

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 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 anti-androgenic 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.

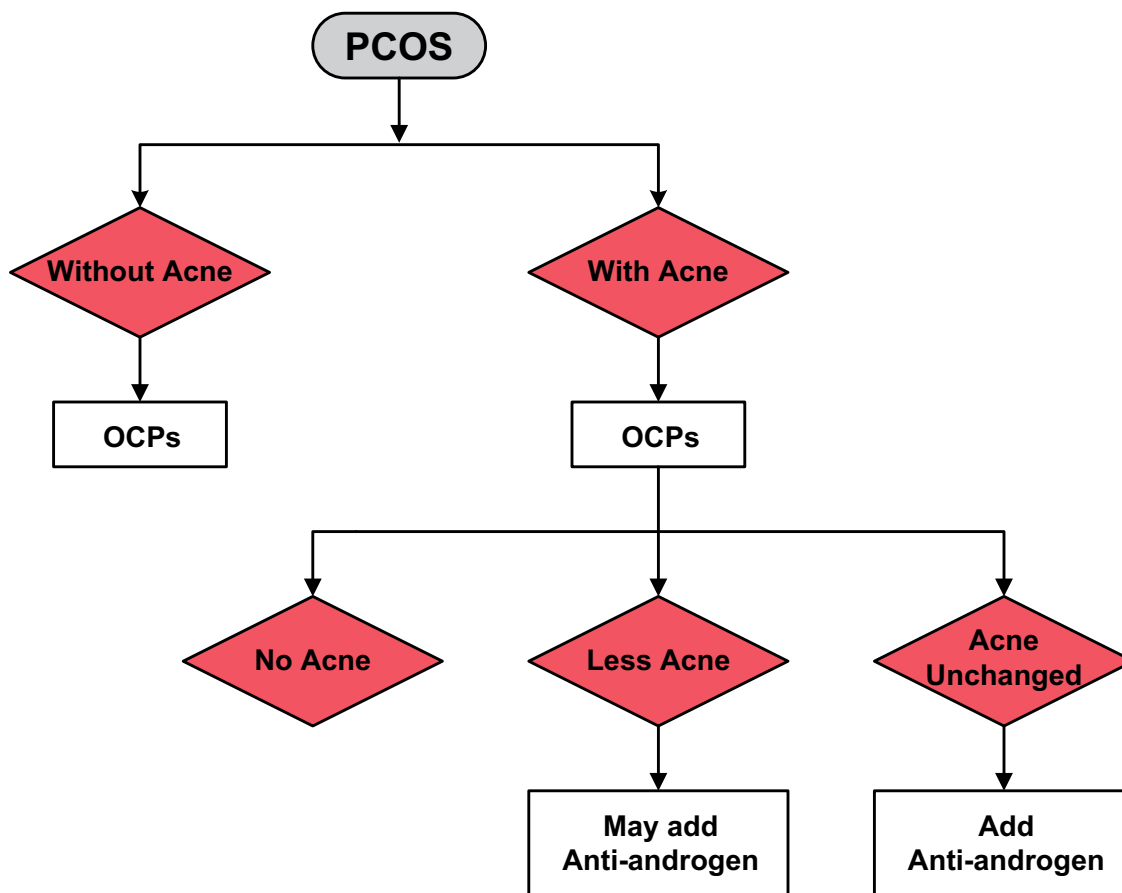


Figure 1. Treatment algorithm for acne in PCOS women

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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Benzoyl Peroxide: Enhancing Antibiotic Efficacy in Acne Management

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ABSTRACT

*Benzoyl peroxide is one of the most widely used topical agents for acne. It has potent antibacterial and mild anti-inflammatory and comedolytic effects. To treat mild to moderate acne, it can be used alone or in combination with topical antibiotics and topical retinoids. The combination of benzoyl peroxide with either erythromycin or clindamycin is synergistic and well-tolerated. In more severe acne, when oral antibiotics are required, benzoyl peroxide can contribute to suppressing the emergence of resistant strains of *Propionibacterium acnes*.*

Key words: acne vulgaris, antibacterial agents, antibiotic resistance, benzoyl peroxide, erythromycin, clindamycin, topical combination therapy

Background

The first description of benzoyl peroxide (BP) in the treatment of acneiform eruptions dates back to 1934, although its use as a topical agent in the management of various skin lesions was pioneered by Loevenhart in 1905.¹ In 1958, Fishman was the first to suggest benzoyl peroxide as a viable treatment for acne.² Pace presented findings of its efficacy before the members of the Canadian Dermatology Association at their meeting in Toronto in June of 1962 (later publishing the findings in 1965³) and after a suitable vehicle (it is insoluble in water) was found for the drug, benzoyl peroxide was adopted by clinicians. Its popularity has increased in recent years with the emergence of antibiotic-resistant strains of *Propionibacterium acnes* (*P. acnes*).

Benzoyl peroxide is available in various strengths (2.5-20%) and vehicles (gels, lotions, solutions, creams, soap bars, pads, masks, and washes), as well as in combination formulation with the topical antibiotics erythromycin or clindamycin phosphate. It is also combined with the topical retinoid adapalene in a formulation that was US FDA approved in December 2008, but is not yet available in Canada.

Pharmacokinetics and Pharmacodynamics

Benzoyl peroxide is lipophilic and when applied to the skin it is capable of penetrating into the pilosebaceous follicle. Within the skin, benzoyl peroxide releases free radical oxygen and benzoic acid. The free radicals oxidize bacterial proteins. Higher concentrations of benzoyl peroxide applied to the skin result in larger amounts of drug in the skin.⁴ The benzoic acid is cleared rapidly by the kidneys and excreted unchanged in the urine.⁵ A second peak of urinary excretion of benzoic acid is detected when the benzoyl peroxide is washed off 24 hours after its application. This was noted especially with higher concentrations of the drug, suggesting that it is retained in the stratum corneum and that hydration increases its penetration.⁴

Inhibiting Antibiotic Resistance

Since the introduction of topical antibiotics in the mid-1970s, antibiotic-resistant strains of *P. acnes* have emerged and increased in numbers over the years.⁶ There is some evidence to suggest that patients with these resistant strains clinically fail to respond to the corresponding oral antibiotic when it is used alone.^{6,7}

Benzoyl peroxide is a very effective broad-spectrum antibacterial agent. It was found to be more effective in reducing the concentration of free fatty acids in sebum than was systemic tetracycline, and efficacy was not affected by *P. acnes* resistance.^{8,9} BP has mild anti-inflammatory and comedolytic effects,¹⁰ thus, it influences three of the four factors involved in acne pathogenesis. BP was initially thought to have sebo-suppressive effects, but Cunliffe showed that a 5% concentration increased sebum secretion rates by 22.5% after 1-2 months, likely by reducing obstruction in the pilosebaceous follicle and allowing sebum to flow more freely to reach the skin surface rather than affecting the sebaceous gland cells.¹¹

Benzoyl peroxide is effective in controlling antibiotic-sensitive and antibiotic-resistant *P. acnes*. Significant reductions of *P. acnes* counts on the skin surface and in the follicle were noted after only 2 days of application of 5% benzoyl peroxide in an aqueous gel, with clinical improvement seen as early as 4 days.¹² Benzoyl peroxide 6% cleanser was shown to reduce counts of antibiotic-susceptible and antibiotic-resistant strains of *P. acnes* equally by at least 2 logs after only 3 weeks of once daily washing for 20 seconds.¹³

Three double-blind studies that enrolled 153 patients with mild to moderately severe acne compared the efficacy of 2.5%, 5%, and 10% benzoyl peroxide gel formulations with the gel vehicle applied twice daily for 8 weeks. The three strengths were significantly more effective than the gel vehicle. Though the three strengths were deemed similar

in their ability to reduce inflammatory lesions, the study was inadequately powered. Consequently, a statistically significant difference between the 2.5% and 5% and the 2.5% and 10% could not be reached. The 2.5% gel was also formulated in a different vehicle than the 5% and 10% gels. Furthermore, the findings showed an increased incidence of irritation related to higher strengths of benzoyl peroxide.¹⁴

The rise of resistant strains of *P. acnes* has been associated with a failure to respond to antibiotic therapy. This resistance was first reported with the topical antibiotics, clindamycin and erythromycin.¹⁵ The combination of benzoyl peroxide and topical antibiotic should prevent the selection of antibiotic-resistant propionibacteria, as well as reduce the number of strains of existing antibiotic-resistant bacteria on the skin. Benzoyl peroxide has also been shown to reduce the amount of erythromycin required to inhibit sensitive propionibacteria by up to 50% less than if erythromycin was used alone.¹⁶

Additionally, benzoyl peroxide can prevent the selection of erythromycin-resistant *Staphylococcus epidermidis* (*S. epidermidis*). During a 16-week study,¹⁷ three groups of 20 patients were treated with benzoyl peroxide alone, BP in combination with 3% erythromycin (BP/E), or erythromycin alone. After 12 weeks of treatment with erythromycin alone, the *S. epidermidis* isolated was completely resistant to erythromycin. There was also an increase in resistance to clindamycin and tetracycline. Those treated with BP or BP/E showed no change in resistance patterns to erythromycin or other antibiotics. These results are of major significance as *S. epidermidis* can cause infections in immunosuppressed and hospitalized patients and can transfer resistance to *Staphylococcus aureus*.¹⁷

In a double-blind study, 37 patients with mild to moderate acne were treated with 5% benzoyl peroxide in combination with 3% erythromycin (BP/E) gel or 3% erythromycin gel alone for 12 weeks. The combination therapy resulted in a greater than 3 log reduction in total *P. acnes* counts and significantly reduced the number of erythromycin-resistant strains by 6 weeks. Erythromycin alone, however, produced less than a 1.5 log reduction in total *P. acnes* counts and did not reduce the number of resistant strains after the same amount of time.¹⁸ Of concern, five patients in each group developed erythromycin-resistant strains de novo at 6 and 12 weeks. In an open study of 21 patients with erythromycin-resistant strains of *P. acnes*, the total count and number of resistant strains were reduced by greater than 2.5 logs after 6 weeks of treatment with the BP/E gel.¹⁸

The combination of benzoyl peroxide and antibiotics has also been shown to have superior efficacy to either product alone. In two double-blind randomized, parallel, vehicle-controlled trials, patients were treated nightly with a combination 5% benzoyl peroxide + 1% clindamycin gel (BP/C), benzoyl peroxide, clindamycin, or vehicle gel. The combination gel was significantly superior to the two individual agents in global improvement and reduction of inflammatory lesions.¹⁹

In a ten week study, the combination of BP/C was more efficacious than benzoyl peroxide alone and statistically comparable to the BP/E combination.²⁰

Safety

Benzoyl peroxide can induce an irritant contact dermatitis that is related to the amount and type of product, its concentration, and its vehicle formulation. Reactivity may be more commonly seen in patients with atopic dermatitis. In combination with a topical antibiotic, BP produces less erythema than when used alone.²¹ The rates reported of true allergic contact dermatitis vary in the literature from 0.2% to 1%.^{21,22} Patch testing to benzoyl peroxide can be difficult to interpret because of its irritant properties.²³

The carcinogenicity and photocarcinogenicity of benzoyl peroxide have been questioned for many years. An article reviewing two case-control epidemiological studies and 23 carcinogenicity studies in rodents concluded that there was no evidence to support an association between skin cancer in humans and the use of benzoyl peroxide.²⁴ Current data suggests that benzoyl peroxide is considered safe in humans and does not accelerate photocarcinogenesis, though more data is needed.²⁵

Benzoyl peroxide is assigned a Category C by the US FDA, and no studies on its use in pregnant women have been published. However, its metabolism and excretion would suggest that it should have no effect on the fetus.²⁶

Other Treatment Considerations

Benzoyl peroxide bleaches clothing and hair, and thus, patients should be warned accordingly when the drug is prescribed. Practical suggestions for patient management may include limiting use on the chest and back to nighttime due to its bleaching effect on clothing, or recommending that the patient wear a white T-shirt under clothing for daytime application.

Conclusion

Benzoyl peroxide is one of the most commonly used and efficacious topical acne agents. It is equally effective against antibiotic-resistant and antibiotic-sensitive strains of *P. acnes*. To avoid antibiotic resistance, the prolonged use of topical or oral antibiotic monotherapy for acne is strongly discouraged without concomitant treatment with benzoyl peroxide. For topical acne therapy benzoyl peroxide can be used as a combination formulation with an antibiotic, and for systemic antibiotic therapy it can be used daily as a wash or leave-on product.²⁷ If found to be too irritating for daily use, even as a wash, a short course (5-7 days) of benzoyl peroxide used monthly may be effective in reducing resistant strains of *P. acnes*. Limitations of benzoyl peroxide include an irritant contact dermatitis and, much less frequently, an allergic contact dermatitis.

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Update on Drugs

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| Name/Company | Approval Dates/Comments |
|--|--|
| Drospirenone / ethinyl estradiol / levomefolate calcium + levomefolate calcium tablets Beyaz™ Bayer HealthCare Pharmaceuticals Inc. | The US FDA approved a new oral contraceptive (OC) in September 2010 to raise folate levels in women who choose an OC for birth control. The addition of levomefolate calcium raises folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking Beyaz™ or shortly after discontinuation. This novel formulation combines the hormone ingredients in the birth control pill Yaz® (drospirenone 3 mg / ethinyl estradiol 20 mcg) with 451 mcg levomefolate calcium. The approval of Beyaz™ is based on Yaz®, which contains the same doses of estrogen and progestin, and is approved for three indications: prevention of pregnancy; treatment of symptoms of premenstrual dysphoric disorder in women who choose an OC for contraception; and treatment of moderate acne vulgaris in women ≥14 years of age, but only if the patient prefers an OC for birth control. |
| Imiquimod 5% cream Perrigo Company | The US FDA approved a generic version of imiquimod 5% cream in September 2010 for the topical treatment of actinic keratoses on the face or scalp, superficial basal cell carcinoma, and external genital and perianal warts in patients ≥12 years of age (innovator brand Aldara® 5% cream, Graceway Pharmaceuticals). |

Drug News

In September 2010, the US FDA issued requirements for gadolinium-based contrast agents (GBCAs) to carry new warnings on their labels to highlight the risk of nephrogenic systemic fibrosis (NSF), a rare and potentially fatal condition, if the drug is administered to certain patients with kidney disease. The symptoms of NSF can include scaling, hardening and tightening of the skin, red or dark patches on the skin, and stiffness. GBCAs are intravenous agents used with magnetic resonance imaging or magnetic resonance angiography to aid in the detection of abnormalities of body organs, blood vessels, and other tissues. An FDA safety review of the most widely used GBCAs determined that Magnevist® (Bayer HealthCare), Omniscan™ (GE Healthcare), and Optimark™ (Covidien) are associated with a greater risk than other GBCAs for NSF in some patients with kidney disease. More specifically, the new warnings for these three GBCAs will be described as inappropriate for use among patients with acute kidney injury or chronic severe kidney disease. Prior to administration, all GBCA labels will emphasize the need to screen patients to detect these types of kidney dysfunction. Additional information is available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm225286.htm>

In September 2010, the US FDA's Anti-Infective Drugs Advisory Committee voted unanimously in favor of approving ceftaroline fosamil (Forest Laboratories Inc.) for the treatment of community acquired bacterial pneumonia and complicated skin and skin structure infections. Ceftaroline is a novel, broad-spectrum injectable cephalosporin antibiotic with activity against both gram-positive bacteria (including methicillin-resistant *Staphylococcus aureus* [MRSA] and *Streptococcus pneumoniae*) and common gram-negative pathogens.