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Polycystic Ovary Syndrome and Acne

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive aged women. It is typically characterized by hyperandrogenism, chronic anovulation, and polycystic ovaries. Women with PCOS often experience dermatologic manifestations of hyperandrogenism, including hirsutism, acne vulgaris, and androgenic alopecia. This article will review the treatments for acne due to androgen excess in PCOS women.

Key Words: *acne vulgaris, hyperandrogenism, polycystic ovary syndrome, PCOS*

Pathophysiology and Prevalence

Polycystic ovary syndrome (PCOS) is typically characterized by excessive ovarian androgen production, failure of ovulation, and slightly enlarged ovaries with numerous peripheral small follicles that appear as cysts. Individuals with this phenotype comprise 5-10% of reproductive aged women.¹⁻³ The disorder is commonly accompanied by insulin resistance and infertility. Clinical manifestations include irregular menstrual bleeding due to anovulation and dermatologic sequelae of hyperandrogenemia, including hirsutism, acne vulgaris, and androgenic alopecia. The prevalence of acne in women with PCOS has been estimated to be 10-34%.⁴⁻⁷ However, in post-pubertal and adolescent PCOS women it is unclear whether acne arises secondary to androgen excess or occurs as a result of normal puberty. During puberty, acne is common and attributable to the surge of adrenal androgens with adrenarche. In adolescent girls, moderate to severe acne has been reported to be greater than 50%.¹

Acne is the most common skin disorder, affecting approximately 40-50 million people in the United States.⁸ This condition results from the formation of comedones, due to sebum accumulation, along with desquamated follicular epithelial cells, which allows colonization by the bacterium, *Propionibacterium acnes* (*P. acnes*).⁹ Androgens may worsen acne formation by increasing sebum production within the pilosebaceous unit. Many PCOS women with acne exhibit facial lesions and up to 50% of individuals demonstrate lesions on the neck, chest, and upper back.¹⁰

Past studies have shown that androgen levels are elevated in women with acne, although the severity of acne has not been positively correlated with any particular hormone, with the exception of the adrenal androgen, dehydroepiandrosterone sulfate (DHEA-S).¹¹⁻¹³ Notably, several studies have demonstrated an inverse relationship with sex-hormone binding globulin (SHBG).^{11,14}

About 50% of normal women with acne do not have clinical or biochemical evidence of hyperandrogenism.¹⁵ Conversely, in many PCOS women hirsutism is not associated with acne. These discrepancies may be due to variable local androgen bioactivity. It has been postulated that androgen levels within the skin are more important mediators of acne than circulating levels.^{13,16}

In the hair follicle, androgen bioactivity is regulated, in part, by 5- α -reductase, which acts to convert free testosterone to the more potent dihydrotestosterone (DHT). This enzyme has two isoforms: type 1 is found in the sebaceous glands and pubic skin and type 2 is located primarily in the hair follicle, genital skin, and adult scalp. The relative activities of these isoenzymes within the hair follicle could account for the variable clinical presentation seen in hyperandrogenic women when the degree of hirsutism is not compatible with the severity of the acne.¹⁰ In addition, 5- α -reductase expression is also stimulated by excess androgen, insulin, and insulin-like growth factor, which likely contributes to increased local androgen bioactivity, resulting in the hirsutism and acne seen in PCOS women.^{10,17}

Treatment

For women with PCOS in whom hirsutism is a major concern, treatment is focused on reducing androgen production, decreasing the fraction of circulating free testosterone, and limiting androgen bioactivity at the hair follicle. In those

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PCOS women with acne vulgaris, clinical benefit may be derived from any of these therapeutic modalities (Figure 1).

Ovarian Suppression

The most common form of ovarian suppression is treatment with combined oral contraceptive pills (OCPs). These drugs suppress gonadotropin secretion and ovarian steroid synthesis, leading to decreased androgen production. The estrogen component has been shown to stimulate SHBG production by the liver, thereby decreasing the bioavailability of serum testosterone.^{10,18} The progestin component of OCPs may lower local androgen effect by inhibiting 5- α -reductase activity in the hair follicle or competitive inhibition for the androgen receptor.^{19,20} The anti-androgenic effects of the progestin, cyproterone acetate, have been well documented, whereas the benefit of drospirenone is less clear.^{21,22} Drospirenone is related to the anti-androgen, spironolactone, although whether the dose contained in OCPs is sufficient to block androgen action clinically has not been established. It is likely that clinical improvement of hirsutism associated with OCPs containing drospirenone may be attributed to overall ovarian suppression. Formulations containing more androgenic progestins, such as levonorgestrel and norgestrel, may be less effective.

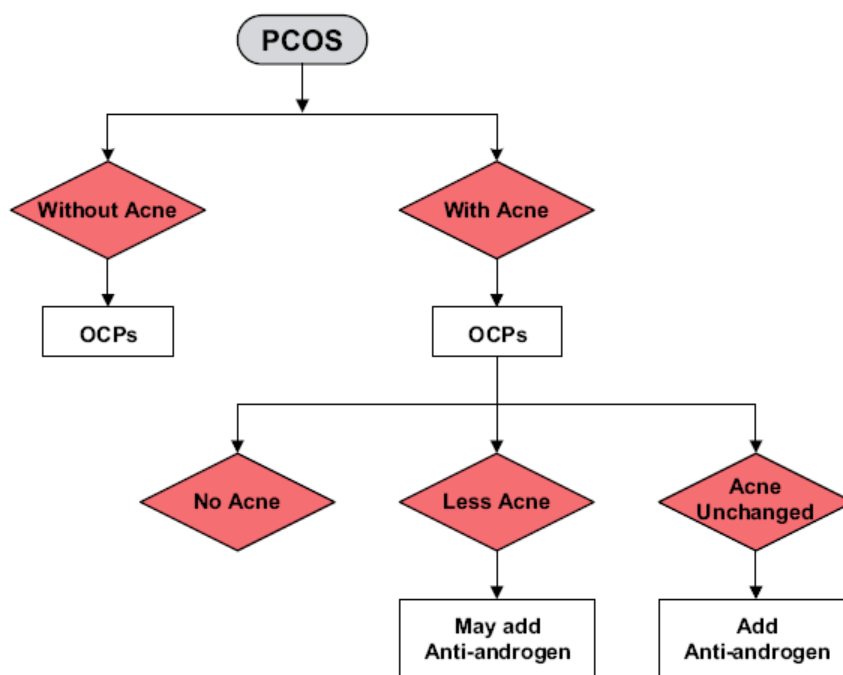
The benefits of lower androgen production by OCPs include improvement of acne vulgaris.²³ A recent Cochrane review showed that OCPs reduced acne lesion count, severity grades, and self-assessed acne.²¹ It is unclear how OCPs compare to alternative acne treatments, such as topical and antibiotic therapies.

Anti-Androgens

Spironolactone

Spironolactone is an aldosterone antagonist with antiandrogenic properties. It has been commonly used to treat hirsutism.²⁴ The mechanism of action includes competition for the androgen receptor, suppression of cytochrome P450, and inhibition of steroidogenesis, as well as reduction in 5- α -reductase activity.²⁴⁻²⁷

Spironolactone also decreases sebum production and improves acne. The therapeutic dose for acne therapy is 50-100 mg per day. The dose of spironolactone used for treating hirsutism is significantly higher, ranging from 100-300 mg daily. Thus, its use for hirsutism would likely prove effective for acne as well. Spironolactone may be used in combination with OCPs in women who have limited response to OCPs alone.⁹ It is important for women to remain on birth control while on spironolactone to avoid feminization of a male fetus in an unplanned pregnancy. Patients should be off the medication for 3 months before conception.



Side-effects of this medication at recommended doses for hirsutism and acne are minimal. Occasionally, polydipsia, polyuria, nausea, headaches, fatigue, and gastritis may occur. In addition, some normal ovulatory women may experience menstrual irregularity. Despite its mild diuretic effect, spironolactone has the potential to induce hyperkalemia. For the healthy PCOS patient this remains a theoretical risk. However, patients should be counseled regarding foods containing high potassium content.

Flutamide

Flutamide is a non-steroidal androgen receptor antagonist indicated for the treatment of prostate cancer and has been found to be effective for treating hirsutism.²⁸⁻³¹

Flutamide may be used for the treatment of mild to moderate acne. It should be used at low doses; 62.5 mg or 125 mg per day have been shown to be effective. The combination of OCPs and flutamide is likely more efficacious than flutamide alone.³² In hirsute women with acne who were treated with OCPs, the addition of flutamide was significantly more effective than spironolactone.³³

The potential for hepatotoxicity limits its use. However, no cases of fatal hepatotoxicity have been reported with doses less than 500 mg per day.³⁰ There have been reports of mild, transient liver impairment at doses ranging from 375-500 mg per day.^{34,35} Women should remain on OCPs for birth control purposes as feminization of a male fetus can occur while on this medication. Patients should be off the medication for 3 months before conception.

Finasteride

As a 5- α -reductase inhibitor, finasteride is commonly used in the treatment of prostatic disorders and has been used to treat hirsutism. Its effectiveness for hirsutism is comparable to that of spironolactone.³⁶ In hyperandrogenic women, the efficacy of this drug for acne has not been well evaluated. In one study, finasteride was shown to decrease acne, but to a lesser degree than flutamide and cyproterone acetate.³⁷ The reduced effect of finasteride on acne may be explained by lower inhibition of 5- α -reductase type 1 activity, which is prominent in the sebaceous gland, as compared with that of 5- α -reductase type 2 expressed primarily in the hair shaft.³⁸

Insulin Sensitizing Agents

Insulin sensitizing agents, such as metformin and thiazolidinediones, have been employed in women with PCOS to decrease androgen production by lowering hyperinsulinemia. The efficacy of this approach to treat hirsutism has been inconsistent, as some, but not all studies have shown benefit. In these investigations, little attention has been given to improvement of acne. In a study of patients with minimal acne, improvement of acne was reported after 12 months of therapy with metformin 1500 mg daily.³⁹ At present, these agents are not recommended as acne therapy for women with PCOS.

Conclusion

Acne is a ubiquitous condition that is often exacerbated by androgen overproduction in women with PCOS. Hormonal agents targeted at reducing hyperandrogenemia and androgen bioactivity may effectively reduce both hirsutism and acne simultaneously. OCPs are recommended as first-line therapy unless otherwise indicated. Anti-androgens may be added to improve the clinical outcome.

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