Endocrine and Reproductive Effects of Polycystic Ovarian Syndrome

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KEYWORDS

• Polycystic ovary syndrome • Reproductive endocrinology • Clomiphene citrate
• Letrozole • Live birth rate • Infertility

KEY POINTS

- Polycystic ovarian syndrome (PCOS) is defined by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries on ultrasonography.
- Weight loss should be encouraged for overweight and obese women with PCOS.
- Combined oral contraceptive pills remain the first-line treatment of hyperandrogenism in women not seeking pregnancy.
- Metformin is no longer indicated as a primary ovulation induction agent.
- Letrozole was found to have higher live birth and ovulation rates in women with PCOS compared with clomiphene in a recent multicenter, randomized trial.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common cause of ovulatory dysfunction in women. Although the clinical expression varies widely, the syndrome is classically described by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. PCOS occurs in 5% to 15% of women, depending on which diagnostic criteria are used.[1] There is a considerable multisystem impact of this disorder that spans from systemic metabolic disturbances to reproductive difficulty to long-term cardiovascular health and cancer risk. The effect of PCOS on endocrine and menstrual function, fertility, and reproductive outcome and the management of these sequelae are discussed in this review.

The diagnostic criteria for PCOS vary depending on different expert groups. It is generally accepted that PCOS is defined as hyperandrogenism and ovulatory

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dysfunction. The commonly used 2003 Rotterdam criteria added ultrasonographic findings of ovarian appearance to the diagnosis. To meet the Rotterdam Consensus criteria, 2 of the 3 features need to be documented.[2] Hyperandrogenism may be diagnosed from clinical findings or by serum testosterone concentrations. Two common clinical signs of hyperandrogenism are hirsutism and acne. Polycystic ovaries are sonographically diagnosed by the presence of 12 or more antral follicles, measuring 2 to 9 mm in diameter, or increased ovarian volume greater than 10 cm^3 on either ovary.[2] Fundamental to the diagnosis of PCOS is the exclusion of other potential causes of the clinical or biochemical findings. The most common endocrinopathies to rule out are thyroid dysfunction and hyperprolactinemia. Less common disorders that may mimic symptoms of PCOS include nonclassic congenital adrenal hyperplasia, Cushing syndrome, androgen-secreting neoplasms, or acromegaly.[3]

The etiology of PCOS remains unclear and is likely multifactorial. Prenatal exposure to testosterone and genetic, and epigenetic effects have been implicated. Insulin resistance is believed to play a significant role, particularly in overweight and obese patients with PCOS. Increased levels of insulin cause decreased amounts of sex hormone binding globulin (SHBG), which, in turn, leads to increased amounts of free circulating androgens.[2]

MENSTRUAL AND ENDOMETRIAL EFFECTS

Oligomenorrhea and secondary amenorrhea are common presenting symptoms among patients with PCOS. Women with amenorrhea have been found to have increased metabolic risk with severe hyperandrogenism and higher antral follicle counts.[1] Although information about spontaneous ovulation rates in women with PCOS is limited, a large randomized controlled trial reported ovulation in up to 32% of cycles.[4] Correctly recognizing PCOS in adolescent females with oligomenorrhea is more difficult than in adults. This difficulty arises because most menstrual cycles are anovulatory during the first 3 years after menarche.[5] Adolescents also commonly have acne and often have high antral follicle counts on sonographic measurement. Given the complexity of diagnosing PCOS in adolescent females, the Endocrine Society has suggested specific diagnostic criteria. In contrast to adults, in whom only 2 of the 3 Rotterdam criteria are necessary to make a diagnosis, adolescents require all 3 elements to confirm the diagnosis, based on the Endocrine Society suggestions. Oligomenorrhea or amenorrhea should be present for at least 2 years after menarche in these females. Primary amenorrhea after the age of 16 years also satisfies the diagnostic criteria. The sonographic findings must include an ovarian volume of greater than 10 cm^3, because polycystic ovaries are a common finding among adolescent girls. Hyperandrogenism must be diagnosed by increased androgen levels, because acne is often a common finding among adolescents.

Menstrual irregularity is not without risk. Women with PCOS are exposed to prolonged amounts of unopposed estrogen, and a relationship between PCOS and endometrial cancer has been described. The severity of oligo-ovulation may correlate with endometrial thickness and subsequent endometrial hyperplasia in women. When comparing aged-matched women with and without PCOS, proliferative endometrium was observed significantly more often in the PCOS group. Data support a 2.7-fold increased risk of endometrial cancer in women with PCOS.[6] It has been suggested that women have a minimum of 4 withdrawal bleeds per year and undergo potential surveillance measures to reduce the risk of endometrial hyperplasia.[1] These measures could include endometrial biopsy or ultrasonography to assess endometrial thickening for women with expended periods of amenorrhea. According to the American College