INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Polycystic Ovary Syndrome***
-October 2023-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a review of pharmacotherapy for treatment of polycystic ovary syndrome (PCOS). Relevant medications currently listed on the IHS National Core Formulary (NCF) include combination oral contraceptive pills (COCPs), finasteride, letrozole, levonorgestrel intrauterine device, metformin, pioglitazone, psychotropic medication for associated mood disorders, spironolactone, and topicals and antibiotics for acne. Following clinical review and analysis, the NPTC made **no modifications** to the NCF.

Discussion:

PCOS is the most common endocrine disorder in reproductive-age women, affecting about 10% worldwide, and is the most common cause of anovulatory infertility.[1] Diagnosis strongly correlates with family history, though relatively few specific gene targets have as yet been identified.[2] Obesity is postulated to be one of a number of environmental and epigenetic cofactors affecting the expression of PCOS, rather than being purely a consequence of the condition itself.[3] In a 2023 population study by Yu, et al. the overall prevalence of PCOS in American Indian/Alaskan Native (AI/AN) women was 6.9%, second only to Hawaiian and Pacific Islanders of the 6 ethnicities defined; overall United States prevalence was found to be 5.2%.[4]

Diagnosis of PCOS requires the presence of at least two of the three Rotterdam 2003 criteria in adults, including menstrual irregularity or oligo-ovulation, clinical or biochemical evidence of hyperandrogenism, and/ or evidence of polycystic ovarian morphology (PCOM) on ultrasound. Diagnosis in adolescence excludes PCOM and can be delayed until up to 3 years after menarche given overlap between PCOS and normal developmental menstrual irregularity, during which time a patient may be considered "at risk" for PCOS if there is evidence of hyperandrogenism.[1]

Endometrial protection is a clinical concern in patients presenting for management of **menstrual irregularity** or oligo-ovulation**.** As a group, women with PCOS are at increased risk for endometrial cancer, though many studies examining this association have not controlled for obesity, a strong and well-established risk factor.[5] Evidence from the general population has suggested a protective effect of OCPs. A 2021 observational study of 256,661 women born in the United Kingdom between 1939 and 1970 showed that "ever use" of OCPs was associated with reduced risk for endometrial cancer (OR 0.68, 95% CI: 0.62–0.75).[6] Progestin-only products can be used for those with a contraindication to COCPs.

Hirsutism is a feature of hyperandrogenism, and is graded using the Ferriman-Gallwey (F-G) scoring system, with higher scores correlating to more excessive unwanted facial and body hair. A 2018 network meta-analysis showed that estrogen-progestin OCPs were superior to placebo in treating hirsutism; pool-weighted mean difference in F-G score versus placebo was -7.20 (95% CI: -11.96 to -2.52).[7] A more recent meta-analysis of 19 studies compared the effectiveness of different kinds of OCPs in PCOS patients. The progestin cyproterone, combined with ethinyl estradiol (EE), most effectively reduced hyperandrogenism but couldn't be recommended first-line in PCOS due to higher venous thromboembolic risk (and is not available in US).[8] The 2023 International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome favors no specific COCP over others, noting no advantage in using >30 mcg EE or any specific progestin for treating hirsutism or menstrual irregularity in adults and adolescents.[9]

Two recent reviews found the antiandrogen spironolactone more effective than placebo and as effective as flutamide for reducing the F-G score in the general population.[7,10] A 2023 review of its use in PCOS patients found spironolactone to be safe in doses of 25-100 mg daily; its addition to COCPs appears more effective for hirsutism than COCPs alone.[11]

Patients for whom **infertility** is the primary concern are initially encouraged to lose ≥5% of body weight to attain more regular ovulation. Where medical induction of ovulation is indicated, letrozole, an aromatase inhibitor approved for adjuvant treatment of breast cancer, is overtaking clomiphene citrate as the first-line treatment-of-choice, though its use in this setting remains off-label. A 2014 RCT established its superiority over clomiphene, showing that ovulation rates were higher with letrozole than with clomiphene (834 of 1352 treatment cycles [61.7%] vs. 688 of 1425 treatment cycles [48.3%], $p<0.001$); women who received letrozole had more cumulative live births (103 of 374 [27.5%] vs. 72 of 376 [19.1%], $p=0.007$; rate ratio for live birth, 1.44, 95% CI: 1.10 to 1.87) without significant differences in congenital anomalies; and there were no significant between-group differences in pregnancy loss (49 of 154 pregnancies in the letrozole group [31.8%] and 30 of 103 pregnancies in the clomiphene group [29.1%]) or twin pregnancy (3.4% and 7.4%, respectively).[12] A 2018 Cochrane review corroborated these findings.[13]

Though not a diagnostic criterion for PCOS, **insulin resistance** is common, and the resulting increase in insulin levels contributes to excessive ovarian androgen secretion. In the 1990s, the biguanide metformin was shown to reduce circulating insulin and testosterone levels. A 2019 meta-analysis by Teede, et al. concluded that when added to OCPs, metformin reduced biochemical measurements of hyperandrogenemia, though a 2020 Cochrane review found OCPs superior to metformin for hirsutism in PCOS patients with a body mass index (BMI) between 25 and 30.[14,15] Several studies have shown that about half of women with PCOS treated with metformin will achieve normal menstrual function and ovulation. However, it remains second-line for normalizing menses when COCPs are not tolerated or are contraindicated, and to letrozole or clomiphene when fertility is desired.[16]

Obesity or overweight is present in the majority of PCOS patients. Lifestyle modification consisting of calorie restriction and exercise is considered first-line treatment for most patients with anovulation, given evidence that a reduction of as little as 5-10% of body weight can restore regular menses and improve pregnancy rates.[17] In a review of several small studies of liraglutide vs. placebo or metformin in patients with PCOS, liraglutide at doses of 3 mg per day led to 2.5-fold more patients achieving at least 5% weight reduction vs. placebo and greater reduction in BMI and waist circumference than metformin 1000 mg BID.[18] In a 2023 proof-of-concept study (no comparator) of 27 PCOS patients, low-dose semaglutide (0.5 mg weekly) normalized menses in 15 women, and in the 21 women considered "responders," treatment for 6 months led to a mean BMI reduction from 34.4 to 29.4.[19]

Findings:

PCOS is generally associated with hyperandrogenemia, affecting menstrual regularity and fertility, and causing excessive hair growth, acne, and occasionally alopecia. Insulin resistance associated with obesity may unmask a genetic tendency for PCOS. When lifestyle modification geared toward weight loss does not improve symptoms or fertility, COCPs, metformin, spironolactone, letrozole, and clomiphene citrate are all considered first- or second-line treatments depending on the patient's goals. Metformin is first-line where the goal is treatment of diabetes or prediabetes. The study of GLP1/GIP receptor agonists to treat aspects of PCOS other than obesity is still in its infancy. Acne and mood disorders are common and should be treated as for patients without PCOS.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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