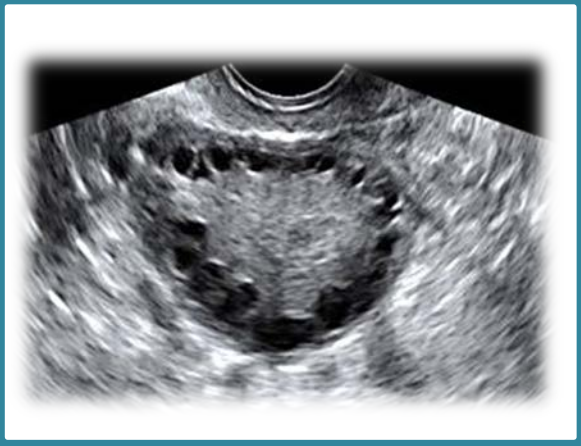
AE-PCOS SOCIETY EDUCATION COMMITTEE

POLYCYSTIC OVARY SYNDROME (PCOS)

A REFERENCE FOR HEALTHCARE PROVIDERS

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, with an approximate prevalence of 5-15% worldwide in all ethnic groups. The cardinal features of PCOS include: ovulatory dysfunction and androgen excess. While the name of the condition implies a distinct abnormality of ovarian morphology, not all women with PCOS will display polycystic ovaries.



Diagnosis

The definition of PCOS stands on two pillars: 1) androgen excess and 2) ovulatory dysfunction.

ANDROGEN EXCESS as defined by the presence of clinical hyperandrogenism and/or biochemical hyperandrogenemia.	
Clinical Hyperandrogenism	Hirsutism or Acne Vulgaris or Androgenetic alopecia
Biochemical Hyperandrogenemia	Total Testosterone or Bioavailable Testosterone with/without mild elevation of dehydroepiandrosterone sulfate (DHEAS)

OVULATORY DYSFUNCTION as defined by clinical evidence of menstrual cycle irregularity and/or ovarian dysmorphology.	
Clinical	Irregular/Infrequent Menses or Amenorrhea or Anovulation
Morphologic	Polycystic ovaries (on ultrasound or other imaging)

However, prior to assuming the diagnosis of PCOS in the presence of hyperandrogenism and menstrual dysfunction, other medical etiologies must be excluded. These include thyroid dysfunction, hyperprolactinemia, hypercortisolism, non-classic/late-onset congenital adrenal hyperplasia as well as hormonally active adrenal or ovarian tumors.

Although luteinizing hormone (LH) elevations and insulin resistance are common among women with PCOS, they are not required for the diagnosis.

Diagnosis (continued)

Care must be taken in the diagnosis of PCOS among adolescents, given the general prevalence of acne and the immaturity of the hypothalamic-pituitary-ovarian (HPO) axis during the first two years after menarche. In the adolescent, a diagnosis of PCOS should be based on a combination of persisting menstrual irregularity beyond the first two years of menarche and biochemical hyperandrogenism, with or without clinical symptoms of androgen excess. The value of examining ovarian morphology on ultrasound has not been established for adolescents and therefore is not routinely recommended.

Implications for Health and Wellness

Reproductive Health & Fertility: Impaired functioning of the HPO axis underlies much of the ovulatory dysfunction in PCOS. However, hyperandrogenemia and hyperinsulinemia are important underpinnings to the ovulatory dysfunction in PCOS since they perpetuate the dysregulation of the HPO axis and stimulate further hyperandrogenism. Local production of androgens in turn contributes to ovarian follicular arrest, anovulation, and the morphologic hallmark of the syndrome – polycystic ovaries on ultrasound. Together, these contributors to ovulatory dysfunction result in infrequent and unpredictable menstrual periods and a heightened risk for infertility.

Hirsutism: Male pattern hair growth on the upper-lip, chin, mid-chest and abdomen can be cosmetically distressing to women. While pharmacological treatment of hirsutism may be helpful, it is often not sufficient for achieving the desired cosmetic effect. Therefore, non-pharmacological methods ranging from shaving, waxing, depilation and epilation to laser therapy and electrolysis are recommended supporting management strategies.

Metabolic Dysfunction: Even without excess adiposity, women with PCOS are more insulin resistant than their non-PCOS counterparts of the same body mass index and age. Insulin resistance leads to increased levels of insulin (hyperinsulinemia) and increases the risk of gestational diabetes and adult-onset/type II diabetes mellitus. Lipid profile abnormalities are also commonly encountered in women with PCOS.

Endometrial Pathology: An increased incidence and prevalence of endometrial polyps, hyperplasia and even endometrial adenocarcinoma are noted in women with PCOS. Chronic anovulation with resulting endometrial exposure to estrogen unopposed by progesterone, insulin resistance, and chronic inflammation are considered to contribute to the risk for endometrial pathology in women with PCOS.

Psychological Distress: High rates of depression and anxiety have been reported in PCOS and appear unrelated to body habitus. However, poor body image, psychosexual dysfunction, and eating disorders commonly associate with PCOS.

Obstructive Sleep Apnea: There is a high prevalence of sleep disorder breathing in women with PCOS, even in those that are not overweight/obese. Although the pathophysiologic mechanism is not clear, androgen excess and insulin resistance have been postulated to contribute to this constellation of disordered sleep.

Treatment and Prevention

Lifestyle modification, particularly in the obese patient with PCOS, represents the first-line approach to treating PCOS and is recognized to impact the spectrum of morbidity associated with this disorder. Dietary adjustments and regular exercise reduce the risk for co-morbidities and improve ovulatory function. As little as a 5% reduction in body weight can lead to an improvement in menstrual cyclicity and subsequently, improve fertility potential and reduce the risk for endometrial pathology.

Combined Hormonal Contraceptive (CHCs): CHCs are currently the first-line pharmacologic approach to PCOS management. CHCs offer menstrual cycle regulation and endometrial protection, but also confer benefit against clinical and biochemical hyperandrogenism. Mechanistically, this is related to a suppression of pituitary LH which, in turn, reduces the stimulatory effect of LH on androgen production by ovarian theca cells. Furthermore, CHCs increase hepatic sex hormone binding globulin (SHBG) which results in a decline of unbound (free) testosterone, improving the clinical manifestations of hyperandrogenism. Lastly, the anti-proliferative effects of the progestin component in CHCs offers protection against endometrial pathologies. While generally well-tolerated, CHCs increase the risk of thromboembolic events 2-6 fold, especially in overweight women.

Progestin: For patients deemed at risk for adverse effects related to estrogen or CHC use (e.g., smokers, those with existing hypertension, or history of thromboembolism), progestin "only" therapy is a viable alternative. Progestin therapy protects the endometrium from proliferative pathology and is very effective in controlling abnormal uterine bleeding. However, the progestin approach has a less robust effect on hyperandrogenemia due to incomplete suppression of ovarian function and/or lack of estrogen-mediated stimulation in SHBG production.

Anti-androgens: These drugs are increasingly used in the treatment of hyperandrogenic disorders. Spironolactone, an aldosterone antagonist recognized for its antihypertensive and potassium-sparing diuretic effects, has proven efficacy against acne, and to a lesser extent against hirsutism. The anti-androgenic effect of spironolactone is carried out through a dual mechanism of androgen receptor blockade and inhibition of 5-alpha reductase, the enzyme responsible for the conversion of testosterone to the more potent dihydrotestosterone (DHT). Its efficacy against acne is partly mediated through reduction of sebum production. In general, spironolactone has a good safety profile and is well-tolerated without serious complications reported. Breast tenderness and fatigue are the most common side-effects. Higher doses of spironolactone can lead to menstrual irregularity, while lower doses, especially in combination with metformin, may enhance regular ovulatory cycles. While on spironolactone, contraceptive measures should be in place for those who are sexually active (see below). The main adverse effect is dose-dependent hyperkalemia, which is circumvented by using doses in the recommended range and screening for renal and liver disease prior to use.

Treatment and Prevention (continued)

Anti-androgens Continued. Other antiandrogens, including flutamide and finasteride, are effective in the treatment of acne, hirsutism, and androgenic alopecia. However flutamide use has the potential for rare hepatotoxicity and, if used, blood tests for liver functions should be checked regularly. Recent reviews have indicated that ultra-low dose flutamide (62.5 mg/day) is highly effective with negligible hepatotoxicity. Given the potential of all anti-androgen therapy to cause birth defects by possibly under-virilizing a male conceptus, reliable contraception is recommended for reproductive age women prescribed anti-androgens.

Insulin Sensitizers: Metformin is the most commonly used insulin sensitizer in women with PCOS. Metformin's main mechanism of action involves a decrease in hepatic gluconeogenesis, but it also mediates improved insulin sensitivity, blocks intestinal carbohydrate absorption, and promotes weight loss. Significant reductions in fasting insulin concentrations, LDL cholesterol, and improvements in systolic and diastolic blood pressure occur with metformin use in women with PCOS. Furthermore, metformin has insulin independent effects on ovarian health and androgen production. Anovulatory women with PCOS seeking fertility are likely to experience improvements in cycle control with the use of metformin. The addition of metformin to ovulation induction strategies offers a potential improvement in ovulation and pregnancy rates, as well as a reduction in the risk of ovarian hyperstimulation syndrome in those undergoing the in vitro fertilization process. Metformin has an excellent safety profile without serious medical risks. Most side effects are gastrointestinal in nature and can be ameliorated by starting with a very low dose and increasing dosage in small increments over the course of a few weeks. The only caution for metformin use is in patients with poor renal function. Lactic acidosis has been reported in elderly patients and those with poor renal function.

Conception Enhancing Treatments: Clomiphene citrate (CC) is conventionally considered the first-line of treatment for women with PCOS seeking conception. CC enhances ovulation by blocking estrogen-mediated negative feedback on pituitary gonadotropin release. This abrogation of estrogen-mediated gonadotropin suppression increases endogenous release of follicle stimulating hormone (FSH) which stimulates ovarian follicle recruitment, growth, and subsequent ovulation. Aromatase inhibitors are increasingly being incorporated into the clinical paradigm for managing anovulatory infertility. Acting in a manner similar, yet distinct from CC, aromatase inhibitors block the enzyme aromatase which in turn, leads to profound reductions in serum and tissue estrogen levels thus abrogating estrogen-mediated negative feedback at the HPO level. The net result is an increased release of pituitary FSH which then induces follicular growth. Unlike CC, aromatase inhibitors do not have adverse effects at the level of the endometrium – which is a benefit for implantation. Letrozole and anastrozole are the two aromatase inhibitors that have demonstrated success in achieving ovulation induction in CC resistant patients with PCOS. Standard ovulation induction with gonadotropins and assisted reproductive techniques are further options for women with PCOS. However, underlying PCOS many enhance the risk of ovarian hyperstimulation syndrome when using the later method.

Resources

Links to additional resources may be found on our website under Resources: **www.ae-society.org**

This pamphlet is designed to be informative and educational. It is not intended as a practice guideline. The information in this document is based on current medical knowledge as of February 2016.