Treatment of Acne With Oral Contraceptives: Criteria for Pill Selection

George T. Koulianos, MD, Mobile, Alabama

Combination oral contraceptives (OCs) (those that contain estrogen and progestin) are widely used in the treatment of acne because they modify an excessively androgenic hormonal environment and can decrease lesions. Dermatologists' knowledge of the most appropriate OC may be hampered by an incomplete understanding of these agents, misleading promotion, and confusion surrounding the new generation of OCs. Despite reports attributing significance to the degree of androgenicity of the progestin components of OCs, in vitro and animal bioassays of androgenicity have little clinical relevance. Because all of today's low-dose combination OCs are estrogen dominant, they are equally beneficial in women with androgenic conditions such as acne. Use of the OC containing the lowest dose of each hormone, consistent with the patient's needs, can enhance compliance by preventing or limiting common early-cycle side effects (eg, nausea/vomiting, breast tenderness, weight gain, headache), while providing acne improvement.

Although oral contraceptives (OCs) are generally reserved for severe cases of acne when other methods have failed, the use of combination OCs (those that contain estrogen and progestin) in the treatment of acne has become common practice. OCs are particularly valuable in patients with clinical evidence of hyperandrogenism (hirsutism, irregular periods). Both gynecologists and dermatologists recognize the abilities of these agents to modify an excessively androgenic hormonal environment and decrease acne lesions in appropriately selected patients.

For many dermatologists, familiarity with OCs is dominated by one or two agents that have been actively promoted to the specialty. Thus, understanding of these preparations may be limited and somewhat skewed. Marketing based on outdated animal bioassays has distorted clinicians' appreciation of OC options. Direct-to-consumer advertising has been another misleading factor; prominent claims about acne, which drive patients to request "the pill," often overshadow more important health concerns and benefits. Finally, the recent development of a new generation of OCs containing progestins, intended to be less androgenic than their earlier counterparts, may have further confused the issue. Although these progestins have proven no better than the older ones, recent discussions of their use in acne therapy have left many physicians and patients with the mistaken impression that only certain OC formulations are appropriate to this indication.

Accounting for different dosage strengths, there are currently more than 40 combination OCs available in the United States—from the older 50-μg estrogen preparations to the ultra-low 20-μg estrogen formulations in the monophasic category, plus a variety of multiphasic pills, including the newest graduated-estrogen design. Review of the reproductive endocrinology literature reveals that all of them are essentially antiandrogenic and, thus, have antiacne potential. Therefore, selection of an optimal agent rests on other considerations important to both the clinician and patient—for example, low incidence of side effects, high degree of patient acceptance, and ease of compliance.

Although management of the OC patient is beyond the scope of dermatologic practice, a grasp of the principles underlying OC use in acne is essential. The following discussion seeks to provide the dermatologist with a more complete understanding of the antiandrogenic properties of today's "pill" formulations, their universal potential for decreasing acne lesions, and clinical criteria that determine the optimal OC choice.

From the Division of Reproductive Endocrinology and Infertility, Mobile Infirmary and Medical Center, Mobile, Alabama.
REPRINT REQUESTS to 3 Mobile Infirmary Circle, Suite 312, Mobile, AL 36607.
This paper has been supported by an unrestricted grant-in-aid from Parke-Davis Women's Healthcare Division.

Androgens and OCs

Hormones and Acne—Acne can reflect multiple etiologies, including such contributing factors as infection, abnormal keratinization, immunologic reaction, and hormonal influences. Generally, the mean serum androgenic profile in acne is the same as in normal patients. The exception is acne secondary to masculinizing disorders such as polycystic ovary syndrome, in which circulating androgen levels are abnormally high. Nevertheless, androgens acting peripherally at the sebaceous follicle are a prerequisite for acne in all patients. These hormones promote development of the condition by causing an increase in sebum production and, possibly, by enhancing follicular hyperkeratosis.

The 3 major sources of androgens are the ovary, the adrenal gland, and the skin. Under the influence of luteinizing hormone, the ovary contributes approximately 50% of circulating androgens—it secretes testosterone (T) and androstenedione, with much of the latter being peripherally converted to T. The adrenal gland contributes the other 50% of T, also largely from conversion of secreted androstenedione. Via the enzyme 5-alpha-reductase, the skin has the ability to metabolize androgens into more potent metabolites (eg, dihydrotestosterone). In addition, relatively nonandrogenic adrenal androgens, such as dehydroepiandrosterone, can be converted to more potent androgens, including T. Thus, patients with normal T levels can have acne secondary to enhanced 5-alpha-reductase activity, which varies from individual to individual and cannot be measured in the clinical setting.

Like other steroid hormones, T circulates in the bloodstream either bound or unbound to plasma proteins. The principal specific steroid-binding protein for T is sex hormone–binding globulin (SHBG), which accounts for 80% to 85% of the total circulating quantity of this substance.[1] Because of the high affinity of T for SHBG, bound T is biologically inactive. As the concentration of SHBG decreases (eg, in polycystic ovary syndrome or obesity), the amount of unbound or free T increases, resulting in increased biologic activity. Conversion of as little as 1% of T from bound to unbound can precipitate a hyperandrogenic state and possible acne pathogenesis. Conversely, an increase in SHBG produces an accompanying increase in uptake of T and a subsequent reduction in concentration of free, biologically active hormone. A number of factors affect production of SHBG in the liver—of greatest clinical relevance is that androgens decrease SHBG and estrogens increase it.

OCs help to relieve acne precisely because they reduce excessive androgens from any source.[2] They stimulate the production of SHBG, thus reducing free and biologically active T derived from both ovarian and adrenal sources. At the same time, OCs suppress the ovarian production of total circulating T by direct gonadotropin suppression.

Androgenicity of Progestins—All combination OCs consist of estrogen and progestin components. They may be monophasic, providing a uniform hormonal dose throughout the pill cycle, or multiphasic, graduating the progestin or, more recently, the estrogen dose in stages.

Since the introduction of OCs almost 4 decades ago, the dose of both hormones has been significantly reduced, resulting in safer formulations with comparable efficacy. In the low-dose OCs (<50 µg estrogen) available in the United States today, the estrogen component is exclusively ethinyl estradiol (EE), while the progestin may be norethindrone; norethindrone acetate (NA); ethynodiol diacetate; norgestrel; levonorgestrel (LNG); or the 2 new progestins, norgestimate and desogestrel (DSG). All of the progestogens are derivatives of 19-nortestosterone and ethisterone, the first orally active synthetic T.

There has been a great deal of discussion concerning the purported androgenicity (or its relative lack) of certain progestins. LNG has had a reputation for being significantly androgenic, whereas the new progestins are reported to minimize this property. Tables listing these OC components and their androgenicity indexes have emerged in papers, handbooks, and even respected medical textbooks. But the literature on the subject can be misleading in several respects. Early estimates of androgenic potency were based on progestin doses much higher than those used today. In addition, early estimates were calculated primarily from in vitro androgen-receptor binding tests and bioassays.[3] Today, researchers emphasize the inadequacies of these methods for assessing clinical effects. Source and type of tissue, choice and purity of reference steroid, purity of test substance, incubation time and temperature, and technique for separating receptor-bound from unbound steroid can all skew receptor-binding results. Comparable methodologic deficiencies apply to bioassays, complicated further by the fact that animal data are of limited utility for extrapolation to human clinical situations.[3,4] Activity in animals is unlikely to have a clinical correlate.[4]

Further confounding the significance of the early findings is that a single substance may, in addition to its androgenic effect, have antiandrogenic, estrogenic, and antiestrogenic properties, none of which is measured by a test specific for androgen activity. Finally, it is impossible to predict the clinical effect of a combination agent from the findings for individual components.[5,6] The nature and proportion of the 2 constituents in a mixture may have a major influence on the effect of the drug combination being studied. Indeed, it is well known that any inherent andro-

Table I.

Effects of Birth Control Pills on SHBG and T

Authors	Health Status	Oral Contraceptive	Change in: SHBG (%)	Total T (%)	Free T (%)
Koulianos and Thorneycroft*[1]	Normal	Triphasil EE 30, 40, 30 µg; LNG 0.05, 0.075, 0.125 mg	+92	–26	–35
	Normal	Lo/Ovral EE 30 µg; NG 0.3 mg	+24	–21	–37
	Normal	Ovcon EE 35 µg; NET 0.4 mg	+271	–3	–49
	Normal	Ortho-Novum 1/35 EE 35 µg; NET 1.0 mg	+92	–36	NR
	Normal	Nordette EE 30 µg; LNG 0.15 mg	+28	–16	–31
Boyd et al[8]	Normal	Estrostep EE 20, 30, 35 µg; NA 1 mg	+296	NR	–64
Redmond et al[11]	Acne	Ortho Tri-Cyclen EE 35 µg; NGM 0.180, 0.215, 0.250 mg	+213.3	+3.1	–43.9
Jung-Hoffmann and Kuhl[17]	Normal	Desogen EE 30 µg; DSG 0.15 mg	+175	–26	–35
Raj et al[18]	PCOD	Loestrin 1.5/30 EE 30 µg; NA 1.5 mg	+118	–51.8	–71.9
	PCOD	Modicon EE 35 µg; NET 0.5 mg	+112.5	+3.7	–50.7

SHBG indicates sex hormone–binding globulin; T, testosterone; EE, ethinyl estradiol; LNG, levonorgestrel; NG, norgestrel; NET, norethindrone; NR, not reported; NA, norethindrone acetate; DSG, desogestrel; NGM, norgestimate; and PCOD, polycystic ovary disease.

* Adapted with permission from Blackwell Science, Ltd.

genic activity of a progestogen in a combination OC is moderated by the presence of the estrogen.[5,6]

Ability of OCs to Suppress Free T—The more reliable in vivo indicators of hormone activity used currently are serum SHBG levels (estrogen/antiestrogen) and the even more precise free T concentration (androgen/antiandrogen). Both indices take into account the critical counterbalancing effect of the OC estrogen component and both should be considered. However, free T is the biologically active substance. Because OCs can decrease free T independent of SHBG by decreasing production of total T, the ability of a particular OC to suppress free T (rather than raise SHBG) is the more important gauge of antiandrogen effectiveness and, ultimately, androgenicity.[1]

Table I lists changes in SHBG and T obtained with a variety of OCs in women with both normal and abnormal hormonal status. Figure 1 illustrates the results of a study by Van der Vange et al[7] in 70 healthy volunteers with 7 combination OC preparations, including one containing the antiandrogen cyproterone acetate. Irrespective of the effects on either SHBG or total T, which can vary considerably among preparations, all the low-dose combination OCs produced a similar decrease in free T and are, therefore, nonandrogenic. For example, NA has previously been thought to be more androgenic than some other progestins. But Boyd et al[8] demonstrated that when combined with estrogen, the resulting preparation has clinical androgenic activity similar to that of formula-

tions containing the newer progestins. Not only did EE/NA increase SHBG 3-fold by day 21 of the cycle, it lowered free T by 64%. Of note in the study by Van der Vange et al,[7] the monophasic pill containing the presumed "less androgenic" DSG lowered free T less than the one containing LNG—often thought of as the most androgenic of the currently used progestins. It has become clear that, regardless of the relative androgenicity of their progestins, all low-dose combination birth control pills are actually estrogen-dominant and, thus, equally beneficial in women with androgenic phenomena such as acne.

For example, after 6 months of treatment with OCs, Palatsi et al[9] obtained a 54.7% decrease in acne lesions with a formulation containing 30 µg EE and 0.15 mg DSG (Desogen®) and a 24.1% improvement with 30 µg EE and 0.3 mg norgestrel (Lo/Ovral®).

Investigating one preparation with the presumed highly androgenic progestin LNG (30, 40, and 30 µg EE and 50, 75, and 125 mg LNG; Triphasil®) and another with the antiandrogenic progestin cyproterone acetate (50 µg EE and 2 mg cyproterone acetate; Diane®), Wishart[10] found them equally effective. Both OCs reduced acne by 72%.

Similarly, Redmond et al[11] reported a reduction of 46.4% in total lesions after 6 months' treatment with 35 µg EE and 0.180, 0.215, and 0.250 mg norgestimate (Ortho Tri-Cyclen®). Even 20 µg OCs containing LNG (Alesse™) and norethindrone acetate (Loestrin®) have demonstrated a reduction in inflammatory lesions, comedones, and total lesions.[12]

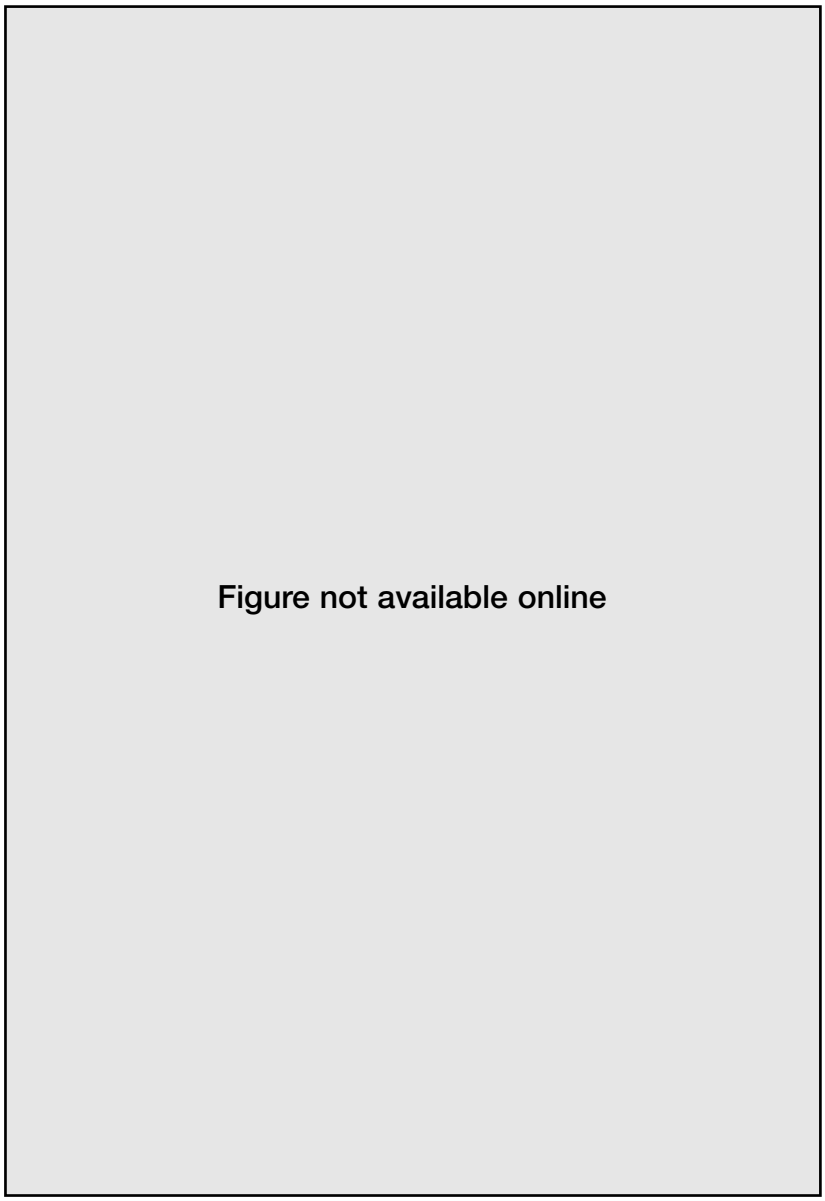

FIGURE 1. Effects of 7 low-dose OC preparations on SHBG and free T in healthy women (from Van der Vange et al,[7] with permission from Elsevier Science).

In fact, because of their ovarian suppression and estrogen component, all combination OCs reduce free T and, thus, all have a positive effect on acne[13] —no preparation has been shown to be superior to another. In the few available studies comparing the benefits of specific OCs in acne,[9,10,12] differences are not statistically significant. Even Ortho Tri-Cyclen, which recently obtained a Food and Drug Administration–approved indication for treating acne, is unremarkable in its clinical effect. In the Redmond et al[11] study, total lesions were reduced 46.4% in the subjects receiving active drug versus 33.9% in the placebo group. This degree of reduction is equally or less comparable than that seen with other products, reported to range from 25% to 80%.[13]

Adverse Effects and Pill Selection

The most serious complication associated with OCs—estrogen-related thrombotic events—was most

apparent in the 1960s and early 1970s during the era of high-dose OCs. The reduced doses of estrogen in today's formulations have largely eliminated this problem[14] and, in general, OCs are well tolerated by most women. Nevertheless, OC use may be accompanied by a number of "nuisance" effects that can be of concern to patients. Despite their lack of clinical importance, these side effects can lead to repeated telephone calls, unscheduled office visits, pill discontinuation, and even a failed therapeutic option.

The most common adverse reactions prompting dissatisfaction with OC therapy include nausea/vomiting, breast tenderness, weight gain, headache, and spotting/breakthrough bleeding. All except intermenstrual bleeding are "early-cycle" effects that may appear as soon as the first week of therapy. They are believed to occur as a result of the sudden increase in estrogen provided by the pill regimen. Pill formulations containing very low doses of estrogen (20 μg EE) are now widely used to help minimize these symptoms. But, appropriate patient counseling has proved equally important—clinicians now acknowledge the possibility of these problems in new OC users, reassure patients that they are transient, and urge them to continue with their OC therapy for at least several cycles.

Breakthrough bleeding and spotting, as well as "late-cycle" effects, are usually transient as well; they are most common during the first few months of OC use and then generally subside. They can, nonetheless, be disruptive and a source of great anxiety for patients. Although these menstrual irregularities have no significance regarding health or contraceptive effectiveness, patients often worry that they are the symptoms of some serious gynecologic problem or a sign that the OC is not working. Many attempts have been made to compare the relative incidence of intermenstrual bleeding with various products. Methodologic differences, as well as interstudy and interpatient variations, have limited the usefulness of available evaluations, and no one current formulation has been convincingly shown to be superior.[15] Many clinicians favor the triphasic formulations. Although, overall, triphasics have failed to improve breakthrough bleeding rates, increasing levels of hormone are believed to provide enhanced endometrial support over the pill cycle. At the same time, these preparations are consistent with the move to low hormone dosage—they all contain relatively low doses of their respective progestin and the estrogen-phasing pill starts with the lowest available dose of EE, 20 μg.

The greatest negative impact on cycle control comes from missed doses. As shown in 2 multicenter trials that analyzed 15,421 cycles, inconsistent OC use increased the risk for bleeding irregularities 280% and 640%.[16] Thus, strict adherence to the pill regimen is the single most important factor in avoiding intermenstrual bleeding. Should an ostensibly compliant acne/OC patient complain of bleeding irregularities that are prolonged or particularly upsetting, it may be useful for her to consult her gynecologist.

Conclusion

The interplay of both estrogen and progestin components renders all currently used OCs estrogen dominant and, thus, effective in treating acne. Pill selection should be based on such clinical criteria as the minimization of side effects and ease of compliance. The Food and Drug Administration's Fertility and Maternal Health Drugs Advisory Committee recommends use of products containing the lowest doses of estrogen and progestin consistent with the needs of the patient. This principle can contribute to preventing or limiting the most common early-cycle, estrogen-related symptoms, while providing acne improvement.

REFERENCES

1. Koulianos GT, Thorneycroft IH. Abnormal sex hormone-binding globulin. In: Schlaff WD, Rock JA, eds. *Decision-Making in Reproductive Endocrinology and Infertility*. Oradell, NJ: Medical Economics Books; 1993:240-245.
2. Lucky AW. Hormonal correlates of acne and hirsutism. *Am J Med.* 1995;98:89-94.
3. Stanczyk FZ. Structure-function relationships, potency, and pharmacokinetics of progestogens. In: Lobo RA, ed. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects*. New York, NY: Raven Press; 1994:69-89.
4. Goldzieher JW. Use and misuse of the term potency with respect to oral contraceptives. *J Repro Med.* 1986;31:533-539.
5. Edgren RA, Sturtevant FM. Potencies of oral contraceptives. *Am J Obstet Gynecol.* 1976;125:1029-1038.
6. Batzer FR. Measurements of androgenicity: the spectrum of progestogen activity. *J Reprod Med.* 1986;31:848-864.
7. Van der Vange N, Blankenstein MA, Kloosterboer HJ, et al. Effects of seven low-dose combined oral contraceptives on sex hormone binding globulin, corticosteroid binding globulin, total and free testosterone. *Contraception.* 1990;41:345-352.
8. Boyd RA, Zegarac EA, Posvar EL, et al. Low androgenicity of a new estrophasic oral contraceptive containing norethindrone acetate (NA) and ethinyl estradiol (EE). *Proceedings of the Endocrine Society*, June 24-27, 1998. New Orleans, LA.
9. Palatsi R, Hirvensalo E, Liukko P, et al. Serum total and unbound testosterone and sex hormone binding globulin (SHBG) in female acne patients treated with two different oral contraceptives. *Acta Dermato-Venereologica.* 1984;64:517-523.
10. Wishart JM. An open study of Triphasil and Diane 50 in the treatment of acne. *Aust J Dermatol.* 1991;32:51-54.
11. Redmond GP, Olson WH, Lippman JS, et al. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial. *Obstet Gynecol.* 1997;89:615-622.

12. Weber ME, Stanczyk FZ, Ballagh SA, et al. Effect of two low-dose oral contraceptives on androgens and acne (abstract). *Obstet Gynecol*. 1999;93:4S-5S.
13. Thorneycroft IH. Update on androgenicity. *Am J Obstet Gynecol*. 1999;180:S288-S294.
14. Castelli WP. Reducing risk in OC users who smoke. *Contemp OB/GYN*. 1996;41:116-126.
15. Thorneycroft IH. Cycle control with oral contraceptives: a review of the literature. *Am J Obstet Gynecol*. 1999;180:S280-S287.
16. Rosenberg MJ, Waugh MS, Higgins JE. The effect of desogestrel, gestodene, and other factors on spotting and bleeding. *Contraception*. 1996;53:85-90.
17. Jung-Hoffmann C, Kuhl H. Divergent effects of two low-dose oral contraceptives on sex hormone-binding globulin and free testosterone. *Am J Obstet Gynecol*. 1987;156:199-203.
18. Raj SG, Raj MHG, Talbert LM, et al. Normalization of testosterone levels using a low estrogen-containing oral contraceptive in women with polycystic ovary syndrome. *Obstet Gynecol*. 1982;60:15-19.