

An Overview of Poly Cystic Ovarian Syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a condition with a range of reproductive and metabolic features that affects reproductive-age women. PCOS typically involves hormonal imbalances, insulin resistance, and metabolic abnormalities, which significantly increase the risk of infertility, type 2 diabetes, and cardiovascular disease (CVD). Women with PCOS suffer from greater body dissatisfaction and are also at increased risk of mood, generalized anxiety, and eating disorders. The symptoms of PCOS include menstrual disorders, hirsutism, acne, baldness, and infertility, changes in endocrine hormones such as increased levels of androgen, estrogen, and prolactin and decreased level of progesterone and metabolic disorders of PCOS includes insulin resistance, diabetes, dyslipidemia, and type 2 diabetes. Polycystic ovary syndrome affects women's health and their quality of life across the life course. During different life stages, the polycystic ovary syndrome phenotype can change, which requires a personalized diagnostic approach and treatment. Environmental factors such as diet and obesity appear to contribute to the phenotype. Treatment should be tailored to the specific concerns and needs of the individual patient and involves restoring fertility, treatment of the metabolic complaints, treatment of androgen excess, and providing endometrial protection. The complexity of the disorder, and the impact on quality of life, requires a timely diagnosis, screening for complications, and management strategies for the long-term health issues associated with polycystic ovary syndrome.

KEYWORDS: PCOS, oligomenorrhoea, hirsutism, hyperandrogenism, LH, FSH

I. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a chronic, complex and the most common endocrine

disorder observed in women of reproductive age and it also affects the adolescents.¹ Up to 70% of affected women remain undiagnosed or have long delays before the condition is recognised.² The prevalence is generally considered to be between 6-20%, depending on the definition and the population studied.³ This syndrome is heterogeneous by nature and is characterized by a combination of signs and symptoms of androgen excess and ovarian dysfunction in the absence of other specific diagnoses.⁴ Women with PCOS often present in their adolescence or early adulthood with symptoms of oligomenorrhoea or hirsutism or infertility.⁵ Although it was previously considered as a disorder of adult women, recent evidence suggests that PCOS is a lifelong syndrome, manifesting since prenatal age.⁶ It is a significant public health issue. The health risks associated with PCOS, however, go far beyond management of these features and likely extend past the reproductive years through and beyond menopause. Women present with diverse features including psychological (anxiety, depression, body image and impaired quality of life)⁷, reproductive (irregular menstrual cycles, hirsutism, infertility and pregnancy complications)⁸ and significant metabolic features (insulin resistance, metabolic syndrome, prediabetes, type 2 diabetes mellitus and cardiovascular risk factors).⁹ There is also an increased rate of weight gain and prevalence of obesity in PCOS, increasing severity of the condition, causing considerable concern for those affected and mandating attention to healthy lifestyle.¹⁰ PCOS has the potential for serious consequences, including increased risk for the development of endometrial hyperplasia and neoplasia.¹¹

Etiology of PCOS

Although the exact cause of PCOS is unknown, it is understood to be a multifactorial condition with a genetic component.

Approximately 20–40% of first-degree female relatives of women with PCOS go on to develop PCOS themselves, compared to an estimated 4–6% prevalence in the general population.¹² Many women with PCOS have female relatives with PCOS, even if it was never diagnosed.¹³ As with type 2 diabetes, it is likely that numerous genes each make a small contribution to the etiology of PCOS; and recent genome-wide association studies have identified candidate genes.¹⁴ Any underlying genetic predisposition is likely complicated by epigenetic and environmental factors such as an unhealthy diet and lack of physical activity.

Pathophysiology

The cause of PCOS has not yet been definitely determined; however, it is mainly characterized by hyperandrogenism, infertility, lack of ovulation,¹⁵ increased level of LH,¹⁶ increased insulin resistance, decreased sex hormone-binding globulin (SHBG)^{17,18} and hirsutism.¹⁹ Because of disrupted secretion rate and metabolism of androgens and estrogens in women with PCOS, the serum concentrations of androgens such as testosterone, androstenedione, and dehydroepiandrosterone are most probably high in such women.²⁰ In addition, the incidence of certain complications such as environmental insulin resistance and hyperinsulinemia is very likely. Such complications lead to obesity at different degrees. Insulin resistance can occur due to impaired signaling pathway of insulin receptor. Therefore, insulin function in the cell is impaired, which causes further increase in insulin secretion to compensate for its shortage. With increase in insulin, the effect of gonadotropins on ovarian function increases, and adiponectin decreases in patients with PCOS due to insulin resistance. Insulin resistance and subsequently excessive increase in insulin levels cause the frequency of GnRH to escalate, which results in increased LH/FSH. These hormone changes in the theca cells and granulosa cells (GCs) cause increase in the synthesis of androgens and decrease in the synthesis of estradiol, and stops the maturation of follicles, leading to impaired ovulation and therefore development of PCOS.²¹

Signs and symptoms

The symptoms of PCOS usually varies with age, young women mainly complaining of reproductive and psychological problems while older women complaining of metabolic symptoms.²² A thorough physical examination,

medical history, and laboratory tests should be conducted to reach the appropriate diagnosis. In addition, on the one hand, testing should include an assessment of the metabolic status of the patient, i.e., measurement of her body mass index (BMI), conduction of a fasting lipid panel, and a 2-h glucose challenge test. On the other hand, screening for thyroid disorders through assessment of thyroid-stimulating hormone levels is considered important as thyroid disorders are a common cause of menstrual irregularity (Kamangar et al., 2015).

Irregular periods- Infrequent, irregular or prolonged menstrual cycles are the most common sign of PCOS. For example, you might have fewer than nine periods a year, more than 35 days between periods and abnormally heavy periods.

Excess androgen- Elevated levels of male hormone may result in physical signs, such as excess facial and body hair (hirsutism), and occasionally severe acne and male-pattern baldness.

Polycystic ovaries- Ovaries might be enlarged and contain follicles that surround the eggs. As a result, the ovaries might fail to function regularly.

Clinical features of polycystic ovary syndrome: Oligomenorrhea/amenorrhea, Infertility/first trimester miscarriage, Obesity, Hirsutism, Acne, Acanthosis nigricans, Male pattern alopecia.

Complications of PCOS can include: Infertility, Gestational diabetes or pregnancy-induced high blood pressure, Miscarriage or premature birth, non-alcoholic steatohepatitis — a severe liver inflammation caused by fat accumulation in the liver, Metabolic syndrome — a cluster of conditions including high blood pressure, high blood sugar, and abnormal cholesterol or triglyceride levels that significantly increase your risk of cardiovascular disease, Type 2 diabetes or prediabetes, Sleep apnea, Depression, anxiety and eating disorders, Abnormal uterine bleeding, Cancer of the uterine lining (endometrial cancer), Obesity is associated with PCOS and can worsen complications of the disorder.

Diagnosis of PCOS

Some sets of criteria for diagnosis have been proposed for PCOS: National Institutes of Health Criteria (NIH), defined in 1990 and include only presence of clinical and/ or biochemical hyperandrogenism and oligo/amenorrhea anovulation (Zawadski and Dunaif, 1992).²³ Later in 2003 the Rotterdam Criteria used polycystic ovarian morphology on ultrasound as a new criterion to be added to the two previous criteria of

NIH. The European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine Rotterdam consensus (ESHRE/ ASRM) developed and enlarged the diagnosis of PCOS, requiring two of three features: anovulation or oligo-ovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology (PCOM) seen on ultrasound. Finally the Androgen Excess Society defined PCOS as hyperandrogenism with ovarian dysfunction or polycystic ovaries (Azziz et al., 2006). Thus the Androgen Excess Society (AES) considered that androgen excess is a central event in the development and pathogenesis of polycystic ovary syndrome, and established that androgen excess should be present and accompanied by oligomenorrhea or PCOM or both of them (Azziz et al., 2006). Exclusion of other androgen excess disorders should be excluded such as non-classical congenital adrenal hyperplasia (NC-CAH), Cushing's syndrome, androgen-secreting tumors, hyperprolactinemia, thyroid diseases, drug-induced androgen excess, as well as other causes of oligomenorrhea or anovulation (Spritzer, 2014).

Medical history & examination As part of the diagnosis, review the medical history and assess the physical symptoms, weight and BMI (body mass index).

Ultrasound An ultrasound of the uterus, ovaries and the pelvis can be carried out to identify whether there are any cysts on your ovaries and whether an ovary is enlarged. A transvaginal ultrasound is a painless test with no radiation. It uses a pen-shaped probe with an ultrasound sensor on the tip, which is inserted into the vagina. This produces a much clearer picture than an abdominal ultrasound. Transvaginal ultrasounds are only performed on women who have been sexually active, otherwise an abdominal scan is done where the ovaries are viewed from the outside through the stomach wall.

Blood tests

Hormonal blood tests

Blood tests are used to assess the levels of androgens in your body. Blood tests for androgens (such as testosterone) and free androgen index (FAI) are the best tests for diagnosing hyperandrogenism (high androgen levels).

Other blood tests that can be useful in identifying high androgen levels include:

- Sex hormone binding-globulin (SHBG)
- Dehydroepiandrosterone sulphate (DHEAS)

- Androstenedione

Blood tests may also be done to assess the levels of other reproductive hormones in your body as these may affect your menstruation. These may include testing your levels of:

- Oestradiol (oestrogen)
- Follicle stimulating hormone (FSH)
- Luteinising hormone (LH)

Blood tests to exclude other conditions that have similar symptoms to PCOS may measure the levels of:

- thyroid stimulating hormone (TSH)
- prolactin
- hormones related to adrenal function (glands found above the kidney), e.g. 17-hydroxyprogesterone

Other tests

Assessing the risk of developing cardiovascular disease and diabetes is important when testing for PCOS because there are links between PCOS and insulin resistance and being overweight. Tests to assess these risks will measure:

- Cholesterol blood test
- Blood pressure
- Glucose metabolism/tolerance blood test

Treatment

Treatment of hirsutism (androgen-related symptoms)^{24,25}

Oral contraceptive pills (OCPs) are first-line for pharmacologic management of hirsutism in premenopausal women. Antiandrogens can be added if there has been no improvement after 6 months of treatment of OCPs. OCPs and antiandrogens have both been effective in the treatment of acne. In severe acne, isotretinoin may offer benefits for some patients. There is limited data for treatment of alopecia, but OCPs and androgen blockers are used. In Combined hormonal contraceptive (CHC), OCPs are a good treatment option for those patients that do not wish to become pregnant, and they are often considered first line for the treatment of PCOS-related hirsutism and acne. CHCs promote negative feedback on the production of LH, causing a decreased synthesis of androgens by the ovaries. Other mechanisms by which CHCs reduce androgens include: 1) decreasing circulating levels of free androgen by increasing the production of sex hormone binding globulin in the liver; 2) decreasing adrenal androgen secretion; and 3) inhibiting peripheral conversion of testosterone to

dihydrotestosterone and binding of dihydrotestosterone to androgen receptors.

Spirolactone, an **aldosterone antagonist**, is an antiandrogen that primarily acts by binding to the androgen receptor as an antagonist. It also inhibits ovarian and adrenal steroidogenesis, directly inhibits 5- α -reductase activity, and competes for androgen receptors in hair follicles.^{108,109} Doses of 25–200 mg per day in one to two divided doses are used.

Lifestyle modification/weight loss :It involves the increase in SHBG that occurs with improvement in insulin sensitivity. With an increase in SHBG, bioavailable (free) testosterone decreases, thus lowering testosterone action. The effect of these treatments on hirsutism, then, is due in part to decreased testosterone action (in addition to lowering testosterone as noted earlier). In the previously mentioned study by Kiddy et al., >5% weight loss resulted in a 40% reduction in hirsutism.

Eflornithine hydrochloride 13.9% cream

Eflornithine is a topical cream that has been approved by the US Food and Drug Administration for removal of unwanted facial hair in females. Eflornithine inhibits the enzyme ornithine decarboxylase in the skin, which inhibits cell division and synthetic functions, thus reducing the rate of hair growth. It should be used twice daily, at least 8 hours apart, on the affected areas of the face and chin.

Management of insulin resistance/type 2 diabetes mellitus risk

Metformin and thiazolidinediones have insulin-lowering effects by improving insulin sensitivity, and in turn can decrease circulating androgen levels. Additionally, these agents have a role in the treatment of PCOS due to the fact that women with PCOS are at an increased risk of insulin resistance, and in turn the development of metabolic disorders and cardiovascular disease. Although no antidiabetic agents have US Food and Drug Administration approval for the treatment of PCOS, metformin is preferred at this time due to the fact that it appears to have the safest risk-benefit ratio, and it can cause weight loss, while thiazolidinediones can increase weight as a result of fluid retention. Although metformin is used for ovulation induction in PCOS.

Management of Menstruation-related disorders

Along with patient complaints of menstrual irregularity, the often chronic

anovulation that is associated with PCOS can increase a patient's risk of endometrial hyperplasia and carcinoma. Using either cyclic progestin or a low dose CHC containing estrogen and progestin can help inhibit endometrial proliferation. Low dose CHCs are the primary recommended treatment option for PCOS-related menstrual disorders and improved menstrual regularity.

Weight loss can improve circulating androgen levels, along with providing numerous other metabolic benefits for patients with PCOS. The benefits of weight loss can be evident with a loss of 5% of initial body weight. An additional treatment that is gaining popularity is acupuncture. The primary benefits that have been suggested with acupuncture are reduced hyperandrogenism and improved menstrual regularity.

Management of infertility

Weight loss is recommended as first-line therapy for the management of infertility in overweight and obese women with PCOS. Anovulation and pregnancy loss are linked with obesity. In addition, obesity is associated with a reduced response to fertility treatments including clomiphene citrate, gonadotropins and laparoscopic ovarian diathermy. Observational studies indicate that weight loss of 5%–10% can increase ovulation and pregnancies. Bariatric surgery has been shown to improve cycle regularity, increase ovulation, and increase spontaneous conception.

Clomiphene citrate

Clomiphene citrate is the drug of first choice for ovulation induction in women with PCOS. Clomiphene citrate is a partially selective estrogen receptor modulator. Its antiestrogenic activity at the hypothalamus induces a change in gonadotropin releasing hormone (GnRH) pulse frequency leading to increased release of follicle stimulating hormone (FSH) from the pituitary gland.

Aromatase inhibitors

Aromatase inhibitors block the conversion of testosterone and androstenedione to estradiol and estrone, respectively. This decrease in estrogenic activity releases the hypothalamus from negative feedback, allowing for an increase in the release of FSH. Letrozole, the most commonly used aromatase inhibitor for ovulation induction, is administered in doses between 2.5–7.5 mg per day

for 5 days starting on day 3 of the menstrual cycle. Putative advantages of letrozole include its lack of antiestrogenic effects on the endometrium, shorter half-life when compared to clomiphene and a higher rate of monofollicular ovulation.

Ovulation induction

Ovulation induction with gonadotropins and laparoscopic ovarian drilling (LOD) are considered to be second line therapies for ovulation induction by the ESHRE/ASRM. The gonadotropin approach is less invasive and is the preferred treatment in women who do not desire surgery. LOD is preferred when the patient has other indications for surgery or when the patient is not able to comply with the frequent follow-up visits required with gonadotropin therapy. The goal of FSH administration for ovulation induction is the development of a single follicle resulting in a singleton live birth. Risks associated with ovulation induction include ovarian hyperstimulation syndrome (OHSS) and pregnancy with multiples. Because women with PCOS are very sensitive to the effects of FSH, a low-dose step-up protocol is recommended.

LOD (laparoscopic ovarian drilling)

LOD involves the use of laser or electrocautery to drill four to ten holes in the surface and the stroma of the ovary. It is indicated for the treatment of infertility in clomiphene-resistant PCOS.¹²³ A single treatment results in the establishment of ovulatory menstrual cycles in 92% of women, and pregnancy in 58%.

In-vitro fertilization (IVF)

In-vitro fertilization (IVF) is recommended as third-line therapy for the management of infertility by the 2008 Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Women with PCOS have similar pregnancy, miscarriage, and live-birth rates with conventional IVF compared to non-PCOS patients.¹⁴⁴ Women with PCOS experienced more cycle cancellations. In addition more oocytes were retrieved per cycle with a lower fertilization rate in women with PCOS. In a recent Cochrane review comparing the GnRH antagonist protocol with the long GnRH agonist protocol in women with PCOS undergoing IVF/ICSI treatment, no significant difference was found in ongoing pregnancy rate or clinical pregnancy rate. However, the rate of OHSS was 10% lower with the antagonist protocol.

Surgery

Surgery can be an option to improve fertility if other treatments doesn't work. Ovarian drilling is a procedure that makes tiny holes in the ovary with a laser or thin heated needle to restore normal ovulation.

Bariatric surgery

This is the most suitable strategy for morbidly obese patients who are not able to achieve weight loss through a combined diet and exercise regimen. There are many approaches like restrictive and malabsorptive procedures, adjustable gastric banding and Roux-en-Y gastric bypass that are frequently used (Badawy&Elnashar, 2011). Studies have reported significant weight loss, however individuals who undergo bariatrics surgery are at a risk of nutritional deficiencies and so the pros and cons must be weighed carefully.

ALTERNATIVE TREATMENT FOR PCOS

1. Ayurvedic drugs²⁶ 2. Chinese Herbal medicines²⁷ 3. Holistic Approach (acupressure)²⁸ 4. Psycho-physiotherapeutic treatment²⁹ 5. Siddha treatment³⁰ 6. Herbal treatment³¹ 7. Natural treatment (nutritional supplements).

MEDICINAL PLANTS FOR PCOS³²

1. Asparagus Racemosus (Shatavari)

Asparagus racemosus, (Asparagaceae) is traditionally used in Indian medicine (Ayurveda). It helps in promoting normal development of ovarian follicles, regulates menstrual cycle and revitalizes the female reproductive system mainly due to its phytoestrogen (natural plant based estrogen). It also helps in combating the hyperinsulinemia.³³

2. Tinospora Cordifolia (Guduchi)

Tinosporacordifolia, (Menispermaceae) is a well known medicinal plant for its hypoglycemic effects.³⁴ Tinospora Cordifolia is a powerful anti-inflammatory herb. Chronic inflammation in tissues is the root cause for insulin imbalance and ovarian cysts. It helps in lowering insulin resistance, revitalizing all the body tissues and boosting a metabolism naturally.

3. Foeniculum vulgare (Shatapushpa)

Foeniculum vulgare, (Apiaceae) seeds are used as a good supplement for management of PCOS. helps in reduce the cellular imbalance which leads to metabolic disturbances in PCOS.³⁵

4. Ocimum tenuiflorum (Holy Basil)

Ocimum tenuiflorum L. (Lamiaceae) is a traditional herbal medicine commonly known as Tulsi. Ocimum tenuiflorum is potentially effective

for polycystic ovarian syndrome. It has got excellent anti-androgenic properties to decreasing the androgen production (Hyperandrogenism).³⁶

5. **Actaeoracemosa (Black Cohosh)**

Actaeoracemosa (Ranunculanae) is used in various disorders of female reproductive system viz. anovulation, infertility, hormonal balance which are important issues in PCOS. Black Cohosh has the ability to induce ovulation in women with polycystic ovarian syndrome (PCOS).³⁷

6. **Lepidiummeyenii (Maca)**

Lepidiummeyenii from Brassicaceae family is a traditional herbal medicine used in relieving menopausal symptoms, stimulates the endocrine system and act as natural hormonal balancer without side effects. Estrogen and progesterone hormones in the body help in encouraging a healthy menstrual cycle. It is an adaptogen and an incredible fertility super food. Lepidiummeyenii restores the levels of testosterone in the males.³⁸

7. **Grifolafrondosa (Maitake Mushroom)**

Grifolafrondosa extract can able to induce the ovulation in women with polycystic ovarian syndrome (PCOS) in animal studies.³⁹

8. **Taraxacumofficinale (Dandelion Root)**

Taraxacumofficinale (Asteraceae) can stimulate the production of SHGB which reduce the free testosterone in the blood which is used in PCOS treatment because menstrual irregularities are often affected by the liver which is being backed up with excessive hormones. It also helps in removal of toxin from the body, thus helping the women who are experiencing fertility problems and menstrual issues.⁴⁰

9. **PergulariaDaemia (Veliparuthi)**

It has potential effect on normalizing menstrual irregularities and regularizing the estrous cycle. So the restoration of the estrous cycle reduces the development of follicular cyst.⁴¹

10. **Areca catechu (Betal Palm)**

Areca catechu (Arecaceae) tenderly maintains the healthy production of female hormones & relieves congestion of the blood vessels in abdominal area. Areca catechu maintains healthy female reproductive system, eases menopausal transition and helps in supporting healthy libido. It helps in increasing the retentive power of the uterus and used to remove debility after child birth.⁴²

II. CONCLUSION

PCOS is a complex disease in which genetic, endocrine, environmental, and behavioral

factors are intertwined, giving rise to a heterogeneous phenotype with reproductive, metabolic, and psychological characteristics that affect women's health and quality of life across the life course. PCOS is treatable with lifestyle changes, medication and some medicinal plants. many of the estimated 1 in 10 women with this condition go without adequate treatment because of underdiagnosis. To facilitate accurate diagnosis and timely treatment, clinicians who see female patients need to be familiar with the diversity of PCOS phenotypes.

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