various traditional practices such as herbal medicine, acupuncture, cupping therapy, massage (Tui Na), dietary therapy, and ancient biofeedback exercises like Tai Chi and Qigong. Central to TCM is the fundamental concept of achieving balance and harmony within the body, conceptualizing health as the equilibrium of opposing forces, namely Yin and Yang [107].

Notably, there is no specific reference to Polycystic Ovary Syndrome (PCOS) in ancient Chinese medicine texts. Instead, based on its clinical presentations, PCOS is categorized under conditions like "irregular menstruation," "amenorrhea," or "infertility." Treatment strategies within TCM primarily revolve around restoring equilibrium among the kidney, Tiangui, Chongren, and uterus. Tiangui, recognized as a vital component for women's reproductive health, plays a role analogous to neuroendocrine hormones that regulate reproduction. Disorders in Tiangui timing, state, and rhythm can contribute to female reproductive issues, and in the case of PCOS patients, ovarian dysfunction may manifest as Tiangui disorders.

Acupuncture, an integral component of traditional medicine with a history spanning over 3,000 years in China, has demonstrated clinical efficacy across various health conditions. This ancient practice has proven effective in addressing cardiovascular diseases, epilepsy, anxiety, circadian rhythm disorders, polycystic ovary syndrome (PCOS), low reproductive capacity, and autonomic nervous system diseases. In the context of Traditional Chinese Medicine (TCM), acupuncture involves the insertion of very thin metal needles into specific points on the body. Notably, acupuncture exhibits a remarkable ability to influence the autonomic nervous system (ANS), achieving a balance between sympathetic and parasympathetic nerve activity. This therapeutic intervention regulates adaptive neurotransmitters in relevant brain regions, leading to a reduction in autonomic response—a quality that has demonstrated positive outcomes for PCOS patients.

A specific acupuncture technique, known as the "regulating pregnancy and du-pulse" method, has shown promising results in enhancing the overall reproductive health of individuals with PCOS. This approach contributes to improvements in the menstrual cycle, increased endometrial thickness, enhanced oocyte growth, and follicle development. Additionally, it effectively lowers serum luteinizing hormone (LH) levels, thus improving ovarian function and increasing the ovulation rate in PCOS patients. The multifaceted impact of acupuncture on various aspects of PCOS highlights its potential as a valuable therapeutic strategy within the realm of traditional medicine.

The modern acupuncture approach to treating Polycystic Ovary Syndrome (PCOS) primarily involves targeting specific acupuncture points, such as Sanyinjiao (SP 6), Guanyuan (CV 4), Zigong (EX-CA 1), Zhongji (CV 3), and Qihai (CV 6). These points are selected based on meridian and zang-fu organ theories, syndrome differentiation, and meridian circulation. While the standard treatment for PCOS includes oral medications, lifestyle adjustments, and surgery, acupuncture offers an alternative, particularly considering that pharmacology-based treatments are effective in only 60% of patients.

Comparative studies indicate that acupuncture, when compared to metformin, shows superiority in improving glucose metabolism with a lower incidence of gastrointestinal adverse effects in women with PCOS. Combining acupuncture with Western medicine treatments has demonstrated improved efficacy and a shortened disease course. For instance, the combination of Letrozole, electroacupuncture (EA), and Traditional Chinese Medicine (TCM) significantly enhances the menstrual cycle, reduces body weight, and lowers levels of LH, LH/FSH, testosterone (T), and

anti-Müllerian hormone (AMH) without adverse reactions.

TCM's effectiveness in PCOS lies in its ability to regulate endocrine function, addressing menstrual irregularities, enhancing ovulation, and improving pregnancy rates. Clinical outcomes with TCM surpass those of Western medicine treatments. A metaanalysis supports the efficacy of combining TCM with letrozole in treating PCOS, showing superior results in regulating ovulation rate, pregnancy rate, number of mature follicles, endometrial thickness, cervical mucus score, and serum levels of FSH, LH, T, and prolactin (PRL). This underscores the potential of integrating TCM into the comprehensive management of PCOS [108].

## **Chinese Herbal Medicine**

Overall, Traditional Chinese Medicine has been known to focus on developing treatments from herbs or plants in general for obstetrical and gynecological conditions. The most prescribed herbs through traditional Chinese medicine include *Cyperus rotundus/ Cyperi Rhizoma* (commonly known as Nut Grass), *Rheum officinale* (Chinese Rhubarb), and *Leonurus artemisia* (Chinese Motherwort) [109]. *Cyperi Rhizoma*, known as Xiang-Fu in traditional Chinese medicine, has been prescribed more for helping with antidepressant activity [110]. Studies have also found that the Cyperi Rhizoma reduces the adhesion of endometriosis fragments and can be used for pain relief from endometriosis which may be experienced by PCOS patients [111].

Chinese Motherwort was considered the third most prescribed single herb for PCOS treatment, having a role in promoting blood flow during menstruation [109]. Motherwort has also been found to help in decreasing fasting blood glucose levels along with exhibiting anti-inflammatory effects [112]. Some Chinese herbal medicines that are now also being used in other systems of medicine include Berberine, Cryptotanshinone and Cuscuta. Berberine is an alkaloid found in the roots and bark of Rhizoma Coptidis. Berberine is believed to lower blood glucose and androgen levels [112]. Multiple animal-based studies have pointed towards berberine being effective in improving the morphology of ovarian tissue but also decreasing the level of insulin resistance [113,114]. Considering such promising effects of berberine, research has found that other herbs such as Berberis amurense Rupr. Also have berberine at a lower cost than Rhizoma Coptidis allowing for supplements to be produced [115].

Cryptotanshinone, derived from the danshen root, may be effective in significantly improving abnormal glucose and lipid metabolism. Studies done with mice are promising as cryptotanshinone reduced LH and Testosterone levels allowing for restoration of the estrous cycle and ovulation [116].

*Cuscuta* are a genus of plants that can harm other plants but have benefits to humans, specifically to PCOS patients. The flavonoids or phytochemical compounds extracted from Cuscuta were found to have the ability to regulate estrogen and androgen secretion and inhibit the expression of ovarian apoptic proteins when administered in PCOS-like rats [117]. 10 Chinese herbal formulas were commonly prescribed for PCOS including JiapWei-Xiao-Yao-San (JWXYS-Supplemented Free Wandered Powder), Gui-Zhi-Fu-Ling-Wan (GZFLW-Cinnamon Twig and Poria Pill) and Dang-Gui-Shao-Yao-San (DGSYS-Lessed Abdomen Stasis-Expelling Decoction).

JWXYS herbal formula has been commonly prescribed to help with premenstrual tension, infertility and climacteric syndrome or menopause syndrome with symptoms including fatigue or anxiety due to the gradual degradation of ovarian function in the female hormone decreasing. It has also been found to help with symptoms of anxiety and depression which may be experienced by PCOS patients [118]. The Cinnamon Twig and Poria Pill herbal formula has been found to exert beneficial effects on Type-2 diabetes symptoms, improving impaired glucose metabolism and decreasing blood glucose levels [119]. The Lessed Abdomen Stasis-Expelling Decoction has been used to suppress uterine contractions as well as dysmenorrhea or painful menstruation, which PCOS patients often experience when having an imbalance of hormones [118].

#### **Complementary/ Alternative Medicine**

Complementary or Alternative medicine involves combining practices from other systems of medicine to create a supposed "more-personalized" treatment plan as long as one's doctors are consulted [120]. Complementary and Alternative Medicine (CAM) encompasses a diverse array of healthcare practices and products that fall outside the realm of conventional medicine. The term "complementary" denotes treatments used alongside mainstream medical care, while "alternative" implies the use of non-mainstream approaches in lieu of conventional medicine [121].

The National Center for Complementary and Integrative Health (NCCIH), formerly the National Center for Complementary and Alternative Medicine (NCCAM), provides a comprehensive definition of CAM. NCCIH categorizes CAM into three types: (1) natural products, which include herbs, vitamins, minerals, probiotics, and dietary supplements; (2) mind and body practices, covering a wide range of procedures like yoga, acupuncture, Tai Chi or Qi Gong, massage therapy, meditation, spinal manipulation, hypnotherapy, and relaxation techniques; and (3) other complementary health approaches, which encompass treatments such as traditional Chinese medicine (TCM), naturopathy, homeopathy, as well as functional medicine [122].



Various treatment methods already discussed in this paper have been used in combination to treat PCOS. Some paths of treatment include using Chinese herbal medicine, acupuncture, tai chi, yoga and Qigong [123]. Traditional herbal medicine, with a rich history spanning thousands of years in eastern Asian countries, constitutes a significant aspect of Complementary and Alternative Medicine (CAM). In the context of managing ovulation induction for subfertility related to PCOS, herbal formulas have demonstrated positive adjunct effects when combined with clomiphene citrate (CC). Recently, letrozole has emerged as an alternative to CC, particularly for ovulating and non-ovulating infertile women with PCOS, especially those averse to CC. Findings from current studies indicate that, concerning cycle ovulation rate, pregnancy rate, and the overall effectiveness of intervention, the combination of herbal formulas with letrozole surpasses the efficacy of letrozole monotherapy in treating PCOS [122].

## Discussion

Though this review aims to look deeper into a variety of systems of medicine, there are still systems of medicine rooted in different cultures that may not be studied or may not be as popular as those mentioned in this paper. Considering that Allopathic/Western medicine is often what is studied through obtaining an MD or DO degree, there seems to be more published work and studies done on treatments falling within the medical system. However, recently the Allopathic system of medicine has been incorporating treatments from other systems of medicine in hopes of creating the most effective treatment plans for each PCOS patient like what is being done through Complementary Medicine.

PCOS presents diverse symptoms, making a standardized treatment approach ineffective for all individuals. The heterogeneity of PCOS arises from diverse factors, including genetic predispositions, hormonal imbalances, and lifestyle variations. Consequently, women with PCOS may experience different combinations and severities of symptoms. Recognizing this diversity, many women turn to alternative treatment plans like Ayurvedic, Traditional Chinese Medicine (TCM), Persian Herbal, and Complementary and Alternative Medicine (CAM) in addition to conventional allopathic or Western medicine. Since Allopathic/Western medicine seems to be the most popular, alternative systems of medicine may be used adjunct by PCOS patients to attain the best results. These alternative approaches often offer personalized strategies, addressing the multifaceted nature of PCOS and considering individual differences. Integrating various traditional and complementary therapies provides a holistic perspective, allowing for a more tailored and comprehensive management of PCOS symptoms and underlying imbalances.

Despite PCOS' widespread prevalence, there does not seem to be as much research due to decreased funding and emphasis on policy [124]. This points to the importance of increasing PCOS awareness. To treat infertility in women with PCOS, a research study notes the use of femara (letrozole) -- a drug used to treat breast cancer -- and clomiphene citrate, indicating that the former may be more effective [124]. Perhaps future therapies can focus on the management of hyperandrogenemia as this is not adequately addressed by modern treatments [124]. Furthermore, since high adrenal androgen production results in symptoms associated with PCOS, regulating the release of ACTH through drugs (specifically tildacerfont) is a future avenue to explore [124]. It seems that metformin is the main drug used by medical professionals to treat PCOS currently; however, the heterogeneous nature of PCOS makes it difficult for modern therapies to approach the disease properly and completely [125]. Future therapies can aim to combat this issue further.

## Conclusion

Polycystic Ovary Syndrome (PCOS) is a prevalent hormonal disorder that has been seen and treated through various methods in different cultures and countries. Even though PCOS affects a majority of the population both in the US and worldwide, the causative factors concerning PCOS are poorly understood. However, current research has found correlations between PCOS and certain mental health and metabolic disturbances. It is crucial to understand the etiology of PCOS and how it pertains to women's health, as it is only through education and awareness that we will be able to adequately care for individuals with this disorder to promote a better quality of life.

Future updates may be made as more research is being done on other treatment methods that have been adopted into Allopathic medicine in recent years. This seems to be because every patient with polycystic ovarian syndrome presents differently but also has their personal preference as to whether they should be dependent on allopathic medications. If physicians or practitioners of respective systems of medicine provide patients with options that fit their preferences, there will be an increased likelihood of adherence and thus better results from those treatments. Nutraceuticals and dietary supplements commonly used to treat/ manage PCOS may be available over the counter (OTC), but it is advisable to still consult a physician or other licensed health practitioner before consumption. Doing so will reduce the risk of medication interactions, the worsening of a preexisting condition, or the progression of a new condition.

By reviewing these alternatives for treating and managing PCOS, individuals may be able to understand the precursors of PCOS symptoms and develop preventative measures in addition to the existing healthy lifestyle recommendations. Future research would be needed to confirm the effectiveness of the treatments described in this comprehensive review due to the complexity of the condition and how it manifests a wide range of symptoms affecting one's metabolic and reproductive systems. Before considering alternative treatment and management plans for PCOS, it is advisable to seek guidance from medical experts, which ensures a comprehensive understanding of one's health condition, including the specific symptoms and underlying factors associated with PCOS.

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