Off-label drug use in the treatment of polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is a complex lifelong disorder with an etiology and pathophysiology that is not yet entirely understood. Women with PCOS have clinical presentations that may vary from adolescence to menopause, including menstrual irregularity/anovulation and symptoms of hyperandrogenism, such as acne and hirsutism. Over a lifetime, treatment needs and requirements can change. Unfortunately, there are no Food and Drug Administration–approved medications that are approved solely for the purpose of PCOS, but the symptoms and presentation of PCOS are often amenable to several approved agents, such as oral contraceptives for the indication of acne and clomiphene citrate for the indication of induction of ovulation. However, to meet the needs of women with PCOS, off-label use of medications has flourished. This review explores the data for those agents that do not carry an indication for PCOS but have been used for treating the signs and symptoms of PCOS. (Fertil Steril® 2015;103:605–11. ©2015 by American Society for Reproductive Medicine.)

Key Words: PCOS, drug therapy, hirsutism, insulin resistance

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Polycystic ovary syndrome (PCOS) is defined by three criteria: hyperandrogenism, menstrual irregularity/anovulation, and polycystic-appearing ovaries. The diagnostic criteria, known as the Rotterdam 2004 criteria requires two of these criteria for diagnosis of the condition (1). The main symptoms of PCOS include irregular bleeding, acne, hirsutism, and ovulatory dysfunction. In addition, though not specifically part of the diagnosis, women with PCOS suffer from metabolic disorders that are related to insulin resistance. It is estimated that >75% of women with PCOS are insulin resistant when measured rigorously (2).

There are few medications that are approved for the most common symptoms of PCOS, leading to the off-label use of medications that were approved for other indications. Overall, there are very few randomized or placebo-controlled trials on the use of these medications for signs and symptoms of PCOS. Given the paucity of available options, however, these medications are commonly used when approved treatments are ineffective or no approved medication exists for the indication. This review discusses the most common non–Food and Drug Administration (FDA)–approved medications in PCOS. The review is organized by common medications used in treatment, recognizing that several off-label medications are used for multiple purposes in PCOS.

FDA-APPROVED MEDICATIONS FOR PCOS

There is no drug specifically approved by the FDA for the indication of PCOS. In addition, there are few medications that are indicated or approved for the treatment of symptoms that are common in PCOS, such as irregular menses, acne, and hirsutism. Eflornithine HCl 1% is indicated for hirsutism and reduction in facial hair and inhibits the enzyme ornithine decarboxylase. In clinical trials, eflornithine decreases unwanted facial hair and improves overall patient satisfaction regarding the reduction in unwanted hair (3). Evidence supports its use in combination with laser hair removal (4). Oral contraceptives containing norethindrone acetate, norgestimate, and drosperinone are approved for acne vulgaris, and medroxyprogesterone acetate is indicated for the control of menstrual irregularity and amenorrhea which are common in PCOS. Although oral contraceptives in general appear to be effective for menstrual control and acne, oral contraceptives containing drosperinone are associated with an increased risk of blood clots (5). Additionally in obese patients with PCOS, oral contraceptives may be associated with worsening insulin resistance (6). The details of these medications, including indications, side effects, and mechanism of action are summarized in Table 1. Both approved and drugs used off label for

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TABLE 1

FDA-approved drugs or typical symptoms associated with PCOS.

Drug (generic)	Mechanism of action	Excretion and half-life	FDA indication	Main side effects	Pertinent drug interactions	Anomaly risk (includes FDA pregnancy category)	Contraindications
Eflornithine HCL 1%	Inhibits enzyme ornithine decarboxylase	<1% absorption; half-life 8 h	Hirsutism reduction in facial hair	Skin irritation	None known	Pregnancy category C	Sensitivity to components
Oral contraceptive: Ethinyl estradiol + norethindrone or norgestimate or drosperinone	Antiandrogen effect increase in SHBG, decrease in free testosterone	Metabolized in the liver; 26–30 h	Moderate acne vulgaris	Headache, migraine, menstrual irregularity, nausea and vomiting, breast tenderness, mood disturbance, venous thromboembolism, hypertension	Any drug that induces enzyme CYP3A4 reduces effectiveness	Pregnancy category X	Renal impairment, adrenal insufficiency, increased risk for venous thromboembolism, abnormal undiagnosed uterine bleeding, breast cancer, liver disease, pregnancy
Medroxyprogesterone acetate	Transforms proliferative to secretory endometrium	Metabolized in the liver; 12.1 h	Treatment of secondary amenorrhea and abnormal bleeding due to hormonal imbalance	Spotting, breast tenderness, thrombosis, increased blood pressure, nausea and vomiting	Induction of CYP3A4 enzyme may reduce effectiveness	Pregnancy category X	Undiagnosed vaginal bleeding, heart disease, liver disease, pregnancy, breast cancer

Vitek. Off-label use of drugs for PCOS. Fertil Steril 2015.

ovulation induction in infertility associated with PCOS are covered in a separate review in this series, so they are not included in this review.

OFF-LABEL USES OF DRUGS FOR COMMON MANIFESTATIONS IN PCOS

The most common symptoms of PCOS include irregular menstrual cycles and hirsutism. However PCOS is also associated with other metabolic abnormalities that warrant treatment. One of the most challenging aspects of PCOS is the high prevalence of metabolic abnormalities, specifically the high incidence of insulin resistance, which is linked to the pathophysiology of PCOS (2). Women with PCOS have high rates of impaired glucose tolerance and diabetes (7). Although there are approved medications for the treatment of diabetes, regardless of its association with PCOS, there are no approved medications that are approved for the treatment of insulin resistance. Women with PCOS are also noted to have high rates of obesity, which complicates the metabolic picture and is one of the most distressing aspects of the condition for many women (8, 9). Women with PCOS often report difficulty with food cravings and appetite, which may be related to insulin resistance, and so they seek out management of insulin resistance as a way to control these symptoms (10). Table 2 summarizes the major drugs used off label in PCOS in the United States.

Metformin, D-chiro-inositol, and Myo-inositol

One of the most common medications being used off label for PCOS is metformin. From its initial description for management of ovulation induction in PCOS, metformin has rapidly risen to be one of the most requested medications for management of the condition (11). A survey of Pubmed reveals >30 meta-analyses of randomized trials and >70 systematic reviews covering the role of metformin therapy in management of PCOS, including ovulation induction, weight loss, menstrual control, preterm birth, miscarriage, and hirsutism. Despite the large number of analyses completed, there are few large scale or randomized placebo-controlled trials (RCTs) using metformin for PCOS, and there remains significant controversy of opinion with little conclusive data on its effectiveness in PCOS. Metformin works as an insulin sensitizing agent. Because insulin resistance is integral to the pathophysiology of PCOS, it is reasonable to anticipate that improvement in insulin resistance will improve many of the symptoms of PCOS. Review of the largest trials of metformin therapy in PCOS suggests that metformin has a limited role in the management of reproductive consequences of PCOS (12). The single largest RCT of metformin in PCOS failed to improve fertility compared with clomiphene citrate (13). For the indication of menstrual cycle regulation, meta-analysis suggested that metformin improved menstrual pattern compared with placebo (12). It is notable, however, that the studies are relatively small (n <30) with significant heterogeneity, increasing concern about the reliability of these findings. When compared with oral contraceptive, metformin therapy was not as effective in improving menstrual patterns in several

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