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Review Article

# Polycystic Ovary Syndrome

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# 다낭성 난소 증후군

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Polycystic ovary syndrome affects 6%-7% of reproductive-aged women, making it the most common endocrine disorder in this population. It is characterized by chronic anovulation and hyperandrogenism. Affected women may present with reproductive manifestations such as irregular menses or infertility, or cutaneous manifestations, including hirsutism, acne, or male-pattern hair loss. Over the past decade, several serious metabolic complications also have been associated with polycystic ovary syndrome including type 2 diabetes mellitus, metabolic syndrome, sleep apnea, and possibly cardiovascular disease and nonalcoholic fatty liver disease. In addition to treating symptoms by regulating menstrual cycles and improving hyperandrogenism, it is imperative that clinicians recognize and treat metabolic complications. Lifestyle therapies are first-line treatment in women with polycystic ovary syndrome, particularly if they are overweight. Pharmacological therapies are also available and should be tailored on an individual basis.
This article reviews the diagnosis, clinical manifestations, metabolic complications, and treatment of the syndrome.

**Key Words:** Anovulation, Diabetes mellitus, Hirsutism, Insulin resistance, Polycystic ovary syndrome

In 1935, Stein and Leventhal published a case series of seven women with amenorrhea, hirsutism, and bilateral polycystic ovaries, a condition that later came to be known as polycystic ovary syndrome (PCOS).[1] PCOS is now recognized as the most common endocrinopathy in reproductive-aged women (affecting 5%-7%), with key features of menstrual irregularity, elevated androgens, and polycystic-appearing ovaries.[1] Although up to 5 million women in the United States may be affected by polycystic ovary syndrome, it is frequently not recognized.[1] Because affected women may not view their symptoms of irregular menses and hirsutism as "medical" complaints, they may not bring them up to their provider.[1] Thus, active provider inquiry

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may be required to uncover the diagnosis.

## Diagnosis

Experts at a 1990 National Institutes of Health conference proposed the following diagnostic criteria: oligo- or anovulation and biochemical or clinical signs of hyperandrogenism, such as hirsutism, acne, or male-pattern hair loss.[1] Recently, an international consensus group broadened the definition by also including ovarian morphology.[2] They proposed that the diagnosis requires 2 of the following 3 criteria: oligo- or anovulation, biochemical or clinical signs of hyperandrogenism, and polycystic ovaries.[1] Table 1 shows the definition of PCOS undergoing several revisions.[3] In their definitions, hyperandrogenism can be documented with either clinical or biochemical data.[1] This is important because some women have mild or no clinical evidence of hyperandrogenism but have elevated serum androgen levels.[1] Although insulin resistance and obesity are common; neither is part of the diagnostic criteria.[1]

### Pathogenesis

Although the etiology of polycystic ovary syndrome is unknown, 3 main hypotheses have been proposed (Table 2).[4] Several candidate genes including those related to insulin

resistance and androgen biosynthesis or action have been associated with the syndrome.[1] Additionally, environmental factors are thought to play an important role.[1]

### Patient evaluation

Evaluation should include a detailed menstrual history and information about the onset and duration of hyperandrogenism symptoms.[1] Polycystic ovary syndrome is typically

characterized by chronic menstrual irregularity and slowly progressive symptoms of hyperandrogenism.[1] The physical examination should include assessment of blood pressure, body mass index, and waist circumference.[1] Skin should be examined for evidence of insulin resistance (acanthosis nigricans, skin tags) and hyperandrogenism (hirsutism, acne, and male-pattern hair loss).[1] Laboratory tests to exclude other etiologies and assess for metabolic complications are summarized in Tables 3.

### Treatment

reatment of polycystic ovary syndrome targets the reproductive, cutaneous, metabolic, and psychological complications.[1] Recommendations to treat each of these components are summarized in Table 4.[1]

Table 1. PCOS definitions 1990-2009[3]

| PCOS definition | Clinical hyperandrogenism (Ferriman-Gallwey score ≥8) or biochemical hyperandrogenism (elevated total/free testosterone) | Oligomenorrhea (less than 6-9 menses per year) or oligo-ovulation | Polycystic ovaries on ultrasound (≥12 antral follicles in one ovary or ovarian volume ≥10cm$^3$) |
|---|---|---|---|
| NICHD(1990)[7] | Yes | Yes | No |
| Rotterdam (2003)[2] | Yes | Yes<br>2 of 3 criteria | Yes |
| AE-PCOS Society[8] (2009) | Yes | Yes<br>1 of 2 criteria | Yes |

PCOS, polycystic ovary syndrome; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; AE-PCOS,

Table 2. Posssible pathogenesis of polycystic ovary syndrome[4]

| |
|---|
| 1. Hypothalamic-pituitary axis abnormalities cause abnormal secretion of gonadotropin releasing hormone and luteinizing hormone, resulting in increased ovarian androgen production. |
| 2. An enzymatic defect of ovarian (± adrenal) steroidogenesis favors excess androgen production. |
| 3. Insulin resistance drives the metabolic and reproductive abnormalities in polycystic ovary syndrome. |

## *Lifestyle interventions*

Lifestyle interventions such as diet and exercise are first-line treatment for women with polycystic ovary syndrome, particularly if they are overweight.[1]

### *1. Weight reduction*

There is some evidence that PCOS-related hyperandrogenism causes central obesity with a high waist/hip ratio independent of the body mass index (BMI).[5] Weight loss improves the endocrine profile and increases the likelihood of ovulation and pregnancy.[5] Normalization of the menstrual cycles and ovulation could occur with modest weight loss as little as 5% of the initial weight.[5] Weight loss can improve not only circulating androgen and glucose levels but also ovulation and pregnancy rates in obese women with PCOS; however, weight loss is only recommended for those who are overweight with a BMI $> 25-27$ kg/m$^2$.[5]

The treatment of obesity includes modifications in lifestyle (diet and exercise) and medical and surgical treatment.[5] All these treatments must be performed during the preconception period and not jointly with reproduction therapies.[5]

### *2. Diet*

Diets recommended for obese PCOS patients are low in calories with a reduced carbohydrate intake, and any form of these diets can produce the 5%-10% loss necessary to re-establish ovarian function in these patients.[5]

### *3. Exercise*

An increase in physical activity is recommended for PCOS patients, although this often presents limitations.[5] A knowledge gap exists regarding the optimal type, duration, and frequency of exercise.[5]

## *Hormonal therapy*

If pregnancy is not desired, hormonal contraceptive agents containing estrogen and progestin can be used to provide endometrial protection and treat symptoms of

Table 3. Laboratory testing to evaluate for metabolic complications of polycystic ovary syndrome[1]

| Laboratory Test | Evaluation for: | Comment |
|---|---|---|
| 2-hr oral glucose tolerance test | Impaired glucose tolerance, type 2 diabetes | Consider this in all women with polycystic ovary syndrome, particularly those with a body mass index >25 kg/m2 or other risk factors for type 2 diabetes such as a positive family history. |
| Fasting lipid profile | Dyslipidemia | Hypertriglyceridemia and decreased high-density lipoprotein are relatively common in women with polycystic ovary syndrome. Elevations in low-density lipoprotein have also been noted. Thus, periodic screening is recommended. |
| Alanine aminotransferase and aspartate aminotransferase | Hepatic steatosis | Consider checking transaminases in women with other risk factors for nonalcoholic fatty liver disease. |

hyperandrogenism.[1]

Cyclic therapy, such as oral contraceptives, induces regular withdrawal bleeding, thus preventing endometrial hyperplasia.[1] It is possible that some women experience a worsening of carbohydrate metabolism while taking oral contraceptives.[1] However, until this issue is resolved with larger randomized controlled clinical trials, hormonal contraceptives remain an effective treatment.[1] In women with contraindications to estrogen-containing therapy, cyclic progestin therapy given every 1 to 3 months can provide endometrial protection by inducing regular en dometrial shedding.[1] Alternatively, a progestin-only contraceptive can be used.1 Progestin-only therapy will not improve hyperandrogenism symptoms.[1]

## Anti-Androgen Therapy

Spironolactone (50-100 mg twice daily) effectively treats hirsutism.[1] Spironolactone is often used in combination with oral contraceptives because of the additive effects of androgen suppression (oral contraceptives) and androgen blockade (spironolactone).[1] Spironolactone is contraindicated during pregnancy because of potential teratogenicity.[1]

## Other Cosmetic Treatments

In addition to using oral contraceptives and anti-androgens to treat hirsutism, permanent hair reduction can be achieved with laser or electrolysis therapy.[1] Because laser therapy relies on the contrast between light and dark for the best effect, it works best in individuals with light skin and dark hair.1 For darker skin, the laser instrument should be designed to treat darker skin tones.[1] Other available therapies include enflorane hydrochloride 13.9% cream to slow hair growth and topical minoxidil to treat male pattern hair loss.[1]

## Metformin

Metformin has become a popular treatment, because it improves ovulation, insulin sensitivity, and possibly hyperandrogenemia.[6] It is commonly used to treat

Table 4. Summary of recommendations for addressing reproductive, cosmetic, metabolic, and psychological complications of polycystic ovary syndrome[1]

| | |
|---|---|
| Metabolic | Assess diabetes and cardiovascular disease risk |
| | Assess risk for nonalcoholic fatty liver disease |
| | Discuss lifestyle therapies such as nutrition and physical activity |
| Cycle control | Assess bleeding pattern and risk for endometrial hyperplasia |
| | Provide therapies to prevent endometrial hyperplasia: estrogen-progestin therapy (oral contraceptives, patch, or vaginal ring) or cyclic progestin (every 1-3 months) |
| Psychosocial | Address body image and eating behaviors |
| | Screen for depression |
| | Discuss stress management |
| | Provide nonjudgmental support |
| Cosmetic | Discuss use of estrogen-containing oral contraceptives to suppress androgens if no contraindications |
| | Consider spironolactone 50-100 mg twice daily for refractory hirsutism or acne |
| | Discuss use of enflornithine hydrochloride 13.9% cream, laser therapy, and electrolysis |
| | Discuss over-the-counter topical minoxidil for male-pattern scalp hair loss |
| Ovulation | Discuss fertility goals |
| | Discuss therapies to increase ovulation frequency: weight loss, metformin |
| | Consider referral to Reproductive Endocrinology for assisted reproductive technologies |
| Sleep apnea | Screen for sleep apnea |
| | Refer for sleep study if indicated |

infertility, either alone or in combination with clomiphene-citrate.[1] Because it increases ovulation in some women, it can also increase the frequency of endometrial shedding and may help with cycle control.[1] Metformin may be useful in women with polycystic ovary syndrome and hyperglycemia.[1]

The decision to prescribe this drug should be made on an individual basis.[1] Patients who do not wish to become pregnant should be counseled about contraception.[1]

### *Laparoscopic ovarian diathermy*

In clomiphene-resistant PCOS women who are unable to comply with the close monitoring necessary for gonadotropin administration, bilateral laparoscopic ovarian surgery with monopolar electrocautery (multiple controlled perforation of the ovary) or laser is an acceptable alternative.[5] Laparoscopic ovarian diathermy restores menstrual regularity in 63%-85% of women, and the beneficial effects on reproductive outcomes seem to last for several years in many women.[5] Treatment with metformin is equally efficacious in correcting the clinical, endocrine, and metabolic abnormalities associated with PCOS.[5]

Polycystic ovary syndrome is a common condition characterized by hyperandrogenism and oligo- or anovulation.[1] The clinical problems that may arise in the course of caring for affected women include endometrial hyperplasia, reduced fertility, and serious metabolic complications.[1] Lifestyle therapies are first-line treatment for prevention of metabolic complications and can improve fertility.[1] Pharmacological therapies are available to regulate menstrual cycles and treat symptoms of hyperandrogenism.[1] Pharmacological therapies can also improve metabolic parameters such as prediabetes in situations where lifestyle interventions are insufficient.[1] In the adolescent where the diagnosis is not clear, it is preferable to follow the symptoms and repeat the evaluation in 6 to 12 months.[3]

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**Peer Reviewer's Commentary**

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorder in reproductive-aged women. Treatment of PCOS targets the reproductive, cutaneous, metabolic, and psychological complications. Lifestyle modifications including weight reduction, diet and exercise are considered as the first-line treatment. Pharmacological therapies such as hormonal contraceptive agents, metformin, and anti-androgen agents are also available. In this review, the pitfalls of diagnosis, clinical manifestations, metabolic complications, and overall treatment of PCOS are summarized.

(Editorial Board)