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Review Article

Polycystic Ovary Syndrome and its Rule in Infertility

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Abstract

Background: Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among adult women in the developed world and is characterized by anovulation, androgen excess (primarily ovarian, but also adrenal in origin) and the appearance of polycystic ovaries on ultrasound. Women with PCOS may have reduced fertility due to the associated endocrine and gynecologic abnormalities that impact ovarian quality and function.

Aim: In this review, we will look into the polycystic ovary and its relation with infertility.

Conclusion: Proper diagnosis and treatment of PCOS is important, because PCOS has many possible metabolic and cardiovascular risks when properly managed. PCOS affects multiple organ systems and is best managed by an inter-professional healthcare team. It is highly recommended to consult the nutritional and physical therapy as these are considered first-line care. The women often require a number of medications to manage the hirsutism, anovulation and menstrual irregularities; hence the pharmacist should ensure that the patient is not developing any adverse reactions to these drugs.

Keywords: *Polycystic Ovary; Infertility; PCOS*

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among adult women in the developed world and is characterized by anovulation, androgen excess (primarily ovarian, but also adrenal in origin) and the appearance of polycystic ovaries on ultrasound [1]. The disorder can be morphological (polycystic ovaries) or predominantly biochemical (hyperandrogenemia) [2]. It is, however, most likely a heterogeneous disorder, and one whose pathophysiology and etiology are discussed [3].

PCOS affects young women with oligo-ovulation (which can lead to oligomenorrhea), infertility, acne and hirsutism. This disease affects between 6% and 20% of reproductive-aged women, depending on diagnostic criteria [4].

Hirsutism, irregular menstruations, chronic anovulation and infertility are typical clinical features. Persistent hyper-androgenism is associated with impaired hypothalamic hypophyseal feedback, hypersecretion of LH, premature granulose cell luteinization, aberrant oocyte maturation and premature arrest of primary activated follicles [5].

Ovarian follicles are cellular aggregates containing a single oocyte and not cysts (which, in medical terms, are fluid-containing membranous sacs or cavities of an irregular nature). The 'polycystic' appearance of the ovaries frequently found in patients with PCOS is caused by the accumulation of ovarian follicles in different stages of maturation and/or atresia [6,7].

PCOS remains one of the most poorly understood medical disorders among patients, physicians and even scientists, and the common misunderstanding of the syndrome and its long-term consequences for the health of both patients and their families has limited the allocation of research and development resources into this area of study [8].

Women with PCOS may have reduced fertility due to the associated endocrine and gynecologic abnormalities that impact ovarian quality and function. Accounting for up to 90% of ovulatory disorders, PCOS-associated persistent periods of anovulation are positively correlated with infertility [9]. Recently in 2015, a study by Hart and Doherty showed that infertility is 10 times more common among women with PCOS in comparison to healthy controls [10].

There is no universally accepted definition of PCOS and expert generated diagnostic criteria have proliferated in recent years. The definition of PCOS has largely been dependent on the technology used to ascertain the condition [11].

Because the primary cause of PCOS is unknown, treatment is directed at the symptoms. Few treatment approaches improve all aspects of the syndrome, and the patient's desire for fertility may prevent her from seeking treatment despite the presence of symptoms. Treatment goals should include correcting anovulation, inhibiting the action of androgens on target tissues, and reducing insulin resistance [12].

Treatment usually requires the corroboration of an interdisciplinary team that can include a family practitioner, a gynecologist, and endocrinologist, a dermatologist, a pediatrician, a psychiatrist, and a psychologist [13]. Oral contraceptives are the most commonly used medications for the long-term treatment of women with PCOS and have been recommended by the Task Force and the Endocrine Society [14].

Pathophysiology and etiology

Several theories arose that attempted to explain the PCOS pathophysiology. Initially, it had been thought that excess intrauterine androgen was a major culprit in the disease development [15].

Although the exact etiology of PCOS is unclear, androgen excess is proposed to be a core defect. Increased androgen levels, primarily produced by the ovaries (with a smaller contribution from the adrenals and peripheral adipose tissue) interfere with hypothalamic sensitivity to negative feedback from the ovary, thereby increasing GnRH pulse frequency [16].

Nearly all causes of PCOS are due to functional ovarian hyperandrogenism (FOH). Two-thirds of PCOS presentations have common functional ovarian hyperandrogenicity, characterized by androgen secretion dysregulation with a 17-hydroxyprogesterone (17-OHP) over-response to gonadotropin stimulation. Around 3% of patients with PCOS have associated acute functional hyperandrogenism of the adrenal. Many lack evidence of hormone secretory abnormalities; most of these patients are obese, postulating reports of their atypical PCOS by practitioners. Specific FOH subpopulation research is of limited clinical use in our present day [18].

A number of conditions share an increased prevalence of PCOS. A history of weight gain also precedes the development of PCOS clinical characteristics and it has been shown that a healthy lifestyle decreases body weight, abdominal fat, reduces testosterone, increases insulin resistance and reduces hirsutism in women with PCOS [19].

Obese women recommended for weight loss assistance had a PCOS rate of 28.3%. Nevertheless, the prevalence of PCOS did not vary significantly in an unselected population, based on obesity status. PCOS prevalence rates were 8.2%, 9.8%, 9.9%, 5.2%, 12.4%, and 11.5% respectively for underweight, normal weight, overweight, slightly obese, moderately obese, and severely obese people. A risk factor for PCOS is family history of PCOS. PCOS is considered an inheritable disorder dependent on the clustering of cases in families [20,21].

No specific environmental substance has been identified as causing PCOS, although certain medications such as valproate have been shown *in vitro* or in clinical series in women with epilepsy to induce hyperandrogenism [17].

Type 1, Type 2, and gestational diabetes have been linked to increased PCOS prevalence. The prevalence of PCOS in type 1 diabetes population was 40.5 percent and control group was 2.6 percent. PCO is extremely common in type 2 diabetes, occurring in 82% of women [22].

In children a number of factors associated with increased risk of PCOS have been identified. Among girls born to overweight mothers, congenital virilization and low birth weight, prenatal causes include high birth weight. Apparent risk factors later in adolescence include premature pubarche, atypical central precocious puberty, obesity syndromes, Nigric acanthosis and metabolic syndrome [23].

Diagnosis

Many cultural recommendations have acknowledged the PCOS diagnosis; many meet two out of three criteria: chronic anovulation, (clinical or biological hyperandrogenism, and anatomy of polycystic ovaries in the absence of any other pathology [24]. Diagnosis of PCOS in adolescents is particularly challenging given the developmental problems of this group. Some characteristics of PCOS, such as acne, menstrual irregularities and hyperinsulinemia, are typical in normal puberty. Menstrual irregularities of anovulatory periods arise during the first 2 to 3 years after menarche due to the immaturity of the hypothalamic-pituitary-ovarian axis [25].

Assessment of ovarian morphology is more accurate when done by transvaginal ultrasound. New ultrasonic machines allow PCOM (polycystic ovarian morphology) to be diagnosed in patients with at least 25 small follicles (2 mm to 9 mm) throughout the ovary. 2004 Rotterdam criteria indicate that PCOM has at least 12 follicles measuring 2 mm to 9 mm in the entire ovary or more than 10 ml in ovarian size [26].

The Endocrine Society Guidelines recommend that all patients test for ovulatory status. Even a woman with menstrual cycles of eumenorrhea may have anovulation that can be assessed using mid-luteal progesterone serum. It is also advised that you exclude other causes of infertility.

Management and treatment

People with PCOS are treated according to the symptoms. These could be infertility due to ovulatory dysfunction, menstrual irregularities or androgen related symptoms [27]. PCOS management should be recommended not only to alleviate the symptoms but also to avoid long-term complications from occurring. The ultimate goals of women's therapy with PCOS include minimizing hyperandrogenic symptoms, treating metabolic abnormalities and reducing risk factors for type 2 diabetes and cardiovascular disease, avoiding endometrial hyperplasia, preparing and achieving healthy pregnancy if desired, and improving general well-being and quality of life [28]. The treatment strategy should be tailored to suit the patient's willingness (or not) to become pregnant, the need for an esthetic solution and the existence of concurrent metabolic changes [28]. Treatment of hyperandrogenism is a key step in the management of women with PCOS. Combined oral contraceptives and antiandrogens are the standard treatment for lowering androgen levels and treating symptoms while protecting endometrials [29].

The first line of treatment in PCOS cases should be lifestyle enhancement. Strong associations exist among excessive weight, insulin resistance, glucose intolerance, menstrual irregularities and infertility. Even modest lifestyle changes can have a significant impact and

reducing body weight by only 2% - 5% has been shown to restore ovulation and increase insulin sensitivity in obese anovulatory women [30]. Among patients with overweight and obesity, weight loss due to changes among diet and physical activity decreases serum insulin and androgen levels and reduces the risk of resistance to glucose and type 2 diabetes [31]. Metformin is the most widely used treatment for the metabolic function of PCOS patients [32]. The therapeutic effects of metformin as an insulin sensitizer and a hypoglycemic agent in women with PCOS have been well established [33]. There is no convincing evidence that metformin decreases BMI compared with placebo in women with PCOS [33]. Adding metformin may have minimal benefit to the BMI of women who receive antiandrogen and oral contraceptive combined [29]. Because metformin often has gastrointestinal side effects, new pharmaceutical formulations for vaginal delivery are under development and have been successful in a preclinical PCOS model so far [34].

The second line of treatment is induction of ovulation (after lifestyle interventions). This step must be followed by careful examination of other causes of infertility, such as male or tubal obstruction, requiring IVF and coexisting with PCOS [28]. In PCOS, anovulation is associated with low FSH concentrations and the arrest in the final stages of maturation of antral follicle growth. For many women, the problem raised is anovulatory infertility. Medicines and other ovulation induction options available. Clomiphene citrate (CC) is one of the first-line ovulation induction therapies in these patients, being inexpensive, simple, having few adverse effects and requiring little monitoring [35]. CC is an estrogen receptor antagonist that interferes with negative estrogen signaling pathway feedback, leading to increased FSH availability. Increased FSH leads to follicular growth, followed by an LH surge and ovulation.

Metformin is associated with increased menstrual cyclicity, enhanced ovulation, and reduced androgen circulation [36]. Metformin probably plays its role in improving ovulation induction in women with PCOS through a variety of acts, including lowering insulin levels and altering the impact of insulin on ovarian androgen biosynthesis, theca cell proliferation and endometrial development. Additionally, it inhibits ovarian gluconeogenesis potentially through a direct effect and thus reduces the production of ovarian androgen [27].

The letrozole aromatase inhibitor may be used as an alternative for ovulation induction in patients who have failed to respond to CC. Many studies suggest that letrozole may be used in ovulation induction as first-line therapy, but this use remains unlabeled [28]. This inhibits the conversion of estradiol and estrone by testosterone and androstenedione, respectively. A reduction in estrogenic activity protects the hypothalamus from negative feedback, causing an increase in FSH release [37].

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop group 2008 suggests *in-vitro* fertilization (IVF) as a third-line treatment for infertility management [38]. Women with PCOS have similar rates of pregnancy, miscarriage and live-birth with conventional IVF compared to patients without PCOS [39]. When treatments with CC, gonadotropins, and letrozole failed, these techniques are used as a last resort.

Ovarian Surgery, the value of laparoscopic ovarian drilling with laser or diathermy as a primary treatment for sub-fertile women with anovulation and PCOS is undetermined, and it is primarily recommended as second-line infertility therapy. Neither drilling by laser or diathermy has any obvious advantage, and there is insufficient evidence to suggest a difference in ovulation or pregnancy rates when drilling is compared with gonadotropin therapy as a secondary treatment [40]. Although gonadotropin treatment and laparoscopic ovarian drilling have demonstrated similar reproductive outcomes, laparoscopic ovarian drilling has some advantages over gonadotropin treatment such as lower cost per pregnancy, improvement in menstrual regularity, and better long-term reproductive performance [41]. Neither therapy is a panacea, as therapies have so far centered on the symptoms but not on the condition itself. In order to make therapy more successful and delay the serious long-term effects of the disease on the health of patients, extensive efforts should be made to investigate the syndrome in full.

Conclusion

Proper diagnosis and treatment of PCOS is important, because PCOS has many possible metabolic and cardiovascular risks when properly managed. PCOS affects multiple organ systems and is best managed by an inter-professional healthcare team. It is highly rec-

ommended to consult the nutritional and physical therapy as these are considered first-line care. The women often require a number of medications to manage the hirsutism, anovulation and menstrual irregularities; hence the pharmacist should ensure that the patient is not developing any adverse reactions to these drugs.

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