

## Effectively Managing the PCOS Conundrum

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Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women, affecting between 8-13% of women.<sup>1</sup> However, the diagnosis is “controversial and assessment and management are inconsistent” as per the international guidelines on PCOS management endorsed by the American Society of Reproductive Medicine<sup>2</sup> Diagnostic criteria have evolved over time with the National Institutes of Health in 1990 requiring only hyperandrogenism and irregular menstruation. In 2003, the presence of polycystic ovaries on ultrasound was added under the Rotterdam Criteria. Next the Androgen Excess Society determined that a diagnosis of PCOS requires the presence of hyperandrogenism with either polycystic ovaries or oligo/amenorrhea and anovulation. Per the *PCOS: State of the Science* article in *Ob. Gyn News*, September 2022, the “only real agreement on diagnosis is the need to eliminate other potential diagnoses first, making PCOS always a diagnosis of exclusion”.<sup>3</sup> For the evaluation of hyperandrogenic symptoms, ordering total and free testosterone, sex hormone binding globulin (abnormally low SHBG is a risk factor for a more severe hirsute presentation<sup>4</sup>), consider DHEA-S (mildly elevated levels will not likely affect management but very high levels can be seen in adrenocortical carcinoma), androstenedione (optional for most women), serum 17-hydroxyprogesterone (measure in the early morning and in the early follicular phase, if cycling) is very important to rule out congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Tests to rule out other causes of oligomenorrhea include HCG, prolactin, TSH, cortisol, FSH, LH (an elevated ratio of LH:FSH of  $>$  or  $=$  2:1 is not necessary for the diagnosis though often seen), consider Anti-mullerian hormone (generally elevated in the upper range of normal or markedly elevated in women with PCOS<sup>5</sup>). Pelvic ultrasound is done to evaluate for polycystic ovarian morphology—Rotterdam criteria includes the presence of 12 or more follicles in either ovary measuring 2 to 9mm and/or increased ovarian volume. However, some reports, show that over 50 percent of normal-cycling women had 12 or more small follicles<sup>6</sup>. If there are no other features of PCOS, then no other evaluation is needed for polycystic ovarian morphology. The diagnosis of a postmenopausal woman is more difficult but can be presumed based on a long-term history of oligomenorrhea and hyperandrogenism during reproductive years.

Women with PCOS have a higher prevalence of cardiometabolic risk factors including insulin resistance, DM2, obesity, dyslipidemia, and increased blood pressure. Hyperinsulinism/insulin resistance is common in women with PCOS but is very weight dependent. It occurs in 65-70% of women with PCOS, in 70-80 % of obese women (BMI  $>$  30) with PCOS, and in 20-25% of lean women (BMI  $<$  25) with PCOS. Consider two-hour oral glucose tolerance tests but if not feasible, fasting glucose and hemoglobin A1C in addition to fasting insulin and lipids are important.<sup>7</sup> Metabolic syndrome occurs in at least two thirds of women with PCOS. The International Diabetes Federation classifies PCOS as a non-modifiable risk factor for DM2, and these women have a more rapid conversion from impaired glucose tolerance to DM2. Ten percent (10%) of women with PCOS will develop DM2 over their lifetime.<sup>8</sup> Androgen excess (as seen with thin scalp hair, increased facial/body hair, clitoromegaly, and/or acne) per the Endocrine Society is seen in 60-80 % of those with PCOS.<sup>9</sup> Mood disorders are also more prevalent in women with PCOS including depression and anxiety, and these patients should be screened using the validated Patient Health Questionnaire Depression Scale (PHQ9) and the Generalized Anxiety Disorder 7 GAD-7).<sup>2</sup>

PCOS is the leading cause of infertility for women. Aromatase inhibitors (letrozole, for example) have supplanted metformin and clomid as the treatment of choice for PCOS anovulation causing infertility. Given the ovulatory dysfunction and oftentimes estrogen dominance, these patients often present with more than just infrequent cycles  $>$  35 days (oligomenorrhea), they can present with heavy, prolonged ( $>$  8 days) periods and/or with just random bleeding. They are at an increased risk of endometrial hyperplasia from chronic anovulation which can lead to endometrial cancer.

As per “Treatment of polycystic ovary syndrome in adults” by Dr. Robert Barbieri and Dr. David Ehrmann, the goals of therapy for women with PCOS include amelioration of hyperandrogenic features, management of underlying metabolic diseases, risk reduction for type 2 DM and CV disease, prevention of endometrial hyperplasia and cancer from chronic anovulation, contraception as ovulation is not predictable, or ovulation induction for those actively

desiring pregnancy. Weight loss is first line intervention for overweight and obese women with PCOS. Combined estrogen-progestin oral contraceptives (COCs) are the mainstay for managing hyperandrogenism and menstrual abnormalities; however, patients must be screened heavily for contraindications. Progestin IUDs will not help hyperandrogenism but are highly effective at preventing hyperplasia and providing safe, highly effective contraception. Cyclic progestins can also be used. Micronized progesterone can be used daily at 200 mg dose to help bleeding, but not as contraception—micronized progesterone is a weaker antagonist of the endometrium and may not provide the needed endometrial response and has been less well-studied for this purpose. Other progestin-only options include micronor norethindrone 0.35 mg (the mini pill), *Slynd* (4 mg Drospirenone only pill), *Nexplanon* (implantable device) and Depo-Provera injection. Metformin can restore ovulatory menses in 30-50 % of patients. Luteal phase progesterone measurements or transvaginal sonogram can be used to monitor the effectiveness of metformin in doing this, per Up To Date recommendations.<sup>10</sup>

Per 2018 Endocrine Society Clinical Practice Guidelines on Hirsutism, combined estrogen/progestin oral contraceptives (COCs) are considered the first-line therapy. Antiandrogen is added after 6 months, if the response is not optimal and in some cases of more severe hirsutism, can be started together. Some women are not candidates for COC and can be treated with spironolactone alone. Spironolactone is typically dosed at 50 mg to 100 mg twice daily. In these cases, one should monitor potassium levels and make sure effective contraception is in place, as spironolactone could prevent development of normal external genitalia in a male fetus. With COCs and/or spironolactone, check a pregnancy test prior to starting. Finasteride (inhibits 5 alpha-reductase type 2) or dutasteride (inhibits both alpha reductase types 1 and 2) can also be used along with effective contraception. Mechanical hair removal or topical creams, like *Vaniqa*, can also be used.

Obesity is one of the more difficult aspects to treat. There is no good evidence that one type of diet is superior to another for women with PCOS. A 5-10 percent weight loss can result in restoration of normal ovulatory cycles, and improved pregnancy rates<sup>11</sup>. Insulin resistance is another component of this and can be present with or without obesity. This provides a good opportunity to review lifestyle changes with education on carbohydrates in the diet, exercise, intermittent fasting and become familiar with supplements including berberine, chromium, cinnamon, diaxinol, omega 3s, bergamot and prescription drugs including metformin along with the newer GLP-1 (glucagon-like peptide 1 receptor agonist) drugs. There is now limited data in women with PCOS suggesting that exenatide and liraglutide are effective in weight reduction as monotherapy or in combination with metformin. Some studies also showed that androgens may be modestly decreased, menstrual frequency may be increased, glucose parameters are general improved, and eating behaviors improve. These drugs are generally well tolerated with nausea being the most significant adverse side effect.<sup>12</sup> Dyslipidemia, obstructive sleep apnea (OSA), and nonalcoholic steatohepatitis (NASH) are all more common in women with PCOS. CPAP was shown to result in improved insulin sensitivity and reduced diastolic blood pressure in women with PCOS and OSA in one report followed by a meta-analysis of eight studies<sup>13</sup>. Metformin and weight loss appear to improve metabolic and hepatic function in women with PCOS. Weight loss is still first line for women with PCOS and anovulatory infertility followed by letrozole, an aromatase inhibitor.

For the purposes of Biote providers and the transitioning women with PCOS, please be mindful of abnormal bleeding. Even if you are only managing testosterone in a premenopausal women, please identify and redirect women with dysfunctional uterine bleeding to a gynecologist. They are often estrogen dominant, and DIM is beneficial for these patients in particular. Consider starting *DIM SGS+* twice a day as soon as you diagnose a patient with PCOS. Though a woman with PCOS will typically have hyperandrogenism, most become quite symptomatic when their formerly high testosterone levels drop by 50 percent or more in their 30-40s. These patients will be concerned about side effects including acne and other hirsute symptoms from testosterone. Testosterone dosing will often need to be reduced 10-20 % and patients closely monitored. Do not hesitate to start spironolactone early. Also remember to discuss how eliminating excess sugar, processed foods, and often times dairy from the diet can not only improve insulin resistance, but aid in the treatment of acne.<sup>14</sup> Yearly labs for a woman with PCOS need to include DHEA-S, free and total testosterone, FSH, estradiol, SHBG, fasting insulin/CMP/lipids, and hemoglobin A1-C. Initiate cardiac screening early for these patients— consider Cleveland Heart Panel and CT calcium score, sometimes Carotid Intima-Media Thickness (CIMT) evaluation. Remember to use this as an opportunity to educate these patients on all aspects of health and focus on prevention of diabetes and heart disease. Support their desires for weight loss by becoming well-versed in discussing exercise needs (aerobic and anaerobic focusing on weightlifting), supplementation (DIM, chromium, cinnamon, diaxinol), and a variety of weight loss methods including medical support with phentermine, *Contrave*, GLP-1 drugs (on and off label), and metformin.

In summary, PCOS is a very common disease process effecting women with “hormone issues”. Many of the women you will see meet criteria for PCOS by having hyperandrogenism and irregular menstruation or the presence of polycystic ovaries on ultrasound. Unfortunately, the diagnosis remains controversial with inconsistent assessment and management of these patients. Biote hopes this offers some insight into how to listen to, diagnose, work up, and then treat these women so they have better quality of life and less long-term comorbidities.

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