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Bintey Zehra
Department of Biotechnology,
Veer Bahadur Singh Purvanchal
University, Uttar Pradesh, India

Khursheed AA
Department of Anatomy, Jamia
Hamdard, New Delhi, India

Polycystic ovarian syndrome: Symptoms, treatment and diagnosis: A review

Bintey Zehra and Khursheed AA

Abstract

Polycystic ovary syndrome (PCOS) is a complex condition branded by elevated hormone levels, menstrual irregularities, and/or tiny cysts on one or each ovary. The disorder can be physiological (polycystic ovaries) or biochemical (hyperandrogenemia). Hyperandrogenism, a hallmark sign of PCOS, can cause inhibition of follicular development, cysts in the ovaries, anovulation, and menstrual changes. Environmental factors implicated in PCOS (e.g., obesity) can be aggravated by poor dietary choices and physical inactivity; infectious agents and toxins may also play a role. The physiopathology of PCOS involves primary defects in the hypothalamic-pituitary axis, insulin secretion and action, and ovarian function. Although the cause of PCOS is unknown, PCOS has been linked to insulin resistance and obesity. Follicular maturation arrest is a hallmark indication that an ovarian abnormality exists. PCOS continues to be a common cause of infertility among women. Although signs and symptoms vary, the three most common factors associated with PCOS include menstrual irregularities, increased androgen levels, and cystic ovaries. PCOS status is expected to have a long-term effect in women, particularly the development of type 2 diabetes, cardiovascular diseases and hormone-dependent disease. According to the National Institutes of Health, PCOS affects approximately 5 million women of childbearing age in the U.S. Costs to the U.S. healthcare system for the identification and management of PCOS are approximately \$4 billion per year.

Keywords: Anovulation, follicular maturation, ovarian follicles, physiopathology

1. Introduction

Polycystic ovary syndrome (PCOS) was first reported in the modern medical literature by Stein and Leventhal in 1935, described seven women suffering from amenorrhea, hirsutism, and enlarged ovaries with multiple cysts [1]. Polycystic Ovary Syndrome is a highly heritable, complex reproductive disorder with unknown underlying genetic factors [2]. PCOS is a hormonal disorder with a potential to lead to various diseases. It also continues to be a common cause of infertility among women [3]. Moreover, PCOS is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology [4]. It is the most common cause of infertility, meaning that the infertility results from the absence of ovulation, the process that releases a mature egg from the ovary every month. Many of the women don't realize that they have PCOS as far as they have trouble getting pregnant. Women with PCOS have a normal number of primordial follicles. Primary follicle and secondary follicles are somewhat increased and also lead to a condition called endometrial hyperplasia, in which the lining of the uterus becomes too thick. This condition increases the risk of endometrial cancer [5]. Another condition associated with PCOS is Metabolic syndrome contributes to both diabetes and Heart disease [5]. Several studies conclude that women with PCOS have an increased prevalence of hypertension, potential mechanisms of hypertension in PCOS include endothelial dysfunction [6]. Lo *et al.* reported that women with PCOS were more likely to have hypertension or elevated blood pressure than controls after adjusting for BMI category, age and diabetes [7]. Shaw *et al.* reported a 3.3-fold greater risk of cardiovascular death or myocardial infarction in 104 postmenopausal women with a history of irregular menses and hyperandrogenemia [8]. Problems with ovulation and elevated androgen levels occur in the majority of women with hirsutism, acne, dark patches of skin with elevated androgen levels, mental health disorders including depression, anxiety, bipolar disorder and binge eating disorder also occur more frequently and the prevalence of polycystic ovaries on pelvic ultrasound exceeds 70% in patients with PCOS. The diagnostic norm for PCOS has been offered by three groups: the National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD) [9]; the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) [10]; and the Androgen Excess and PCOS Society [11]. There is no cure but diet, exercise, and medicines can help control the symptoms. Birth control pills help women have normal periods, reduce male

Correspondence

Bintey Zehra
Department of Biotechnology,
Veer Bahadur Singh Purvanchal
University, Uttar Pradesh, India

hormone levels, and clear acne. Treatments for infertility caused by PCOS may include medicines, surgery, and *in vitro* fertilization [12].

2. Pcos Symptoms

Symptoms of PCOS may begin shortly after puberty, but can also develop during early adulthood. Women with PCOS frequently have irregular or missed periods as a result of anovulation, although some women may establish cysts on their ovaries. In addition to nonappearance of ovulation, high levels of androgens, ovarian cysts and PCOS have many signs and symptoms [13, 14].

2.1 Other symptoms include

- **Menstrual irregularities:** Menstrual disturbances commonly observed in PCOS include oligomenorrhea, amenorrhea, and prolonged erratic menstrual bleeding [15].
- **Weight gain:** Obesity, weight gain, or trouble losing weight, especially around the waist.
- **Fatigue:** Many women with PCOS report increased fatigue and low energy, related issues such as poor sleep.
- **Hirsutism:** Hirsutism is a common clinical presentation of hyperandrogenism occurring in up to 70% of women with PCOS [16]. Areas affected by extreme hair growth may include the face, arms, back, chest, thumbs, toes, abdomen and link to PCOS due to hormonal changes.
- **Thinning hair on the head:** The high level of androgens causes hair loss or thinning of the scalp.
- **Infertility:** Because a dominant follicle does not develop, ovulation does not ensue [17].
- **Acne:** Hormonal changes concern to androgens can lead to acne problems. Dark patches of skin are also connected to PCOS. Some experts recommend that women presenting with acne be asked about their menstrual history and be evaluated for other signs of hyperandrogenism [18].
- **Mood changes:** Depression and anxiety are common symptoms [19].
- **Pelvic pain:** Pelvic pain may occur with periods, along with heavy bleeding. Headaches
- **Sleep problems:** Women with PCOS often report problems such as insomnia or poor sleep. PCOS has been linked to a sleep disorder called sleep apnea.

2.2 Causes of PCOS

Genetic and environmental contributors to hormonal disturbances combine with other factors, including obesity, ovarian dysfunction and hypothalamic-pituitary abnormalities to contribute to the pathology of PCOS [20, 21].

Genes, insulin resistance, and inflammation have all been linked to excess androgen production.

2.2.1 Genes

Studies show that PCOS runs in families [22]. It's likely that many genes not just one contribute to the condition [23].

Some clinical genetic studies have pointed to an autosomal dominant inheritance [24, 25], while others showed that it was more likely that the syndrome is a complex trait with oligogenic basis [26, 27].

Two possible methods used to identify a genetic locus for PCOS genes: a) association studies where a predisposing allele is expected to be found more frequently in the affected population than the normal individuals. b) linkage studies

where the families are investigated to determine if particular genomic landmarks are distributed independently or in linkage with the phenotype. Studies showed that the enzyme complex aromatase converts androgens to estrogens. This enzyme complex is composed of the cytochrome P450 aromatase and the NADPH cytochrome P450 reductase [28]. Aromatase deficiency has been reported in a number of hyperandrogenic patients [29, 30]. It has been demonstrated that granulosa cells obtained from medium-sized follicles of women with PCOS have little aromatase activity [31]. Similarly, it has been shown that when compared to the control follicles, all PCOS follicles contained low levels of P450arom mRNA, estradiol, and lower aromatase stimulating bioactivity [32]. These studies show that, aromatase activity conceivably decreased in PCOS follicles, and that the possible androgen excess perhaps contributes to abnormal follicle development.

2.2.2 Insulin resistance

Up to 70 percent of women with PCOS have insulin resistance, meaning that their cells can't use insulin properly [33]. Insulin resistance and hyperandrogenism play a key role in the pathophysiology of PCOS and insulin resistance affect ~85% (75% of lean and 95% of overweight) of cases (Stepito *et al.*, 2013).

Insulin is produced by pancreas aids the body consume sugar from foods for as an energy source. In case the cells can't use insulin efficiently, the body's demand for insulin upsurges. As a result, pancreas creates more insulin to compensate. Additional insulin incites the ovaries to produce more male hormones.

Studies showed that the hyperinsulinemia in PCOS may be the result of primary insulin resistance or the direct effect of pancreatic β -cell disorder as defects in both insulin action [34, 35], and in pancreatic β -cell function have been reported [36, 37].

Obesity is a major cause of insulin resistance. Both obesity and insulin resistance can increase the risk for type 2 diabetes [38]. Insulin resistance is a pathophysiological contributor in around 50% to 80% of women with PCOS [39]. The DASH (Dietary Approaches to Stop Hypertension) eating plan, developed by the NIH, has been shown to be effective in decreasing insulin resistance when combined with weight loss and physical activity.

2.2.3 Inflammation

Women suffering from PCOS over and over again have amplified levels of swelling in their body. Being overweight may also contribute to inflammation. Studies have linked excess inflammation to higher androgen levels [40].

Studies reveal that genes involved in chronic inflammation, such as TNFR2 (type-2 TNF receptor) gene [41], IL-6, IL-6 signal transducer gp 130, IL-6 receptor [42] genes have also been investigated for association with PCOS, but without significant results. In addition to the genes mentioned above, many different genes such as 17α -hydroxysteroid dehydrogenases [43], dopamine receptor [44, 45], aldosterone synthetase [46], and glycogen synthetase [47] have been studied, however, results were controversial, without clear conclusions.

3. Pcos Treatment

Birth control pills and other medicines can help to readjust the menstrual cycle and treat PCOS symptoms like hair growth and acne. Common medical treatments include:

3.1 Birth control

Taking estrogen and progestin daily can restore a normal hormone balance, regulate ovulation, relieve symptoms like excess hair growth, and protect against endometrial cancer. Treatment with progestin before ovulation induction is counterproductive in helping women with PCOS achieve pregnancy," said Esther Eisenberg, M.D., of the Reproductive Sciences Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

3.2 Metformin

Metformin is a drug used to treat type 2 diabetes and also treats PCOS by improving insulin levels. Metformin has had an increasing role in PCOS management improving clinical features (ovulation, cycle regulation, and potentially hirsutism) with positive cardiometabolic effects [48].

One study found that taking metformin while making changes to diet and exercise improves weight loss, lowers blood sugar, and restores a normal menstrual cycle better than changes to diet and exercise alone [49]. Metformin may also be beneficial for women with PCOS with metabolic syndrome and/or obesity [50]. In its 2008 consensus statement, the ESHRE/ASRM concluded that metformin is less effective than clomiphene in inducing ovulation and that there was no advantage to adding metformin to clomiphene [51].

3.3 Clomiphene

Clomiphene is a fertility drug that can help women with PCOS get pregnant. However, it increases the risk for twins and other multiple births [52]. Clomiphene citrate is the drug of the first choice for ovulation induction in women with PCOS [53]. Studies reveal that the starting dose of clomiphene citrate is 50 mg per day for 5 days starting on days 2–5 following a spontaneous or progestin-induced withdrawal bleeding. If ovulation does not ensue, the dose is increased by 50 mg per cycle to a maximum dose of 150 mg/day. Other treatments to trigger ovulation include another oral medication called letrozole and gonadotropins which are hormones that are given by injection. *In vitro* fertilization and *in vitro* maturation may be other fertility treatment options. One in 10 women who conceive with the aid of clomiphene will have multiple pregnancies, most commonly twins [54]. The American College of Obstetricians and Gynecologists (ACOG) recommends that clomiphene should be the primary medication for PCOS patients with infertility.

3.4 Hair removal treatment

Female hirsutism is an embarrassing condition that threatens a woman's perception of her femininity and her self-esteem which can lead to high levels of depression and anxiety. There are various causes of excessive facial hair in women, the most common is polycystic ovary syndrome (PCOS). A few treatments can help get rid of unwanted hair or stop it from growing, these include the prescription cream eflornithine hydrochloride (Vaniqa), acne products, and cosmetic treatments such as laser therapy and electrolysis to curb hirsutism on face and body. Dr. Andrea Dunaif from Northwestern University typically starts patients with spironolactone. A 6-month testing is needed to show effects on unwanted hair, and she generally starts women at an extra dose, the unwanted hair doesn't disappear, however, grows in finer and lighter. In 1963, Dr. Leon Goldman, the father of laser medicine who invented ruby laser in 1960 for treating a variety of pigmented lesions, published first-ever scientific article devoted to the subject of laser-skin interactions and the

use of laser in medicine [55]. In 2009, for the first time, a surgical laser system was advertised in the UK Podiatry magazine indicated for the treatment of onychomycosis. Lasers are often marketed as a means of improving a practice's income, however mechanism of action of lasers in the treatment of onychomycosis remains unclear. Moreover, by using a pulsed beam instead of a continuous beam, these lasers can deliver a selective photothermolysis [56].

3.5 Surgery

Surgery could be an option to refine fertility if other treatments don't work. Ovarian drilling is a practice that makes little holes in the ovary with laser treatment or fine heated needle to restore normal ovulation.

3.5.1 Surgery choices

1. Ovarian wedge abscission is the surgical removal of part of an ovary done to help regulate menstrual cycles and start normal ovulation.
2. Laparoscopic ovarian puncture, a surgical medication that can trigger ovulation in women who have PCOS and who have not counteracted to weight loss and fertility medicine [57].

3.6 Treatment Overview

Regular exercise, a healthy diet (balanced diet), weight control, and not smoking (level of Androgen is excess in women who smoke) are all important parts of treatment for polycystic ovary syndrome (PCOS).

4. Diagnosis

PCOS is diagnosed in women who have notably these three symptoms:

4.1 High androgen levels

All women produce small amounts of androgens in tissues including the ovaries and the adrenal glands. High levels of androgens can prevent ovulation and affect the menstrual cycle. Most common androgen-related symptoms associated with PCOS are acne, hirsutism, and alopecia. More than 80% of adults with PCOS have hyperandrogenemia [58] although acne may be the presenting symptom of underlying hyperandrogenism [59].

4.2 Irregular menses

Menstrual irregularity is a common feature of PCOS, occurring in more than 75% of the adult PCOS population [58]. Researchers suggest that a possible diagnosis of PCOS can be based upon a long-term history of oligomenorrhea and hyperandrogenism during the reproductive years. The presence of PCOS morphology on ultrasound would grant additional supportive information. Although irregular menstrual cycles cannot be the basic symptoms of PCOS, they enclose an important symptom that should be followed in the adolescent.

4.3 Cysts in the ovaries

Ovarian cysts are small fluid-filled sacs that develop in a woman's ovaries. Most cysts do not cause harm, but some are problematic such as rupture, bleeding, or pain. In some cases, ovarian cysts can cause problems with menstrual periods such as abnormal or irregular bleeding, due to ovarian cysts [60]. The European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) sponsored a workshop in

Rotterdam. During the workshop, polycystic ovarian morphology on pelvic ultrasound was added to the NICHD/NIH criteria. By adding the polycystic ovaries criterion, the Rotterdam definition enhances the diagnosis of PCOS to women with oligo-ovulation and polycystic ovaries. In October 2013, the Endocrine Society unleashed new guidelines for the diagnosis and treatment of PCOS.

5. Recent PCOS Studies

With the latest development and breakthroughs in biomedical research and clinical medicine a broad spectrum of information about treatment option, new clinical development and advance research to facilitate the information, the work carried from prominent researchers and physicians.

University of Birmingham (March 13, 2017) discovered that a new class of male sex hormones known as androgens plays a key role in the development of polycystic ovary syndrome (PCOS). This research eradicated new ground by showing that a novel class of androgen, known as 11-oxygenated C19 steroids, is the principal contributor to androgen excess in women with PCOS. Department of Women's Health, University of Sydney, Royal North Shore Hospital, NSW 2065, Australia (February 17, 2016) published a journal Polycystic Ovarian Syndrome and Eating Disorder Quality of Life: A Pilot Study; to compare 'quality of life related to eating and exercise (QOLED)' in women with and without PCOS who are seeking fertility treatment. These findings support the assessment of disordered eating and lifestyle change as the first-line treatment of women with PCOS. It is also suggested that eating disorders may create a hormonal environment predisposing individuals to the development of PCOS [61]. Department of Obstetrics and Gynecology, IVF Division, Benha Faculty of Medicine, Egypt (August 07, 2013) published a journal Agnucaston and Clomiphene Citrate in Infertile Patients with Polycystic Ovaries; showing that combined agnucaston with clomiphene citrate result in the pregnancy rate 30 out of 50 (60%) while the clomiphene only result a pregnancy rate 15 out of 50 (30%). Department of Obstetrics and Gynecology, University Clinical Center "Sisters of Mercy", Zagreb, Croatia (March 30, 2012) published a journal Infertility Treatment in Patients with Polycystic Ovary Syndrome (PCOS). The third line of treatment IVF: a complex and expensive process of a controlled ovarian hyperstimulation with GnRH analogues, gonadotropins and careful ultrasound and laboratory assessments that proved to be highly effective.

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