Hormonal Contraceptives for Acne Management

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Acne vulgaris affects 42 million people, more than half of whom are women older than 25 years. Treatment for acne includes oral and topical antibiotics, retinoids, and hormonal therapy in the form of oral contraceptives (OCs). OCs reduce acne lesions by increasing estrogen levels and sex hormone-binding globulins, and by decreasing free testosterone and androgen levels. Several studies have shown that drospirenone, a progestin available in certain OCs, minimizes the potential negative effect the progestin has on acne. Women who seek contraception and teenagers with acne who refuse antibiotics or in whom topical antibiotics are ineffective might be candidates for drospirenone-containing OCs.


In the United States, acne vulgaris affects 42 million people, including 85% of adolescents, as well as 40% of men and 54% of women older than 25 years.1-2 According to Stern, each year more than 5 million prescriptions for oral antibiotics are dispensed, including 1.4 million prescriptions for isotretinoin.

Acne has a complex etiology. It is an androgen-mediated disorder that involves abnormal keratinization, bacterial growth, and immune-driven hypersensitivity. The condition is aggravated by extrinsic factors, including stress, friction, occlusion by comedogenic products (eg, pomades), medications (eg, anabolic steroids, antiepileptic drugs, progestin-only contraceptives), medical conditions (eg, Cushing disease), and possibly diet.

Treatments for acne include oral or topical antibiotics and retinoids and hormone therapy. Oral antibiotics are considered first-line therapy for patients with moderate to severe inflammatory acne. Oral isotretinoin is indicated for patients with severe nodular acne and cases resistant to other treatments. Long-term topical or oral antibiotics, however, come with a price: possible bacterial resistance.

The goal with hormone therapy is to block hormonal effects (spironolactone) or to suppress hormone production (OCs).4,5 Oral contraceptives (OCs) are useful for women who also seek the contraceptive benefits of the pill. For reproductive-aged women, a variety of contraceptives are available (Table 1). When treating acne, estrogen is the beneficial hormone, whereas a progestin-only pill, which tends to exacerbate acne, should be avoided. OCs reduce acne lesions by supplying estrogen and increasing sex hormone-binding globulin (SHBG), decreasing free testosterone, and suppressing ovarian production of androgens.4 The overall therapeutic effect of OCs in acne is potentially brought about by (1) stimulation of SHBG, which decreases testosterone concentrations; (2) inhibition of 5-α-reductase, an enzyme that converts testosterone to dihydrotestosterone (an active androgen in the skin; (3) decreased production of ovarian androgens; and (4) decreased production of adrenal androgens. This process results in decreased sebum production and hair growth.6-9

The Roles of Estrogen and Progestin

Estrogen in doses higher than those found in modern OCs suppresses sebum and, therefore, development
Hormonal Contraceptives

Table 1.
Hormonal Contraceptives That Are Available in the United States

<table>
<thead>
<tr>
<th>Estrogen Combinations</th>
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<tr>
<td>Monophasic</td>
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<td>Triphasic</td>
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<tr>
<td>Extended cycle</td>
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<tr>
<td>Transdermal patch</td>
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<td>Vaginal ring</td>
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<th>Progestin-Only Compounds</th>
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<tr>
<td>Implants</td>
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<tr>
<td>Levonorgestrel-releasing intrauterine system</td>
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<td>Depot medroxyprogesterone acetate injections</td>
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of acne lesions. Through the metabolism of estrogen in the liver, this hormone also increases SHBG. In addition, because OCs suppress the ovary, testosterone production is reduced.

Some progestins are more androgenic than others, and those with androgenic tendencies may exacerbate acne. Drospirenone, the progestin in certain OCs (ethyl estradiol [EE 20 mg/drospirenone 3 mg [Yaz]], EE 30 mg/drospirenone 3 mg [Yasmin]), has both antimineralocorticoid and antiandrogenic effects, thus minimizing the potentially negative effect that progestins can have on acne.

**How Effective Are Drospirenone-Containing OCs in Treating Acne?**

Studies have shown that combination OCs are particularly effective in treating acne.

In a multicenter, double-blind, randomized, placebo-controlled study conducted at 28 centers in the United States, Maloney et al.11 assessed the safety and efficacy of an OC (EE 20 mg/drospirenone 3 mg) administered in 6 treatment cycles over 24 consecutive days of active treatment followed by a 4-day hormone-free interval, and compared it with placebo in the treatment of acne vulgaris. This formulation was approved by the US Food and Drug Administration.

![Figure 1](image-url). Change in adjusted mean number of lesions (papules, pustules, open and closed comedones) from baseline to end point (full analysis set). The P values show the difference between the DRSP 3 mg/EE 20 μg 24/4 COC and placebo groups. COC indicates combined oral contraceptive; DRSP, drospirenone; EE, ethinyl estradiol. Reprinted from Maloney JM, Lee-Rugh S, Kunz M, et al. Drospirenone 3 mg/ethinyl estradiol 20 μg COC in the treatment of acne vulgaris: investigator and subject self-assessment. Poster presented at: 55th Annual Clinical Meeting of the American College of Obstetricians and Gynecologists; May 5-9, 2007; San Diego, CA. 15 Courtesy of Bayer HealthCare Pharmaceuticals.
for the treatment of acne vulgaris in females at least 14 years of age who have reached menarche and want an OC for birth control. The study randomized 538 women to EE 20 μg/drospirenone 3 mg (n=270) or placebo (n=268). The mean age of subjects was 25 years.10,11

Subjects were assessed at screening; at baseline during randomization; on day 15 (±3 days) of treatment cycles 1, 3, and 6; and at a follow-up visit (days 8–15) after treatment was completed.10,11

The primary efficacy variables were percentage change in inflammatory, noninflammatory, and total lesion counts from baseline and percentage of subjects classified as having clear skin (score 0) or almost-clear skin (score 1) on the 6-point investigator’s static global assessment scale. Safety was assessed with changes reported in laboratory values (hematologic, blood chemistry, urinalysis), with physical and gynecologic examinations, and with measurement of vital signs.10,11

The baseline lesion count was comparable between subjects in the EE 20 μg/drospirenone 3 mg and placebo groups. A significantly larger reduction in mean percentage change in inflammatory, noninflammatory, and total lesion counts from baseline occurred in the EE 20 μg/drospirenone 3 mg group (P<.0001) (Figure 1).10 Adverse events were consistent with hormonal contraceptive use and did not raise safety concerns. The EE 20 μg/drospirenone 3 mg formulation was rated by women as significantly more effective than placebo for the treatment of acne (P<.0001). A greater proportion of women were rated as having significantly clearer or almost-clear skin by cycle 3 (Figure 2).11 These findings were consistent with investigator assessment and the reduction of lesion counts in subjects randomized to the OC. It was concluded that this formulation of EE and drospirenone is effective for women who have moderate acne vulgaris and want contraception.10,11

Two double-blind, randomized, controlled trials were conducted to examine EE 20 μg/drospirenone 3 mg versus placebo in a total of 889 women. Treatment took place for 6 cycles consisting of 24 consecutive days of active treatment followed by a 4-day hormone-free phase. Subjects showed substantial improvement in inflammatory, noninflammatory, and total lesion counts (Table 2).12
binds to the renin-angiotensin-aldosterone system, blocks the aldosterone receptor on the kidney, and promotes excretion of sodium and water, thus decreasing bloating, breast tenderness, and water weight gain. The 24/4 regimen with EE 20 μg/drospirenone 3 mg extends the antimineralocorticoid and antiandrogenic activity by 3 days, and the 30-hour half-life of drospirenone extends the progesterogenic effect through the 4 days with hormone-free pills.

In an earlier multicenter, double-blind, randomized study, van Vloeten et al\(^\text{13}\) compared EE 30 μg/drospirenone 3 mg with EE 35 μg/cyproterone 2 mg (Diane-35; not available in the United States) over 9 treatment cycles. Each cycle comprised 21 consecutive days of active treatment followed by a 7-day hormone-free interval. The study randomized 128 women who had mild to moderate facial acne with or without seborrhea and/or hirsutism to EE 30 μg/drospirenone 3 mg or EE 35 μg/cyproterone 2 mg. The per protocol set included 91 subjects (EE 30 μg/drospirenone 3 mg, n=58; EE 35 μg/cyproterone 2 mg, n=33). End-of-study assessments of acne treatment were made by dermatologists, gynecologists, and subjects. The median acne lesion count decreased in both treatment groups through cycle 9. Total acne lesion count was reduced by 62.5% and 58.8% in the EE 30 μg/drospirenone 3 mg and EE 35 μg/cyproterone 2 mg groups, respectively. Both preparations were effective in reducing sebum production and hair growth on the upper lip and chin, resulted in a 3-fold increase in SHBG, and reduced levels of androgens and luteinizing hormone.\(^\text{13}\) Both treatments proved beneficial in reducing noninflammatory lesions (open and closed comedones) and inflammatory lesions (papules, pustules, and nodules). By cycle 9, inflammatory and noninflammatory lesions were reduced by 73.5% and 50%, respectively, in the EE 30 μg/drospirenone 3 mg group and by 75% and 60%, respectively, in the EE 35 μg/cyproterone 2 mg group. Subjects, dermatologists, and gynecologists gave subjective ratings of excellent, good, or moderate improvement in most cases in both groups. Few cases were considered aggravated or unimproved.

Thorneycroft et al\(^\text{14}\) conducted a double-blind study in 1154 women to compare the efficacy and tolerability of EE 30 μg/drospirenone 3 mg (n=568) with those of a triphasic OC (EE 35 μg plus norgestimate 180/215/250 μg [Ortho Tri-Cyclen]; n=586) in treating acne vulgaris. These preparations were administered for 6 treatment cycles, each comprising 21 consecutive days of active treatment followed by a 7-day hormone-free interval. Both OCs were comparable in decreasing inflammatory lesion counts. Investigator and subject evaluations also were comparable. Both preparations increased SHBG levels and decreased androgen levels, and both were well tolerated in this group of women with mild to moderate acne.\(^\text{14}\)

### Table 2.

**Efficacy Results for Acne Trials**

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<th>Study 1</th>
<th>Study 2</th>
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<tr>
<td></td>
<td>Yaz (n=228)</td>
<td>Placebo (n=230)</td>
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<tr>
<td>Total lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline count</td>
<td>80</td>
<td>80</td>
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<tr>
<td>Mean absolute (%) reduction</td>
<td>33 (42%)</td>
<td>21 (25%)</td>
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*Evaluated at day 15 of cycle 6, last observation carried forward for the intent-to-treat population.

\(^\text{1}\)Ethinyl estradiol 20 μg/drospirenone 3 mg.
a low-dose OC, women who have acne and premenstrual dysphoric disorder, and teenagers with certain considerations (see below).

Patients who do not qualify include women with a contraindication to OC therapy, including thromboembolic disorders, severe or uncontrolled hypertension, migraine with focal neurologic symptoms, some malignancies, and pregnancy; men; and heavy smokers (≥15 cigarettes per day) older than 35 years.

Teenagers: Antibiotics Versus OCs—In the author's experience, many teenagers prefer OCs over antibiotics. Those who qualify for OC use may have persistent papular, pustular acne and may have used combination products without good results. They may have some cystic acne and are candidates for OCs because they want contraception.

Teenagers Who Fail Topical Solutions—Teenagers with nodulocystic acne unresponsive to treatment with minocycline, topical retinoids, and benzoyl peroxide are candidates for isotretinoin but may want to try other products, including OCs, first. They must want contraception and may experience moderate symptoms related to premenstrual syndrome. They would benefit from isotretinoin but deserve a trial with an OC. If the acne has not improved after several months of adding an OC to their acne regimen, then isotretinoin can be started.

Women With Hormonally Driven Acne—Women who want contraception and have acne that is hormonally driven also may be candidates for an OC. Chronic low-grade acne, usually cystic, affecting the lower face, jawline, and neck often responds well to hormonal therapy (Figure 3). Other candidates are women who want contraception and have menstrual flares of acne. They are nonsmokers who are frustrated with the chronic nature of their acne and have been on topical retinoids and antibiotics but are not improving. These patients are good candidates for an OC. Adding an OC would help most women with acne that is not responding to standard oral or topical therapy. In the author's experience, when the acne finally clears, topical medications often are no longer necessary, provided the patient remains on the OC.

Women With Low-Grade Acne—A 28-year-old black woman was treated with a course of isotretinoin and now has acne scars (Figure 4). She has low-grade acne, with occasional cystic lesions, usually not comedonal. She does not want to take antibiotics because of recurring yeast infections. Her skin is oily and subject to random papules and pustules. She wants contraception. To control her acne, this patient would like something in addition to her current medication. An OC would be a suitable option.

Women With Androgenic Symptoms—A 24-year-old woman with acne, hirsutism, and androgenic alopecia is bothered by acne and some facial hair, and her menses are irregular. For this patient, a workup is required to rule out other serious conditions. There are multiple signs of hyperandrogenism (ie, hirsutism, androgenic alopecia, voice deepening, acanthosis nigricans), which also must be addressed. Workup for this patient should include measurement of free and total testosterone to rule out or diagnose ovarian tumors, dehydroepiandrosterone sulfate to identify adrenal problems, and 24-hour urine cortisol to check for signs of Cushing disease. In addition, clinical evaluation is warranted to check for polycystic ovary syndrome (PCOS), a diagnosis established by presence of hirsutism, acne, or male-pattern alopecia together with evidence of anovulation (<9 menstrual periods per year or
cycles >40 days). Hormone testing is relatively insensitive for the diagnosis of PCOS.

If this patient is seeking contraception, a trial of an OC may be worthwhile.

Comment

Although acne is considered a disorder of adolescents, it persists in many patients older than 25 years. Goulden and colleagues found that 12% of the 427 women in their study population experienced adult acne. In 82% of affected adults, persistent acne rather than late-onset acne was implicated. Acne may also result from an androgen disorder, which can manifest as acne vulgaris, hirsutism, seborrhea, or androgenic alopecia. Several studies have demonstrated the effectiveness of OCs in decreasing total acne lesion counts and clinical androgenicity. Their effectiveness lies in part in their ability to decrease androgen expression, an important factor in the development of acne. If an OC does not provide adequate clearing, it can be combined with other acne or hormonal treatments as described. Although OCs do not represent first-line therapy or monotherapy, they can serve as a good solution for many patients with mild to moderate acne vulgaris.

REFERENCES