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Oral Contraception and Acne

This activity is jointly sponsored by Annenberg Center for Health Sciences and Quadrant Medical Education.

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Faculty and Disclosure Information for "Oral Contraception and Acne"

Intended Audience:

This activity is appropriate for physicians and clinicians in dermatology and related subspecialties.

Statement of Need:

Acne affects more than 85% of teenagers but frequently continues into adulthood. Although there are more than 2 million visits to office-based physicians per year for patients in the age range of 15 to 19 years, the mean age at presentation for treatment is 24 years, with 10% of visits taking place when patients are between the ages of 35 and 44 years. The social, psychological, and emotional impairment that can result from acne has been reported to be similar to that associated with epilepsy, asthma, diabetes, and arthritis. Scarring can lead to lifelong problems in regard to self-esteem. Acne is a follicular disease, the principal abnormality of which is impaction and distention of the pilosebaceous unit.

Although no uniform approach to the management of acne exists, combination oral contraceptives, which contain an estrogen and a progestin, often are prescribed for women. Therapy with combination oral contraceptives is often useful in women with hyperandrogenism and in women with normal serum androgen levels.

A wide variety of prescription topical medications is available in different dosing forms and strengths and administered according to various dosing schedules to clear acne. The selection of the specific therapeutic class to treat acne depends upon patient skin type, age, gender, and acne severity at presentation. In an effort to achieve compliance, long-term control, and resolution of moderate to severe acne, dermatologists may combine therapies.

Learning Objectives:

Upon completion of this activity, participants should be better able to:

1. Describe the female patients most likely to benefit from acne management with such hormonal treatments as oral contraceptives (OCs).
2. Discuss the relationships between sex hormone–binding globulin, androgenicity, and acne.
3. Explain the mechanism of action of OCs in acne management.
4. Recall how to dose OCs for optimal safety and efficacy in acne management.
5. Recognize the need to collaborate with OB/GYNs in promoting adherence among women seeking both acne management and contraceptive protection.

Faculty:

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Faculty and Disclosure Information *continued*

LP; Intendis, Inc; Johnson & Johnson Ortho, Inc; QLT Inc; and Stiefel Laboratories, Inc. Dr. O'Connell reports no conflict of interest. Dr. Westhoff has received research support from Duramed Pharmaceuticals, Inc, and Organon. She is a consultant and speaker for Bayer HealthCare Pharmaceuticals; Duramed Pharmaceuticals, Inc; and Organon. Dr. Rich received an honorarium from OrthoNeutrogena and is on the advisory board for 3M Pharmaceuticals; Abbott Laboratories; Amgen Inc; Genentech, Inc; Medicis Pharmaceutical Corporation; Novartis Pharmaceuticals Corporation; and Schering-Plough Corporation. She has done clinical research for Allergan, Inc; Altana; Barrier Therapeutics; Bavarian Nordic; Centocor, Inc; Dermik Laboratories; DermTech International, Inc; Dow Pharmaceutical Sciences, Inc; DUSA Pharmaceuticals, Inc; Galderma Laboratories, LP; Genentech, Inc; Hill Dermaceuticals, Inc; Intendis, Inc; MacroChem; Medicis Pharmaceutical Corporation; MediQuest Therapeutics, Inc; Medivir; Merz Pharma; NanoBio Corporation; Neutrogena Corporation; Novartis Pharmaceuticals Corporation; Novum Pharmaceutical Research Services; Pfizer Inc; Photocure; Schering-Plough Corporation; Stiefel Laboratories, Inc; Symbio; Teva Pharmaceuticals; Tolmar Inc; Warner-Lambert Company; and Xoma. She also has been a speaker for 3M Pharmaceuticals, CollaGenex Pharmaceuticals Inc, Connetics Corporation, and Novartis Pharmaceuticals Corporation. Dr. Sondheimer receives research support from Wyeth and is a speaker for Organon. Dr. Harper is a consultant and speaker for Intendis, Inc.

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The estimated time to complete the activity is 2.5 hours.

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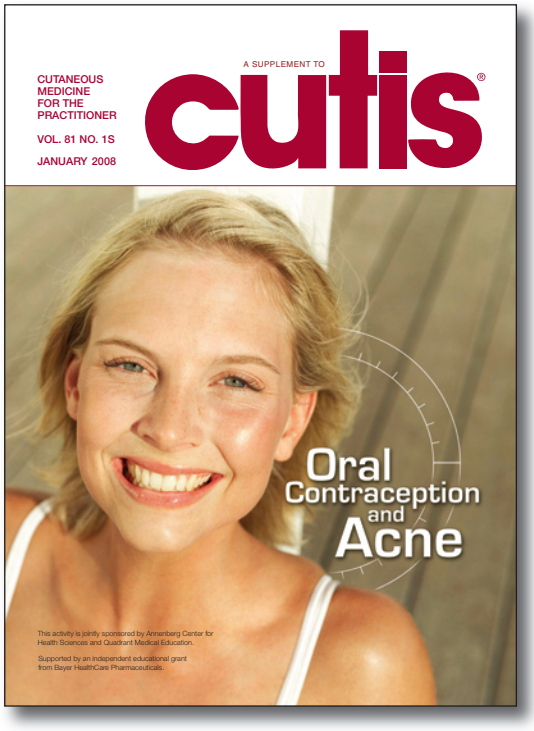

Oral Contraception and Acne

Overview of Acne and Its Treatment

Diane M. Thiboutot, MD, Chair

Acne affects more than 85% of teenagers in the United States and often continues into adulthood. The most deleterious form can result in permanent scarring on the face, chest, and back. Although the pathogenic features of acne are well known, the initiating factor remains unknown. Isotretinoin is effective against all of the pathogenic features of acne but is contraindicated in pregnant women and has been associated with elevations in triglyceride levels. Combination regimens appear to be effective, but physicians should avoid prescribing complicated treatment regimens. Hormone therapy has been found to improve acne in some women and should be considered in appropriate candidates. Although the list of available and effective agents appears to be extensive, several are contraindicated in pregnant women, and long-term use of antibiotics to target inflammation has been linked to agranulocytosis and Stevens-Johnson syndrome. Further investigation into agents that can reduce sebum production is warranted.

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Up to 95% of teenagers in the Western world are reported to have acne.[1] This condition often continues into adulthood. Severe scarring acne, the most debilitating form, often is accompanied by substantial physical and psychological morbidity. This type of acne leads to permanent scarring not only on the face but also on the chest and back. Dealing with physical challenges such as scarring is difficult at any age but particularly during adolescence, when issues of self-esteem often emerge. Thus, one challenge faced by dermatologists is to bring patients in for treatment as early as possible to prevent permanent scarring and damaging psychological sequelae.

Acne has 4 main pathogenic features—sebum overproduction, follicular hyperkeratinization, *Propionibacterium acnes* colonization, and inflammation—but the initiating factor remains unknown. It was once thought that keratinocytes within the follicle become cohesive and plug the follicle. Whether this is the initiating event in acne is still not clear.

Sebum Production

Sebum production is required for development of acne. Sebum is continually secreted by the sebaceous glands onto the surface of the skin and possibly is regulated by a type of circadian variation. Human sebum contains unique fatty acids that support the growth of *P acnes*, which colonizes humans exclusively. Thus, without sebum, acne cannot occur. Sebum production can be reduced with isotretinoin (a teratogen) and hormonal contraceptive therapies used in women.

Androgenic hormones stimulate sebum production. Estrogens administered in high doses suppress sebum production, but such doses are no longer available in oral contraceptives (OCs). Retinoids (eg, isotretinoin) are potent inhibitors of sebum production. Corticotropin-releasing hormone and insulin-like growth factor 1 have been reported to increase lipid production in cultures of sebaceous gland specimens. Lipid production is increased in sebocytes treated with agonists of the peroxisome proliferator–activated receptors, which are the transcription factors involved in regulating lipogenic genes.

Normalizing Follicular Keratinization

Several topical retinoids, including tretinoin, adapalene, and tazarotene, target follicular hyperkeratinization, which is an alteration in the keratinization pattern of the cells that line the hair follicle. These agents are effective in normalizing the keratinization pattern within the follicle.

Benzoyl peroxide has some activity against both open and closed comedones. However, the mechanism

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Table 1.

Antibiotics/Antimicrobials Effective Against *Propionibacterium acnes*

Topical
Azelaic acid
Clindamycin
Combination therapy: benzoyl peroxide + oral antibiotic
Erythromycin
Sodium sulfacetamide
Oral
Clindamycin (low dose only: 150 mg/d)
Doxycycline (50–200 mg/d)
Erythromycin (250–1500 mg/d)
Minocycline (50–200 mg/d)
Tetracycline (250–1500 mg/d)

of action on those lesions is not well understood. Benzoyl peroxide kills *P acnes*. Azelaic acid also can affect keratinization, as can α-hydroxy and β-hydroxy acids, but these agents are weak against keratinization, compared with topical retinoids.

Tretinoin, adapalene, and tazarotene are available in a variety of strengths and formulations and are used once daily to normalize follicular keratinization in the treatment of acne. They also help to speed the resolution of comedones and to inhibit microcomedone formation (microcomedones are visible only microscopically and are precursors of acne lesions).

Combating *P acnes*

Benzoyl peroxide is the most potent agent against *P acnes*. Within 2 weeks of use, it can substantially reduce the number of lesions. Benzoyl peroxide is available in a variety of formulations, including cleansers and gels. Clinically, it has activity against open and closed comedones and inflammatory lesions. Benzoyl peroxide is becoming increasingly important as a therapeutic agent because *P acnes* is becoming increasingly resistant to antibiotics. Emerging and continuing bacterial resistance has preempted monotherapy with topical or oral antibiotics.

Azelaic acid also is useful against *P acnes*. Oral retinoids (eg, isotretinoin) can reduce *P acnes* by removing the nutrient source for the bacteria indirectly by suppressing sebum production. In a therapeutic regimen, benzoyl peroxide has a bactericidal effect. Only a small percentage of patients develop contact dermatitis from an allergic reaction to benzoyl peroxide. Several topical and oral antibiotics are effective in reducing *P acnes* (Table 1).

Long-term use of some antibiotics in chronic acne has been linked to agranulocytosis and Stevens-Johnson syndrome. Many medications (eg, isotretinoin) are contraindicated in pregnant women because of potential teratogenic effects. Thus, the list of usable agents is less extensive than it initially appears.

Altering Hormone Secretion and Transport

Hormone therapy has been known to improve acne in some women through its effects on hormone secretion and transport.[2-4] Because hormone therapy (eg, OCs, glucocorticoids, antiandrogens) reduces the effects of androgens on sebum production, it is used exclusively in women. In patients with late-onset congenital adrenal hyperplasia, low-dose glucocorticoids are effective. The antiandrogen most commonly used in dermatology is spironolactone, but this agent is not approved for treatment of acne.

Table 2.

Treatments for Acne Lesions

	Degree of Acne				
	Mild		Moderate		Severe
	Comedonal	Papular/ Pustular	Papular/ Pustular	Nodular*	Nodular†
First line‡	Topical retinoid	Topical retinoid + topical antibiotic	Topical retinoid + oral antibiotic ± benzoyl peroxide	Topical retinoid + oral antibiotic ± benzoyl peroxide	Oral isotretinoin
Alternatives‡	Azelaic acid/ salicylic acid	Topical retinoid + topical antibiotic ± benzoyl peroxide	Topical retinoid + alternative oral antibiotic ± benzoyl peroxide	Oral isotretinoin§ or alternative oral antibiotic + topical retinoid ± benzoyl peroxide/topical antibiotic	High-dose oral antibiotic + topical retinoid + benzoyl peroxide
For women	NA‖	NA‖	Hormone¶ + topical retinoid ± benzoyl peroxide/ topical antibiotic	Alternative hormone¶ + topical retinoid ± benzoyl peroxide/ topical antibiotic	Alternative hormone¶ + oral antibiotic + topical retinoid ± benzoyl peroxide
Maintenance therapy: Topical retinoid ± benzoyl peroxide					

*Papulopustular acne with some nodular lesions.
†Conglobate acne.
‡Use physical therapies as necessary.
§After failure of previous options.
‖NA indicates information is not available.
¶Antiandrogens, oral contraceptives.

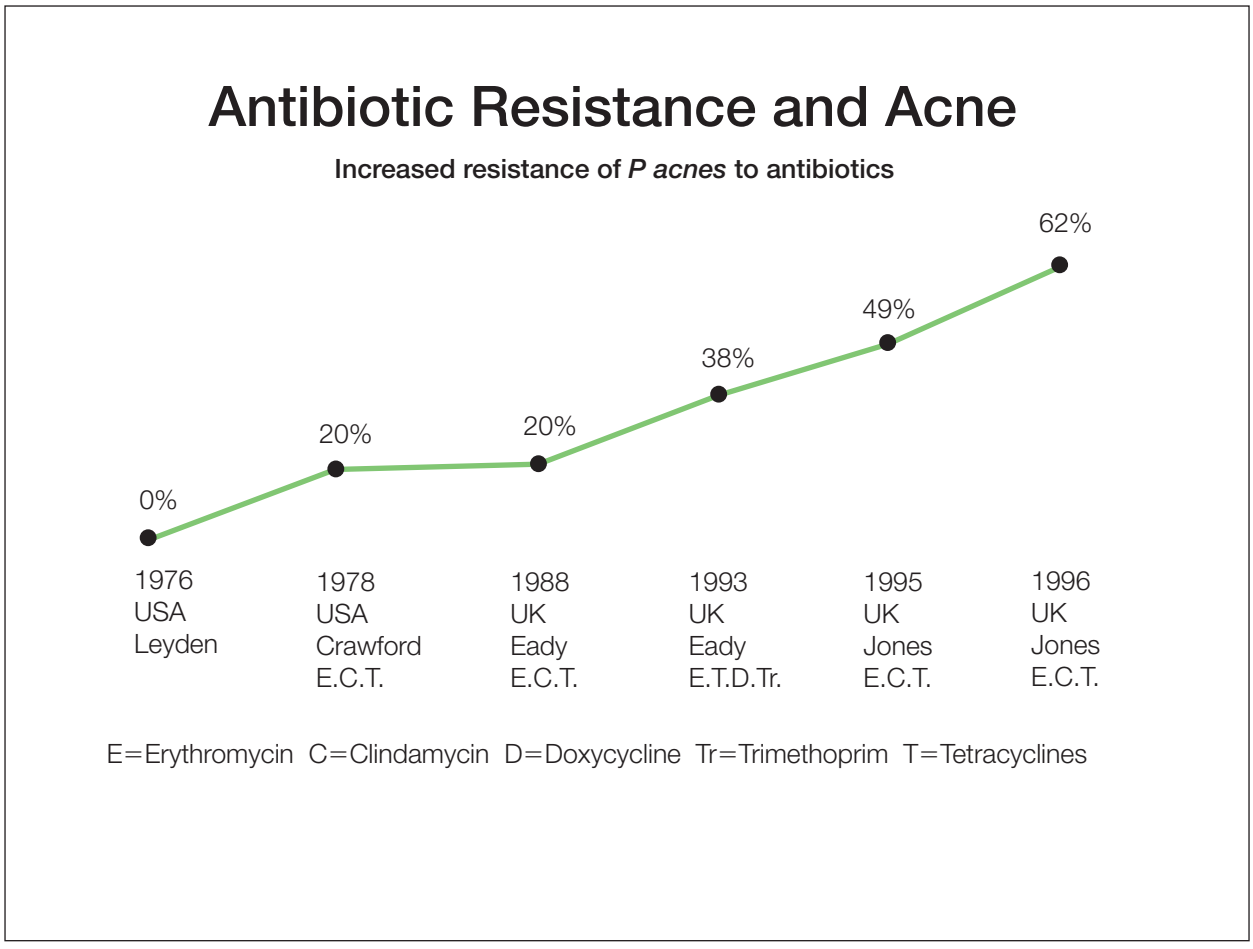
Adapted from Gollnick H, Cunliffe W, Berson D, et al, and the Global Alliance to Improve Outcomes in Acne. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2003;49(suppl 1):S1-S37.[7]

The US Food and Drug Administration has approved several OCs for the treatment of acne, including ethinyl estradiol 20/30/35 μg plus norethindrone 1 mg (Estrostep), ethinyl estradiol 35 μg plus norgestimate 180/215/250 μg (Ortho Tri-Cyclen), and ethinyl estradiol 20 μg plus drospirenone 3 mg (Yaz).

Isotretinoin is the only agent that affects all the pathogenic features of acne as well as all the types of acne lesions. Its use, however, is limited by teratogenicity and the risk of elevated triglyceride levels and possible psychological disturbances (depression, suicide).

Targeting Inflammation

Therapeutic agents that target acne inflammation include benzoyl peroxide, antibiotics, azelaic acid, and retinoids. Benzoyl peroxide reduces inflammation by killing *P acnes*. Topical and oral antibiotics and retinoids also are used to reduce inflammation. Topical retinoids (eg, adapalene, tretinoin) can actually down-regulate expression of toll-like receptor 2 on the surface of inflammatory cells within the infiltrate surrounding acne lesions.[5] Thus, these retinoids also affect the inflammation elicited when *P acnes* interacts with the receptor. Topical dapsone was recently approved as an



Increased resistance of *Propionibacterium acnes* to antibiotics in acne treatment. Adapted from Eady EA. Bacterial resistance in acne. *Dermatology*. 1998;196:59-66.[8]

anti-inflammatory for use in acne and should be available in the near future.

Combination Therapy

There are several types of acne lesions. Inflammatory lesions include papules, pustules, cysts, and nodules. *P acnes* contributes to the development of inflammation in these lesions. Each pathogenic factor requires a different therapy. Thus, combination therapy is the mainstay of acne treatment. However, failure of a therapeutic regimen after 6 to 8 weeks should prompt a change in medications.[6] Complex therapeutic regimens add to expense, can cause irritation, and disrupt patient adherence.

First-line treatment often includes a topical retinoid with or without benzoyl peroxide. Alternatives are listed in Table 2.[7] For women with acne, hormone therapy often is recommended in combination with other treatments.

Use of Antibiotics Decreasing

The increasing resistance of *P acnes* to antibiotics has prompted physicians to avoid using these agents in acne treatment, especially as monotherapy (Figure).[8] In addition, some patients are concerned about long-term use of antibiotics, particularly with regard to the possible connection between antibiotics and breast cancer. In a case-control study of 2266 women with breast cancer, increasing cumulative days of antibiotic use was associated with increased risk of breast cancer (odds ratio for 1001 days, 2.07; 95% CI, 1.48 to 2.89; $P<.001$).[9]

Other reasons for less use of antibiotics in acne treatment include increased attention to laser and light therapies such as visible light, photodynamic therapy (red, blue), and mid-infrared laser. Large well-controlled clinical trials are needed to demonstrate the place of these methods in acne treatment.

Comment

Acne is a widespread condition that has negative effects on physical appearance as well as potential negative psychological effects. Only isotretinoin and hormone therapies effectively reduce sebum, a key feature in acne pathogenesis. Failure to respond

to a therapeutic regimen should prompt a regimen change. Combining treatment regimens for acne appears to be effective, but physicians should avoid complicated treatment regimens. Investigation of the potential of OCs as treatment for moderate acne vulgaris in women with no known contraindications should continue; the need for mechanisms to reduce sebum production remains unmet in many patients.

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Pharmacology of Hormonal Contraceptives and Acne

Katharine O'Connell, MD, MPH; Carolyn Westhoff, MD, MSc

Higher free testosterone levels in women are a function of lower levels of sex hormone–binding globulins (SHBG), higher levels of total testosterone, or both. When free testosterone levels are decreased, sebum production, a pathogenic feature of acne vulgaris, is also decreased. Oral contraceptives (OCs) decrease free testosterone levels by reducing testosterone production by the ovaries and adrenal glands, increasing SHBG, and inhibiting conversion of free testosterone to dihydrotestosterone. Studies have shown that the progestin component of OCs lowers androgen levels, which are directly associated with the development of acne lesions. Currently, 3 OCs have received approval for acne from the US Food and Drug Administration. For patients with acne who are already benefiting from OC treatment, there is no need to change the OC; however, when an OC proves insufficient against sebum production, switching to a formulation that is approved for acne is recommended.

Cutis. 2008;81(suppl 1):8-12.

Four pathogenic factors are involved in acne development: (1) follicular epidermal hyperproliferation and follicular plugging, (2) increased production of sebum from sebaceous glands, (3) enhanced bacterial colonization of follicles with *Propionibacterium acnes*, and (4) release of inflammatory mediators (eg, cytokines, tumor necrosis factor) into hair follicles and surrounding dermis. The effect of androgens is primarily through the first 2 pathways. Sebum production is increased either by overstimulation of the gland by androgens at high levels or by oversensitivity to androgens at normal levels. Androgens also enhance follicular hyperkeratosis; 5α-reductase activity has been demonstrated in the infrainfundibular segments of sebaceous follicles.[1] Enzymatic activity also can lead to conversion of testosterone to dihydrotestosterone (DHT) at follicle sites.

Approximately 1% to 2% of serum testosterone is active and unbound; the remainder is bound to 1 of 2 proteins, either albumin or sex hormone–binding globulin (SHBG). Albumin has a high capacity but low affinity for testosterone, so it readily dissociates from testosterone. SHBG, on the other hand, has a high affinity but low capacity for testosterone and binds to testosterone preferentially over estrogen.

Women with acne, hirsutism, or irregular menses (symptoms of hyperandrogenism) may have higher free testosterone levels—due to lower levels of SHBG, higher levels of total testosterone, or both. Higher free testosterone then results in increased sebum production and hair growth. Free testosterone is the primary androgen associated with acne. Testosterone is produced directly by the ovaries and the adrenal glands. Free testosterone levels are determined by both total testosterone and SHBG levels. In susceptible skin cells, free testosterone is then converted to DHT by the 5α-reductase enzyme. DHT in turn acts on the glands' androgen receptors to promote sebum production (Figure 1).[2-5] Sebum production is lessened when free testosterone levels are decreased.

Oral contraceptives (OCs) decrease free testosterone in 3 ways. First, they decrease testosterone production by the ovaries, adrenal glands, and peripheral sources and suppress production of luteinizing hormone from the pituitary gland, which in turn decreases androgen (testosterone, androstenedione) synthesis by the ovaries; they also reduce adrenal production of dehydroepiandrosterone sulfate (DHEAS) and androstenedione. Peripherally, OCs decrease 3α-androsterone glucuronide (3α-diol G), a DHT metabolite that correlates highly with

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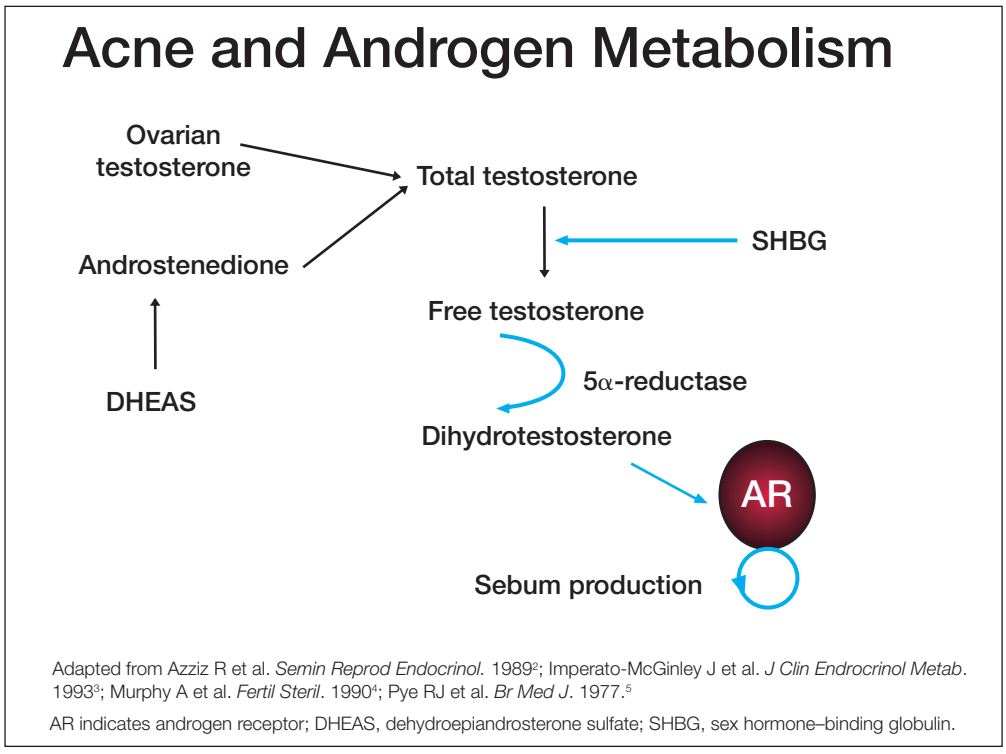
Dr. O'Connell reports no conflict of interest. Dr. Westhoff has received research support from Duramed Pharmaceuticals, Inc, and Organon. She is a consultant and speaker for Bayer HealthCare Pharmaceuticals; Duramed Pharmaceuticals, Inc; and Organon.



Adapted from Azziz R et al. *Semin Reprod Endocrinol.* 1989[2]; Imperato-McGinley J et al. *J Clin Endrocrinol Metab*. 1993[3]; Murphy A et al. *Fertil Steril*. 1990[4]; Pye RJ et al. *Br Med J*. 1977.[5]

AR indicates androgen receptor; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone–binding globulin.

Figure 1. Acne and androgen metabolism.

5α-reductase activity. The exact mechanism by which OCs reduce androgen production by the adrenal glands is not known, though it has been demonstrated with radioimmune assays.

Second, they decrease testosterone bioavailability by increasing SHBG. Their ethinyl estradiol (EE) component increases SHBG to bind testosterone and thereby lower free testosterone levels. Estrogen and progestin work synergistically to decrease unbound testosterone by a mean of 45%.[6,7]

Third, they inhibit conversion of free testosterone to DHT. Their progestin component directly inhibits the enzymatic activity of 5α-reductase in the hair follicles and skin.[8] Progesterone, norethindrone, and levonorgestrel have been shown to directly reduce 5α-reductase activity in vitro.[8,9] EE, however, appears not to affect the enzymatic activity of 5α-reductase.[8] Progestins also competitively inhibit androgen receptors in the sebaceous glands and thereby reduce DHT uptake.

In summary, laboratory testing has confirmed that OC treatment substantially reduces testosterone precursors and DHT—including free (bioavailable) testosterone, 3α-diol G, and DHEAS—and increases SHBG.

The physiologic results of increasing SHBG may be limited by a ceiling effect. Comparing 2 low-dose OC pills that differed only in their progestin component (levonorgestrel vs norethindrone), Thorneycroft et al[7] found different degrees of increase in SHBG (with EE/levonorgestrel, 106%; with EE/norethindrone, 234%). Decreases in bioavailable testosterone were similar (with EE/levonorgestrel, 31%; EE/norethindrone, 26%). Total testosterone decreased 27% with the EE/levonorgestrel pill but remained unchanged with the EE/norethindrone pill. Thus, despite differing effects on SHBG, the effects on free testosterone were similar.[7]

Thorneycroft et al[7] further demonstrated that SHBG binding capacity and affinity do not increase in direct proportion to concentration. The larger SHBG increase obtained with EE/norethindrone did not result in a proportionately higher amount of bound testosterone. Thus, the magnitude of SHBG increase does not predict androgenic activity. Despite the large difference in SHBG increases produced by the 2 progestins, these agents had similar clinical effects in decreasing the total number of acne lesions from baseline to treatment cycle 3 (Figure 2).[7]

Serum Markers Versus Clinical Outcomes

Clinical outcomes generally parallel laboratory findings with regard to changed numbers of inflammatory lesions, noninflammatory lesions, and total lesions. Serum markers, however, do not always correlate with clinical findings; reductions in total lesion count may not have corresponding directional changes in biochemistry values. In an individual patient, an increase or decrease (or no change at all) in serum androgen levels may not parallel actual progression or improvement in acne lesions.

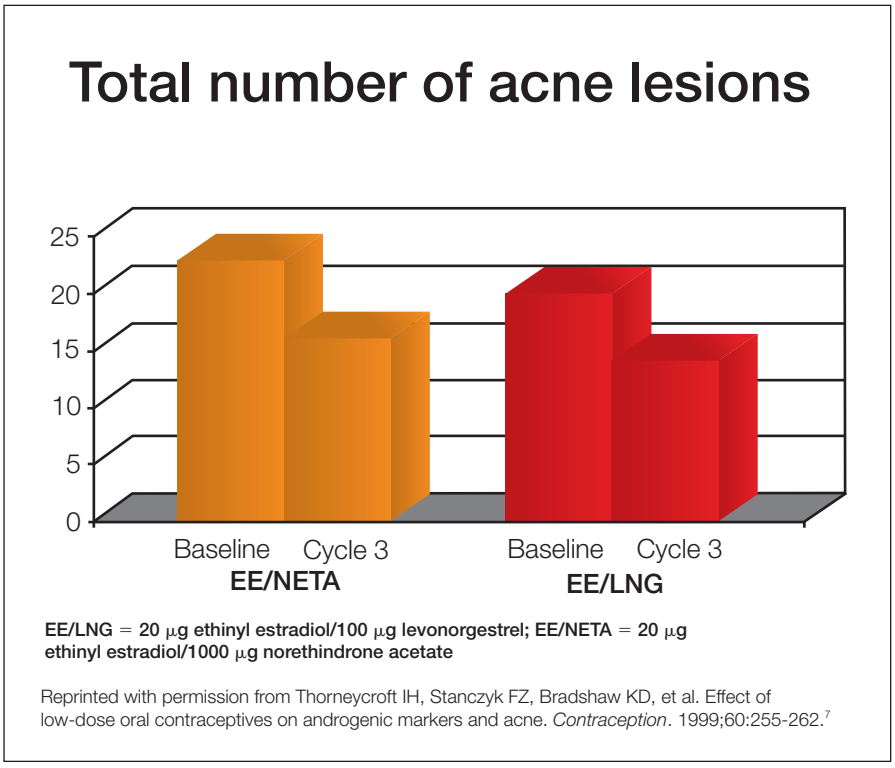


Figure 2. Total number of acne lesions.

In the study by Thorneycroft et al,[7] baseline lesion counts correlated only with serum DHT levels. None of the other androgens correlated with what was seen clinically at baseline. Over the course of the study, the levonorgestrel group's reduction in total lesion count correlated with increased SHBG and with reductions in almost all the androgens. In the norethindrone group, although reduction in total lesion count also correlated with increased SHBG, it correlated with reductions in only 2 androgens (androstenedione, 3α-diol G). Levonorgestrel and norethindrone yielded similar clinical effects, but hormone assays would not have been useful in predicting which subject would respond or what the response would be.

Lemay and Langley[10] used 6 cycles of a triphasic OC (EE 30/40/30 μg plus levonorgestrel 50/75/125 μg) to determine its efficacy in reducing inflammatory and noninflammatory mild to moderate acne lesions. These lesions decreased by 80% in approximately 70% of the subjects. Despite decreases in all androgens and an increase in SHBG, no individual correlation was found between acne scores and values for serum androgens, 3α-diol G, or SHBG before or after treatment.[10]

Palatsi et al[11] compared women's serum levels of DHEAS, SHBG, and other biochemical parameters before and after acne treatment with an OC. One group received EE/desogestrel; the other, EE/levonorgestrel. After 6 treatment cycles, acne severity was decreased in both groups. SHBG increased 250% in the EE/desogestrel group versus 30% in the EE/levonorgestrel group, but free testosterone decreased 30% to 40% in both groups.[11]

Rosen et al[12] compared the clinical efficacy of 2 OCs (EE 30 μg plus desogestrel 150 μg vs EE 30 μg plus levonorgestrel 150 μg) in treating acne in 34 women over a 9-month period. The groups had similar mean decreases in acne lesion counts (EE/desogestrel, 58%; EE/levonorgestrel, 53%), and both groups had increases in SHBG and nonsignificant decreases in free testosterone. Total testosterone and DHEAS levels did not change significantly.[12]

The only study showing correlations between serum markers and reductions in acne lesion counts was a randomized placebo-controlled trial, conducted by Leyden et al,[13] of an OC containing EE 20 μg and levonorgestrel 100 μg. Six treatment cycles were monitored for 371 patients with at least moderate acne. The OC group improved over the placebo group with regard to all lesion counts, clinical global assessment, and patient self-assessment, and there were reductions in free testosterone, DHEAS, and serum androgen levels. There was a positive correlation between change in total lesion count and changes in androgen levels after 6 treatment cycles, with an almost significant inverse correlation between total lesion count and change in SHBG.[13]

Oral Contraceptives With Acne Benefits

	Ethinyl Estradiol, μg	Progestin
FDA Approved for Acne*		
Estrostep	20/30/35	Norethindrone 1 mg
Ortho Tri-Cyclen	35	Norgestimate 180/215/250 μg
Yaz	20	Drospirenone 3 mg
Acne Benefits Examined in Studies[12-16]		
Alesse	20	Levonorgestrel 100 μg
Yasmin	30	Drospirenone 3 mg
Microgynon	30	Levonorgestrel 150 μg
Nordette	30	Levonorgestrel 150 μg
Levlen	30	Levonorgestrel 150 μg
Femodene	30	Gestodene 75 μg
Femovan	30	Gestodene 75 μg
Ortho-Cept	30	Desogestrel 150 μg
Unavailable in United States		
Diane-35	35	Cyproterone 2 mg

*FDA indicates US Food and Drug Administration.

Therefore, different progestins may affect androgen levels differently. Notwithstanding the changes in androgen levels, however, different progestins may provide equivalent reductions in clinical androgenicity. Serum markers only seldom correlate with clinical outcomes in individual women, and only clinical outcomes should be used as the basis for evaluating effectiveness of a treatment. Thus, unless clinicians are testing for other pathology (eg, an androgen-secreting tumor), they should not measure or monitor serum androgen levels.

Measuring Androgen Levels

In summary, many studies have shown clinical improvement in acne after OC treatment, but few studies have shown correlating changes in androgen levels. Use of serum androgen assays comes with many challenges. Assays are often designed to measure androgen levels in males, which are much higher than those in females. Assays and techniques used vary by study and laboratory. Thus, there are no absolute numbers that can be used for reference ranges or for posttreatment targets. Hormone levels also vary substantially throughout the treatment cycle. Serum measurements, therefore, are likely to be unreliable. In addition, there are no reliable data on optimal timing of these measurements in patients with acne. Most important, androgen trends across the population cannot predict an individual's clinical course. Therefore, measurement of testosterone levels usually is not helpful in the clinical management of women with acne.

OCs Indicated for Acne

Three OCs have received approval from the US Food and Drug Administration for the treatment of acne. These low-dose estrogen (EE <50 μg) products have different progestins. EE 20/30/35 μg plus norethindrone 1 mg (Estrostep) is indicated for treatment of moderate acne vulgaris in females who are at least 15 years old, have reached menarche, and require or request an OC for contraception. EE 35 μg plus norgestimate 180/215/250 μg (Ortho Tri-Cyclen) is indicated for treatment of moderate acne vulgaris in females who are at least 15 years old, have reached menarche, and require

or request an OC for contraception. EE 20 μg plus drospirenone 3 mg (Yaz) is indicated for treatment of moderate acne vulgaris in females who are at least 14 years old, have reached menarche, and require or request an OC for contraception.

Studies have shown acne benefits with use of other OCs, such as EE 30 μg plus drospirenone 3 mg (Yasmin) and EE 20 μg plus levonorgestrel 100 μg (Alesse).[13-16] Although only 3 OCs are indicated for acne, many others likely would be beneficial. The Table lists all the OCs that have been studied for use in patients with acne. EE 35 μg plus cyproterone 2 mg (Diane-35) is unavailable in the United States; its first indication was not as an OC but as an acne product and the indication for contraception followed.

For initial OC treatment of acne, an OC with a US Food and Drug Administration indication is advised. For patients already benefiting from OC treatment for acne, there is no need to change the OC; when an OC is ineffective for acne, however, a switch to an acne treatment–approved formulation is recommended.

Comment

Androgens are an important factor in the pathogenesis of acne formation. OCs can substantially reduce the effects of androgens by reducing their levels and bioavailability. Serum androgen levels cannot be used to predict an individual's clinical course, so clinical improvement in acne lesions should be the marker of effectiveness. In the United States, 3 OC formulations are approved by the US Food and Drug Administration for treatment of acne: EE 20/30/35 μg plus norethindrone 1 mg, EE 35 μg plus norgestimate 180/215/250 μg, and EE 20 μg plus drospirenone 3 mg.

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Hormonal Contraceptives for Acne Management

Phoebe Rich, MD

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 with moderate acne vulgaris who seek contraception and teenagers with acne who refuse antibiotics or in whom topical antibiotics are ineffective might be candidates for drospirenone-containing OCs.

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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,[3] each year more than 5 million prescriptions for oral antibiotics are dispensed, including 1.4 million prescriptions for isotretinoin.

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Novartis Pharmaceuticals Corporation; Novum Pharmaceutical Research Services; Pfizer Inc; Photocure; Schering-Plough Corporation; Stiefel Laboratories, Inc; Symbio; Teva Pharmaceuticals; Tolmar Inc; Warner-Lambert Company; and Xoma. She also has been a speaker for 3M Pharmaceuticals, CollaGenex Pharmaceuticals Inc, Connetics Corporation, and Novartis Pharmaceuticals Corporation.

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

Table 1.

Hormonal Contraceptives That Are Available in the United States

Estrogen Combinations
Monophasic
Triphasic
Extended cycle
Transdermal patch
Vaginal ring
Progestin-Only Compounds
Implants
Levonorgestrel-releasing intrauterine system
Depot medroxyprogesterone acetate injections

of acne lesions. Through the metabolization 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 (ethinyl estradiol [EE 20 μg/drospirenone 3 mg [Yaz], EE 30 μg/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[10,11] assessed the safety and efficacy of an OC (EE 20 μg/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

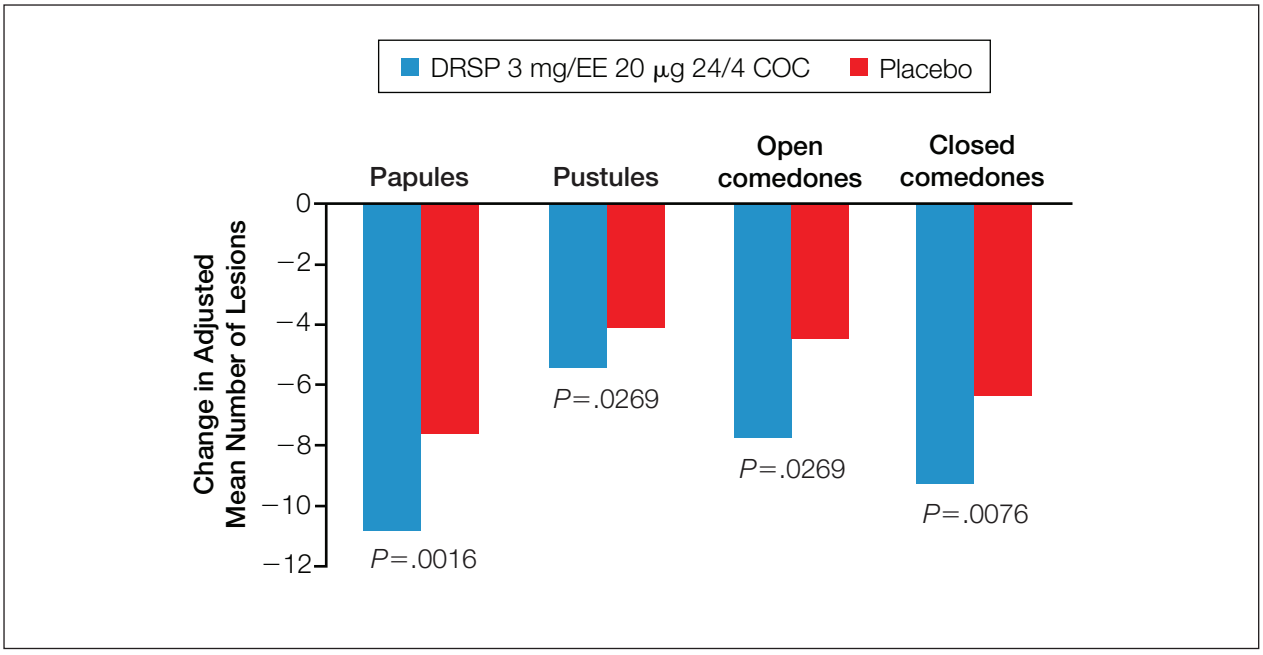

Figure 1. Change in adjusted mean number of lesions (papules, pustules, open and closed comedones) from baseline to end point (full analysis set). The *P* values show the difference between the DRSP 3 mg/EE 20 μg 24/4 COC and placebo groups. COC indicates combined oral contraceptive; DRSP, drospirenone; EE, ethinyl estradiol. Reprinted from Maloney JM, Lee-Rugh S, Kunz M, et al. Drospirenone 3 mg/ethinylestradiol 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.[10] Courtesy of Bayer HealthCare Pharmaceuticals.

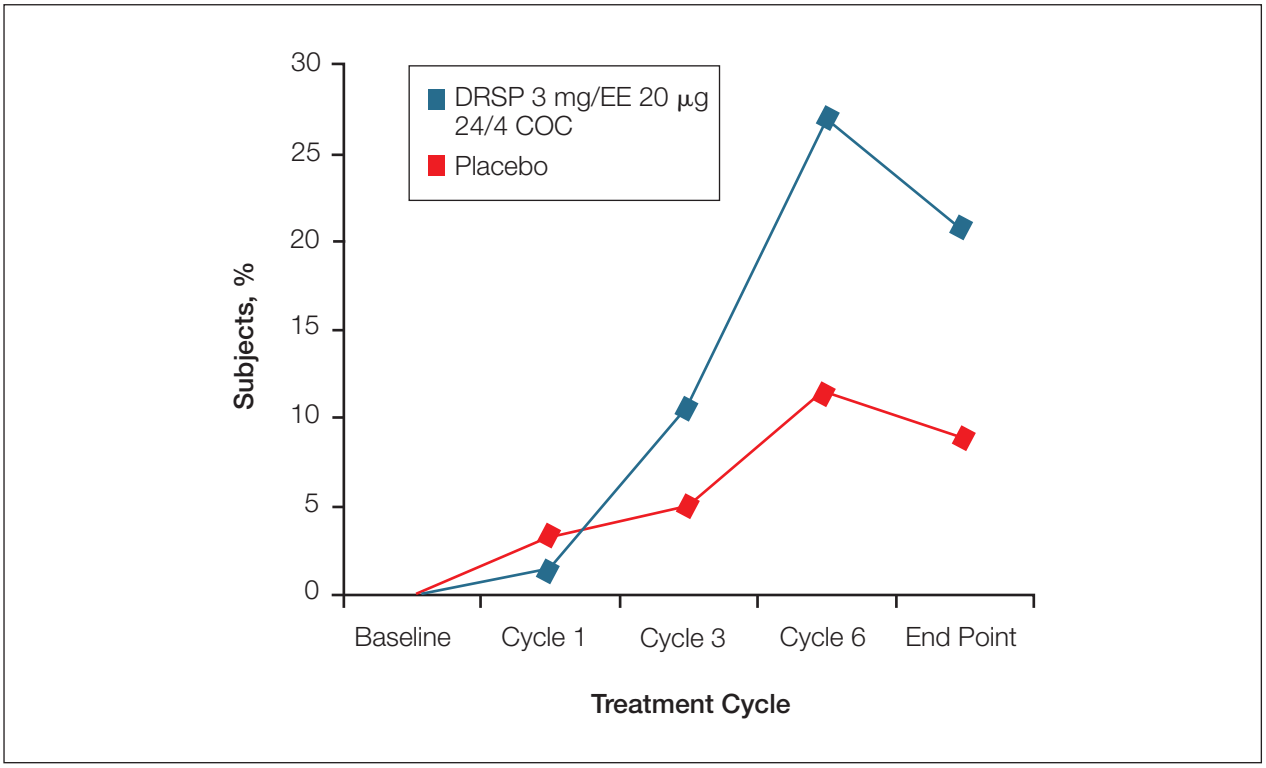

Figure 2. Percentage of subjects rated as clear (score 0) or almost clear (score 1) on the investigator's static global assessment scale by treatment group and cycle (full analysis set). COC indicates combined oral contraceptive; DRSP, drospirenone; EE, ethinyl estradiol. Reprinted from Maloney JM, Kunz M, Lee-Rugh S, et al. Drospirenone 3 mg/ethinylestradiol 20 μg COC in the treatment of acne vulgaris: lesion count, ISGA. Poster presented at: 55th Annual Clinical Meeting of the American College of Obstetricians and Gynecologists; May 5-9, 2007; San Diego, CA.[11] 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] Drospirenone

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 progestogenic effect through the 4 days with hormone-free pills.

In an earlier multicenter, double-blind, randomized study, van Vloten et al[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.[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[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.[14]

Who Qualifies and Does Not Qualify for Acne Treatment With OCs Containing Drospirenone?

Patients who qualify must want contraception. They include healthy nonsmoking women with recalcitrant lower face, jawline, and neck acne, women with hyperandrogenic conditions, women who have had difficulty adhering to an OC schedule because of untoward side effects from high estrogen levels but who are now willing to take

Table 2.

Efficacy Results for Acne Trials*[12]

	Study 1		Study 2	
	Yaz† (n=228)	Placebo (n=230)	Yaz (n=218)	Placebo (n=213)
Total lesions				
Mean baseline count	80	80	76	76
Mean absolute (%) reduction	33 (42%)	21 (25%)	33 (46%)	22 (31%)

*Evaluated at day 15 of cycle 6, last observation carried forward for the intent-to-treat population.
†Ethinyl estradiol 20 μg/drospirenone 3 mg.

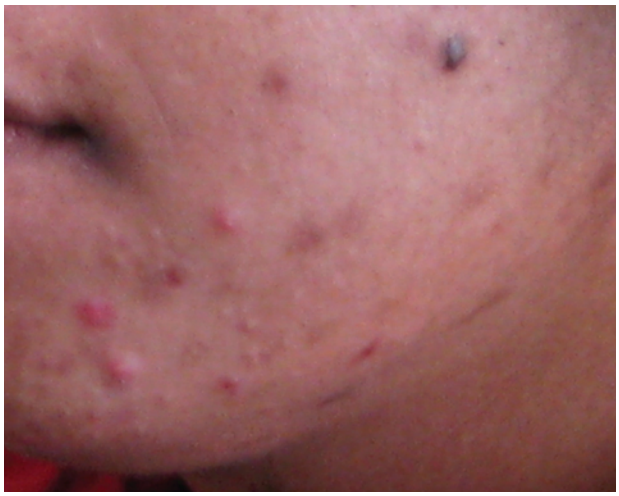

Figure 3. Woman with chronic low-grade cystic acne.

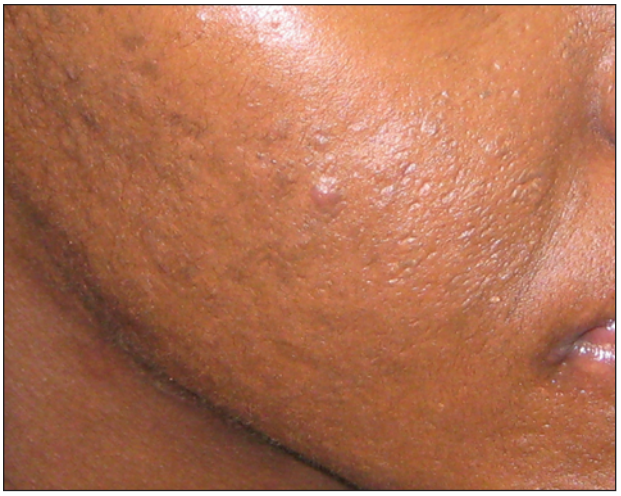

Figure 4. Woman with low-grade acne and scarring.

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[1] 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.

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Oral Contraceptives: Mechanism of Action, Dosing, Safety, and Efficacy

Steven J. Sondheimer, MD

The most widely used form of hormonal contraception is the combination oral contraceptive (OC). Combination OCs can be monophasic, providing the same dose of estrogen and progestin daily, or multiphasic, offering varying doses of hormones throughout a 21- or 28-day cycle.

The objective of OCs is to suppress ovulation by manipulating events throughout the ovulatory cycle to prevent pregnancy. The progestin and estrogen components of OCs suppress the midcycle surge of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The overall effect is to decidualize the endometrial bed and suppress mitotic activity. Initial formulations of OCs in the 1960s attempted to mimic the natural cycle; however, providing high doses of estrogen rather than lower doses of combined estrogen and progestin resulted in greater risk of serious adverse events. Today, OCs provide far lower levels of estrogen and progestin. The availability of formulations with drospirenone, a unique progestin pharmacokinetically similar to progestin and similar in structure to spironolactone, should widen usage of OCs. Although OCs are still associated with increased risk in certain patients and are contraindicated in others, they remain effective but require diligent usage.

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At the beginning of a normal ovulatory cycle, estrogen and progesterone levels are low. During the follicular phase, the follicle begins as a small ovarian cyst detectable only by ultrasound. As the cyst enlarges, the follicle also increases in size, producing more estrogen. When the follicle is approximately 2 cm, it ruptures and the oocyte is extruded. The follicle then undergoes a metamorphosis, turning into a corpus luteum (literally meaning "yellow body"). The yellow color results from steroid (estrogen, progesterone) production.

Progesterone levels increase slightly before ovulation and then again after formation of the corpus luteum. After about 14 days, the corpus luteum regresses, estrogen and progesterone levels fall, and menstruation occurs as a result of the decrease in estrogen and progesterone.

During the follicular phase of the cycle, the lining of the womb, the endometrium, goes through cell division, or mitotic activity. Within hours of the increase in progesterone, mitotic activity ceases. In the presence of progesterone, mitotic activity cannot occur.

The ovulation signal is the midcycle surge in luteinizing hormone (LH) caused by the elevation in estrogen level just before the LH surge from the dominant follicle. Because follicular growth is 3-dimensional, estrogen levels increase exponentially. LH has 2 roles: steroidogenesis during most of the cycle and induction of prostaglandins and other substances that cause digestion of the follicle wall.

MECHANISM OF ORAL CONTRACEPTION

The main birth control mechanism of oral contraceptives (OCs) is to suppress ovulation. Increased progesterone levels indicate that ovulation has occurred. Before ovulation, when estrogen levels are high and progesterone levels are low, the cervical mucus is clear and copious (women using the rhythm method of contraception are taught to recognize that cervical mucus increases just before ovulation). When ovulation occurs, mucus viscosity changes because of the presence of progesterone, and penetration by sperm is prevented.

OCs provide progestin daily. Their main effect is endometrial suppression. Negative feedback to the hypothalamus and the pituitary gland suppresses the LH surge. In rodents, negative feedback occurs mainly at the level of the hypothalamus in the normal menstrual cycle. In humans, negative feedback occurs at both levels—the hypothalamus

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and the pituitary gland. Suppression of the midcycle LH surge occurs alongside a decrease in gonadotropin-releasing hormone pulse frequency, suppression of LH and steroidogenesis, and suppression of folliculogenesis and follicle-stimulating hormone (FSH). OCs suppress ovulation, formation of the corpus luteum, and progesterone.

Combination OCs contain an estrogen and a progestin. The estrogen suppresses FSH, which in turn suppresses follicle growth. Thus, the estrogen component exerts its main effect on FSH. In the normal menstrual cycle, as estrogen levels increase during the follicular stage, FSH levels are suppressed. The progestin in the OC suppresses LH by decreasing gonadotropin-releasing hormone pulse frequency and possibly also by exerting a direct effect on the pituitary gland. Thus, progestin suppresses steroidogenesis, the LH surge, and as a result, ovulation. In a low percentage of patients, a follicle can grow without a mild elevation in progestin. Thus, the only way to judge the efficacy of an OC is to observe how effective it is in preventing pregnancy.

Under the influence of progestin, a decrease in water content renders cervical mucus impermeable. Because cervical mucus is a glycoprotein, its structure changes as the water content decreases. On occasion, midcycle mucus is tested (by allowing it to dry) just before ovulation. At that time, ferning creates channels in which sperm swim to reach the fallopian tube, where fertilization occurs. Thus, when water content decreases, there are no channels by which sperm can reach the endometrial cavity and ultimately the fallopian tube. Progestin then decreases the cervical mucus water content and changes the glycoprotein structure—that is, the ferning effect is lost.

The postovulatory interval is referred to as the *luteal phase*; from the endometrial point of view, however, it is called the *secretory phase*. OCs exhaust the secretory endometrium, and the endometrial bed becomes decidualized with exhausted and atrophied glands. OCs also suppress mitotic activity in the endometrium.

With complete suppression of mitotic activity and a relatively thin endometrium, women often have less menstrual bleeding and cramping. When the volume of tissue is suppressed and prostaglandins are diminished, the incidence of endometrial cancer is also decreased.

CONTRACEPTIVE DOSING

When sequential OCs were first introduced in the 1960s, the intent was to provide estrogen in a manner that would mimic the natural menstrual cycle. This form of contraception had more adverse events associated with its use, due more likely to high dosing of estrogen than to the sequential nature of the OCs.

The fixed combination (21 active pills, 7 inert pills) that eventually was derived remains the most popular type of OC. During the 7 hormone-free days, folliculogenesis occurs, which is what had been intended with the original sequential OCs. During the hormone-free interval, FSH and LH levels remain suppressed; however, by the third or fourth day, these levels start to increase, along with estrogen levels. At the end of the 7-day period, the active component of the OC is reintroduced, once again suppressing FSH and LH levels.

High estrogen levels have been the main cause of serious side effects from OCs. The dose of progestin also has been lowered from the first formulations. The original progestins were derived from testosterone. Newer 19-nortestosterone derivatives have been structurally modified to reduce androgenic activity.

In the 1970s, the high estrogen content of the pill was found to be associated with serious vascular side effects. Thrombosis, both venous and arterial, appeared to be related to higher estrogen doses in early formulations.[1] Consequently, doses were lowered and the shift was made to phasic preparations, which reduced the risk of thromboembolism associated with OC use.[2] Androgenicity was believed to be the cause of some of the side effects. The newer formulations appeared to be less androgenic and to possibly have less impact on carbohydrate and lipoprotein metabolism.[3] Cycle control was similar to that of older products. Changes in coagulation-promoting and antithrombotic factors were minor.[3]

The fixed combination followed by unopposed estrogen was eventually derived. Theoretically, this formulation lessens withdrawal symptoms such as headaches and mood changes.

Even more recently, a fixed-combination OC was developed with 24 days of active pills and 4 days of inert pills. In addition, a unique progestin, drospirenone—which is closest in pharmacokinetics to progesterone itself and similar in structure to spironolactone—was developed.

RISKS ASSOCIATED WITH OCs

The most serious risks associated with modern OC use are vascular—venous and arterial. Venous complications occur in a low-flow environment; arterial complications occur in a high-flow environment. Venous thrombosis is a risk faced to some extent by all women who are using OCs. In fact, the estrogen component of OCs increases the risk for deep venous thrombosis and pulmonary embolism 3- to 4-fold.[4]

Table 1.

Conditions That Preclude Use of Hormonal Contraception

Atherosclerosis
Biliary disease
Breast cancer
Deep venous thrombosis or pulmonary embolism (history)
Diabetes mellitus with end-organ disease
Heart disease, prior myocardial infarction, or stroke
Hypertension (uncontrolled)
Immobilization (prolonged)
Liver disease
Migraine with focal neurologic symptoms
Pregnancy
Smoking, especially in women age >35 y

Table 2.

Medications That Decrease Serum Concentrations of Hormonal Contraception

Anticonvulsants
Anti-infective agents
Barbiturates
Carbamazepine
Phenytoin
Rifampin
Topiramate
Vigabatrin

Deep venous thrombosis also can lead to a pulmonary embolism; however, today this complication remains relatively rare.

Even rarer are arterial complications, which appear to be related, at least epidemiologically, to the estrogen component. However, predicting who will have these problems with estrogen doses lower than 35 μg is difficult.

Risk for arterial events associated with OCs was first publicized in the early 1970s.[1,5] Preventing these complications rests not so much on changing the OCs themselves but on monitoring women who are taking the pill. These events are more likely to occur in high-risk patients, such as smokers older than 35 years (Table 1).

Risk for venous thrombotic events is relatively small and may be a function of an inherent bias in patient populations studied. Venous problems are more likely to occur in OC-naïve patients—this is possibly related to study bias in that more events will occur in this population than in the population of women who have been taking the pill for a long time—and in females with factor V Leiden deficiency and other genetic risks.[6,7] Testing for potential problems would be too costly and would preclude use of OCs in too many women who might never develop deep venous thrombosis or a related complication. Complications associated with OCs are more likely in older obese women and in women with risk factors for venous thrombosis.[7,8]

Whereas venous thrombosis has a low risk of mortality, arterial events are associated with higher risks, and these events are less likely to occur in young women. The risk of arterial events is highest in women who already have arterial disease. Thus, in women with healthy arterial vessels, OCs and estrogen-containing hormone pills will not increase risk for arterial events. On the other hand, women with arterial vessel damage should not take hormone therapy that might increase the risk of clotting in the damaged vessel.

Patient History

Most potential problems can be discovered in the patient history. The only part of the physical examination that has ever been shown useful in determining eligibility for OC use is blood pressure measurement. It is recommended that blood pressure be checked before patients start an OC because having uncontrolled hypertension before therapy is a major contraindication[9] (Table 1).

EFFICACY OF OCs

OCs prevent pregnancy. Most of the prevention failures that occur with OCs are the result of improper use. Several factors should be considered: fertility level, medication interactions, and perfect versus real-world use.

Fertility Level

Fertility decreases with age: This is especially true in women older than 30 years.[10]

Medication Interactions

Medications that induce hepatic enzymes can decrease serum concentrations of ethinyl estradiol (EE) and progestin when used concomitantly with OCs, vaginal rings, and subdermal implants (Table 2).

Rifampin—The only antibiotic clearly shown to decrease serum concentrations of hormonal contraceptives by increasing their metabolism is rifampin. Although traditionally used to treat tuberculosis, rifampin also is used for methicillin-resistant staphylococcal infections. Some physicians encourage women who are taking OCs and an antibiotic to also use condoms. Recommending condoms for young sexually active women also is useful because they are at increased risk for sexually transmitted diseases.

Topiramate—Topiramate is used primarily for seizure management but also for migraine prevention. This medication induces hepatic enzymes and can decrease the serum concentration of EE and progestin. Efficacy of combination OCs also is reduced in women who are taking enzyme-inducing antiepileptic medications, such as phenytoin, phenobarbital, and carbamazepine. In a study of 12 women with a history of epilepsy, Rosenfeld et al[11] assessed the efficacy of topiramate (100-400 mg every 12 hours) used in combination with an OC (EE 35 μg plus norethindrone 1 mg). Topiramate interacted modestly with the OC but did not reduce contraceptive efficacy. The reduction in serum estrogen could increase incidence of breakthrough bleeding. Thus, an OC used in combination with topiramate should contain at least 35 μg of estrogen. For most women, especially young women, combination OCs are safe and beneficial.

Perfect Versus Real-world Use

Many studies base their findings on perfect use, but missed pills are part of real-world experience and should be taken into account. The Pearl index, the most common way to measure the effectiveness of birth control in clinical studies, is computed in 2 ways: by dividing the number of pregnancies by the total number of months of exposure, then multiplying that number by 1200; or by dividing the number of pregnancies by the number of menstrual cycles experienced by women and multiplying that number by 1300, based on mean length of menstrual cycle (28 days) or 13 cycles per year. Pregnancy rate in the first year is a more accurate measure of the effectiveness of an OC because a woman's likelihood of becoming pregnant decreases with long-term use. Generally, however, the longer the hormone-free interval, the greater the chance of ovulation. Contraceptive failure occurs for many reasons, including method and usage. Failure rates tend to decline, however, with longer duration of use. The Pearl index requires a lengthy exposure to the contraceptive (at least 1 year) but fails to compare methods over various durations of use.

The life table analysis is not hampered by this limitation because it calculates a failure rate for each month of use. The cumulative failure rate compares methods for a specific length of exposure. Women who leave a study for any reason (apart from an unintended pregnancy) are not included in the analysis.

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Tailoring Individualized Treatment Plans for Acne

Julie C. Harper, MD

Because acne is a complex multifactorial disorder, combination treatment may be required to target its various pathogenic factors. Combination treatments also offer the most improvement over the shortest time. Oral contraceptives (OCs) are an excellent treatment, and clinicians should consider them a first-line option as part of combination therapy in women with acne.

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Topical Agents

First-line therapy for acne is traditionally a topical retinoid. Topical retinoids eliminate the microcomedone, which is the precursor to the inflammatory acne lesion. Topical retinoids also have an anti-inflammatory effect.

Benzoyl peroxide also is an important agent in the treatment of mild to moderate acne. It effectively kills both the sensitive and resistant strains of *Propionibacterium acnes*. The antibiotics prescribed for acne kill the antibiotic-sensitive strains of *P acnes* but often allow the resistant strains to proliferate. Because benzoyl peroxide kills both the sensitive and resistant strains of *P acnes*, it eliminates this selection pressure. Benzoyl peroxide also has weak comedolytic and anti-inflammatory activity.

The topical antibiotics most commonly used, either alone or in combination, are clindamycin and erythromycin. Both clindamycin and erythromycin are antimicrobial agents and have some anti-inflammatory effects.

Oral contraceptives (OCs) are useful additions to a comprehensive acne treatment plan for many female patients. Those patients who benefit the most include females who do not respond appropriately to traditional combination therapy and whose medical history does not preclude OC use. OCs may be used early in the treatment of acne, particularly when they are being used for another reason, such as to prevent pregnancy. Women who are planning to take isotretinoin, are unable or unwilling to take systemic antibiotics, or have signs of hyperandrogenism also can benefit from having an OC added to their acne treatment regimen.

Spironolactone

Dermatologists tend to choose spironolactone over an OC for acne treatment, but both agents have risks and benefits. OCs should be considered for all women who want contraception, do not smoke, do not have a history of migraine headaches exacerbated by hormones, are normotensive, and do not have other risk factors for arterial occlusive events.

Spironolactone is an antiandrogen. It inhibits 5α-reductase and androgen biosynthesis and binds the androgen receptor. Because the side effects of spironolactone include polyuria, menstrual disturbances, gynecomastia, dizziness, headache, and weight gain, it is best used with an OC. Coadministration can reduce the risk of an exposed pregnancy and feminization of a male fetus. It also lessens the menstrual disturbances associated with spironolactone.

Spironolactone is more useful in postmenopausal women, who do not need contraception and for whom menstrual disturbances are no longer an issue. It also can be useful in women with hirsutism. Dosages range from 50 to 200 mg/d. Checking the patient's potassium level is important when using higher daily doses of spironolactone, particularly when combining this agent with an OC, because hyperkalemia can occur, especially in patients with renal problems.

Drospirenone is a spironolactone analogue with antimineralocorticoid and antiandrogenic activity. Clinicians who prescribe a combination of spironolactone and a drospirenone-containing OC should note that the drospirenone component of the OC is comparable to a 25-mg dose of spironolactone.

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Contraindications That Preclude Use of an OC for Acne*

- Age >35 y and heavy smoker (>15 cigarettes daily)
- Breast cancer (current)
- Breastfeeding <6 wk postpartum
- Cirrhosis or liver tumor (benign or malignant)
- Deep venous thrombosis (history or current)
- Diabetes mellitus with nephropathy, retinopathy, neuropathy, vascular disease
- Heart disease (history)
- Hypertension (uncontrolled)
- Migraine headaches (with focal neurologic symptoms at any age, or without focal neurologic symptoms but age >35 y); patients with menstrual migraines are candidates for OCs
- Pregnancy
- Stroke (history)

*OC indicates oral contraceptive.

Patient Counseling

Regardless of age or sexual activity, females who take isotretinoin also should take an OC. In the iPledge program, females of childbearing potential are required to wait 30 days and to have 2 negative pregnancy test results at least 30 days apart before starting their isotretinoin regimen. However, once registered in the iPledge program, patients may delay reregistering for up to 90 days. It takes 3 months (or 3 cycles) for an OC to improve acne. Some patients choose to register in the iPledge program, begin taking an OC, and then delay taking the second pregnancy test until closer to the 90-day cutoff. At that point, if the acne is well controlled, isotretinoin is not needed. If the OC is not controlling the acne, the results of the second pregnancy test can be obtained and treatment with isotretinoin can begin. Before women with clinical signs of hyperandrogenism are started on OC therapy, basic laboratory evaluations must be conducted to measure the levels of free and total testosterone, dehydroepiandrosterone sulfate, and luteinizing and/or follicle-stimulating hormones. When testosterone and dehydroepiandrosterone sulfate test results are equivocal and clinical suspicion is high, 17-hydroxyprogesterone levels also should be checked to evaluate more closely for an adrenal origin of the androgenic hormone.

Before prescribing an OC, clinicians must check for contraindications. Any contraindication listed in the Table precludes use of an OC.

Side Effects Associated With OCs

Patients should be told about the potential side effects of OCs, including irregular bleeding. When patients are aware that irregular bleeding is a side effect, they are more likely to adhere to therapy. Patients also should be counseled that their bleeding patterns may change in the first few months of therapy as part of the normal course of events. Spotting does not warrant changing a therapeutic regimen. Patients should be urged to use panty liners and counseled to stay on the regimen for 3 months before considering switching to another regimen.

Patients also should be given reasonable expectations regarding results. Acne will improve only after the patient has taken the OC for 3 months or more. Many topical and systemic agents can have a positive impact on acne in as few as 4 to 8 weeks. As stated previously, combination therapy results in more rapid improvement.

In addition, patients should be asked what they have heard from friends and relatives regarding side effects so that any unfounded or preconceived notions can be dispelled. For example, weight gain, which patients often associate with OC use, was not proven to be an issue in a clinical trial by Gallo et al.[1]

OCs and Antibiotics

The American College of Obstetrics and Gynecology noted that, with the exception of rifampin, antibiotics do not decrease the effectiveness of OCs.[2] Approximately 76% of alleged interactions between antibiotics and OCs involve rifampin. Rifampin is a potent inducer of cytochrome P-450, which increases the metabolism of OCs and other medications. Hypothetically, other antibiotics may decrease the gut flora that is needed to further degrade the inactive metabolites of OCs during enterohepatic recirculation and to lower the circulating hormone levels. This hypothesis has not been substantiated in the clinical setting.

The dermatology literature includes reports of evaluations of the risk of pregnancy in women receiving both antibiotics and OCs. Of 281 women surveyed to determine the incidence of pregnancy during use of oral antibiotics and OCs for acne, 34 women used antibiotics and low-estrogen OCs for a combined total of 71 years.[3] The overall pregnancy rate was 1.4%,[3] whereas the typical OC failure rate is 5%.[4]

Case Report

A 23-year-old woman presented with diffuse inflammatory acne on the lower face, jawline, and neck. The acne was worse at presentation than it had been when the patient was in her teens. She had been treated with minocycline for 3 months during her teens, with some improvement. She was not pregnant and was not planning to become pregnant.

The patient's medical history revealed that she had no limitations to OC use—she did not smoke and did not have a history of breast cancer, hypertension, diabetes mellitus, heart disease, stroke, or migraine. A measurement of her blood pressure level confirmed a lack of hypertension.

The next step was to target treatment to the 4 pathogenic factors involved in acne. A once-daily topical retinoid was added to the patient's therapeutic regimen to treat the follicular epithelial hyperproliferation. The patient was already taking minocycline, which was continued in order to eliminate *P acnes*. An OC was added because the patient desired contraception and in order to reduce excess sebum production; however, it is important in such cases to continue the minocycline until the OC takes effect (at which time the minocycline can be discontinued). A benzoyl peroxide product also was prescribed to minimize the development of bacterial resistance.

The prescribed therapeutic regimen treated the follicular plugging (retinoid), inflammation (minocycline, topical retinoid), *P acnes* (minocycline, benzoyl peroxide), and excess sebum production (OC). The patient then was counseled regarding the use and safety of each prescribed product. She also was reminded that her acne would improve (40%−50%) only after 8 weeks of treatment and would diminish further only after 3 to 4 months of combination therapy.

Patient Instruction and Follow-up

Patients should be urged to read the OC package insert because adhering to the proper therapeutic regimen is essential. Treatment with OCs can be initiated in several ways. Patients may take the first active pill on the Sunday of their next menses or within the first 24 hours of their next menses. The OC also can be started on the day of the initial visit, but only if the result of a pregnancy test is negative. A follow-up visit should be scheduled at 6 to 8 weeks, by which time the regimen should have cleared 50% of the acne. If the patient is tolerating the medications well, she should be reminded that it is still too early to see more substantial improvement in her acne.

Patients should return for a second follow-up visit after another 6 to 8 weeks. At this time, the acne should be 80% improved because the OC will have begun to take effect (do not assume the OC is monotherapy for acne because it is not—the acne should be 80% better because of the combination therapy). At this time, the minocycline should be stopped, but the topical retinoid, benzoyl peroxide, and OC should be continued. The patient should be advised to schedule a well-woman examination with her gynecologist or primary care provider, and a return visit should be scheduled in 3 months.

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Improving Outcomes Through Collaboration

Chair: Diane M. Thiboutot, MD

Julie C. Harper, MD; Katharine O'Connell, MD, MPH; Phoebe Rich, MD; Steven J. Sondheimer, MD

A roundtable was convened to examine the issues surrounding the use of hormonal therapy in the treatment of acne. Obstetrician-gynecologists (OB/GYNs) and dermatologists often have varying views with regard to the use of oral contraceptives (OCs) and other agents in patients with acne. If polycystic ovary syndrome (PCOS), the most common hormonal cause of acne, has been diagnosed, the use of OCs is not usually disputed. Hormonal evaluation is recommended for certain conditions such as virilization. Although PCOS is often the source of the problem, it is important to rule out a testosterone-producing tumor or an adrenal tumor. It was determined, however, that the perception that OCs cause cervical and breast cancer persists among some dermatologists. Even in women with a family history of breast cancer, OCs do not increase the risk. Nor is cervical cancer related to OC use; rather, it results from human papillomavirus. Thus, patients should be assured that OCs will not increase their risk for either of these cancers. Female patients should be advised to see their gynecologists annually for breast and pelvic examinations and to discuss their concerns surrounding the use of OCs.

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SONDHEIMER: Do dermatologists routinely determine androgen levels before treating a patient with hormonal medication for acne?

THIBOUTOT: If there is reason to suspect that something besides acne is going on, especially in the presence of virilizing signs, hair loss, or severe hirsutism, then obtaining baseline levels may be useful in ruling out a more serious condition, such as a testosterone-secreting tumor.

SONDHEIMER: Of course, another consideration is age at onset of acne. If a woman in her 30s comes in with severe acne or acne that has been treatment resistant, we may conduct an initial screening to rule out a more serious problem. Few conditions would lead a physician to obtain androgen levels, except, as you mentioned, an androgen-producing tumor. As a reproductive endocrinologist for 20 years, I have seen only 2 or 3 cases in menopausal women. It is a rare event, and it is usually suspected on the basis of severity of symptoms. The most common hormonal cause of acne is polycystic ovary syndrome (PCOS). But is measuring androgen levels really that helpful? A diagnosis of PCOS can be made on the basis of a history of irregular periods from menarche and increased facial hair and acne. In this case, the cause—PCOS—is very clear.

HARPER: What is your treatment of choice for PCOS?

O'CONNELL: My choice is an oral contraceptive (OC).

HARPER: I agree with that answer. For a woman who does not want to become pregnant, OCs are fine. But if you have a patient who wants to become pregnant, it is more complicated. Or, what do you do for the woman whose periods are not regular? When do you check hormone levels? How do you make sure that the hormone levels at any single given time will be meaningful?

SONDHEIMER: If someone comes in with irregular or missed periods, the first test to conduct is a pregnancy test. Sexually active women engaged in heterosexual intercourse, with irregular periods, can and do get pregnant.

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There are only 2 common categories of irregular periods. One is PCOS, which is probably the most common, and it is usually diagnosed by the history and confirmed by a mildly elevated testosterone level and inconsistently by an increased luteinizing hormone to follicle-stimulating hormone ratio. However, if it looks like PCOS, it probably is PCOS.

The other major cause of irregular periods—though dermatologists do not deal with it as much—is hypothalamic in etiology. Most patients in this category are hypoestrogenic and, in my experience, tend to not have acne. These patients include runners, anorexics, women under a lot of stress, and women who are underweight. PCOS is still the most common cause of irregular periods.

When a woman wants to become pregnant, all her options should be reviewed. She may need to discontinue acne therapy and use milder over-the-counter products during pregnancy and during the time leading up to pregnancy.

O'CONNELL: In addition, as much as we would like to have completely definitive hormone levels to support each diagnosis, including PCOS, they do not yet exist. A pelvic ultrasound, of course, may not be that helpful unless the classic "pearl necklace" appearance of the ovary is noted.

SONDHEIMER: The point is that young women have many ovarian follicles, including antral follicles and early antral follicles, and women with any of these other conditions will have the same. Consequently, the ultrasound pictures, in young women particularly, may all look the same and not provide much useful information.

HARPER: If a woman comes into my office and is already taking an OC but still has signs of hirsutism, I sometimes check hormone levels. How long should I wait between stopping an OC and checking the hormones?

O'CONNELL: If the patient is still having signs of hirsutism, do not stop the OC. My guess is that if she comes off the OC, she will have increased hirsutism as well as elevated androgen levels. OCs will suppress gonadotropin levels, but if symptoms persist, testosterone levels may not be suppressed to the point of stopping unwanted hair growth.

SONDHEIMER: And if in those select patients you do ultimately decide to stop the OC, a month is probably sufficient—at least one cycle. Virilization (including male-pattern baldness and clitoromegaly) always requires hormone evaluation. Although most often PCOS is the culprit, there is always the chance that a tumor is present; this is a time to really look for a testosterone-producing tumor or an adrenal tumor.

Gynecologic Examinations

HARPER: The perception that persists among dermatology patients is that OCs cause cervical cancer and breast cancer and that this risk is why they need to have breast and pelvic examinations. So anything you can do or say to dispel these fears or to put them into perspective would be helpful.

SONDHEIMER: It is very important to assure women that OCs do not increase the risk for breast cancer, even in women with a family history of breast cancer. Additionally, cervical cancer has been shown to be related to HPV (human papillomavirus) and not to OCs. So a family history of cervical or breast cancer is not a contraindication for OC use. It is important to bear in mind that the reasons for not providing an OC are not going to be discovered on gynecologic examination. You are going to discover them by medical history. A history of deep venous thrombosis or uncontrolled hypertension is a far more important issue.

O'CONNELL: I often tell my patients that the best studies have shown that there is no breast cancer risk, and the best studies have also shown that an OC can still protect you against ovarian and uterine cancers. Even if all the studies are wrong about breast cancer, your likelihood of dying from cancer is much less if you are taking an OC, even if you have a family history of cancer. Given that breast and ovarian cancers can cluster because of the *BRCA* gene, the best thing you can do if you have a family history of breast and ovarian cancers is to go on the pill.

SONDHEIMER: We wish we could say, as we do with endometrial and ovarian cancers, that OCs are protective against breast cancer, because I think there was a time when that was thought to be the case. This turns out not to be true. OCs are not protective against breast cancer, but they do not cause it.

HARPER: In my practice, I prescribe a lot of OCs for acne and usually tell my patients that I do not do pelvic or breast examinations in the office and that I would like them to see their gynecologist once a year while they are on this medication. Am I overworking that?

O'CONNELL: Not at all. Women should see their gynecologists every year. Even with the new guidelines that require Papanicolaou (Pap) testing only every 2 to 3 years, I still encourage all female patients to come in for breast and pelvic examinations and to discuss issues and concerns as they emerge, contraception being one of them. However, I would not withhold the pill from a patient who does not see her gynecologist. It is best not to hold the pill prescription hostage until the next Pap test as a means of getting her to come into the office.

SONDHEIMER: From our perspective, preventing pregnancy is the most important thing. You can still reinforce the message that it is good to go for an annual checkup. But give her the refill nonetheless.

THIBOUTOT: Is testing necessary for pre–sexually active adolescents?

O'CONNELL: In most cases, testing is not needed in this group. In our family planning clinic in New York City, girls come in after they become sexually active, but they have no desire to get on the table and have a Pap test. So that's fine. I forgo the pelvic examination. I'd rather she get birth control from me than not get it.

SONDHEIMER: One question comes up frequently: Are teenagers or young women more likely to engage in risky behavior or have intercourse if they are taking OCs for acne? This appears not to be the case. Risky behavior is more related to alcohol and drug use among youth and is far less related to taking OCs. However, there is something to be said for having young women talk with their doctors. Teenagers should be counseled about sexual activity, contraception, alcohol, drugs, and the impact of making poor decisions. Going to a gynecologist does not necessarily mean having a pelvic examination. It can mean just having a discussion and knowing there is someone to talk with and feel comfortable with. But again, I would not hold the prescription hostage and withhold an OC.

Demographics of Acne

SONDHEIMER: Why are women more likely than men to have acne?

THIBOUTOT: That is the million-dollar question. Acne is more prevalent in women than in men. Acne in adults differs from acne in teenagers in that it is more chronic, low grade, and intermittent, and tender nodules often present under the surface of the skin. It is difficult to say whether older women are more sensitive than younger women to low levels of androgen hormones. On average, women with acne may have higher levels of insulin-like growth factor 1 compared with women without acne.[1]

HARPER: There is always the possibility that it is a function of using facial products. Men do not put cosmetics or creams on their face, whereas women use many facial products, especially as they age. It could also be a function of stress.

Safety and Education

SONDHEIMER: Modern hormonal contraceptives have benefits beyond contraception, so there is no reason not to take them. There is evidence that it is better for women to use them than not to use them—especially women with a family history of ovarian cancer, women with premenstrual dysphoric disorder, endometriosis, dysmenorrhea, or acne and women who want reliable birth control.

HARPER: I think it also helps to be able to say that a product is approved for acne by the US Food and Drug Administration (FDA). People become more comfortable and reassured when taking an FDA-approved medication for acne.

THIBOUTOT: On the other hand, it is important to educate patients about correct use of OCs for acne. Some of our patients with acne believe that because they are not using the pills as a contraceptive, it does not matter if they miss taking a few here and there. I explain to them the mechanism by which the hormones help acne, which is by preventing both ovulation and an increase in androgens.

Side Effects

SONDHEIMER: There are 180 million women in the United States, and each has a different perception about what is acceptable regarding side effects. One subgroup believes that irregular bleeding is a sign of ill health, particularly a sign of malignancy, though this is not at all true. I think reassuring patients and telling them that they will have irregular bleeding, that it is not dangerous and not a sign of anything bad, is important. Most of the time, symptoms disappear after 3 cycles. We need to reassure patients that spotting and bleeding are not signs of anything bad.

O'CONNELL: At Columbia University, we conducted a small trial with 76 adolescents who

experienced dysmenorrhea while on the pill.[2] We asked them to describe what they experienced. Among the things they reported were less painful periods, lighter periods, more nausea, less nausea, more headaches, fewer headaches, less acne, and more acne. Whatever happened, they generally attributed to the pill.

SONDHEIMER: I think that is what we have traditionally said, and it makes sense. Most of the progestins are 19-nortestosterone derivatives, so they have some androgenic activity. Even though the dose is low, there may be individual variations in susceptibility to those androgens.

HARPER: Does switching OCs provide a better outcome?

O'CONNELL: Complaints about the side effects of an OC are often comparable to complaints about a placebo. However, when a patient complains about a specific OC, I usually recommend switching to another product.

THIBOUTOT: By 3 months, most side effects such as breakthrough bleeding will have lessened. It usually takes this amount of time to determine if the OC is helping the acne. If, after that time, the patient is still unsatisfied, I switch to another OC to see if there is an actual difference. Maybe it is the hormone in the OC, maybe not.

RICH: Is there a scientific explanation for the rebound acne effect that occurs when some patients discontinue the pill?

SONDHEIMER: Some women develop acne while taking a continuous formulation, and a small percentage of them stop the OC because of the acne. Over time, however, the body's physical contours change—this is unrelated to use of OCs—but the pills can mask those changes.

Someone once asked if there is such a thing as "postpill amenorrhea." Patients sometimes claim, "I was on the pill for 5 years. I stopped the pill, and then my period never returned. The pill probably caused me to stop getting my period." As it turns out, this is not the case. Their amenorrhea was probably related to a lifestyle change, such as becoming a marathon runner while on the pill, or having underlying PCOS. In the latter case, stopping the pill would unmask what was being helped by the OCs. In fact, many women commence OC use to regulate irregular menstrual cycles, and they expect that their cycles will be regular when they stop.

How to Start an Oral Contraceptive

- Administer a urine pregnancy test in your office
- Document a negative result, and the patient may start the pill that day (regardless of where she is in her cycle)[5]
- If the patient is not within 7 days of the start of menses, she should use backup contraception for 1 week
- If bleeding does not begin while she is taking the inactive pills, she should take another pregnancy test

Side Effects of Oral Contraceptives

- Breakthrough bleeding (more common with missed pills; does not imply lower efficacy)
- Other commonly reported side effects include:
  - —Breast tenderness
  - —Headache
  - —Nausea
- Most side effects resolve within several months of use

Summary Points

- Oral contraceptives are a highly effective method of contraception for most patients
- Noncontraceptive health benefits include decreases in:
  - —Acne
  - —Anemia
  - —Benign breast cysts
  - —Dysmenorrhea
  - —Hirsutism
  - —Ovarian cysts
- Additional health benefits include:
  - —Protection against endometrial cancer
  - —Protection against ovarian cancer
  - —Regular and lighter bleeding
- Contraindications to combined oral contraceptives include:
  - —Breast cancer (personal history)
  - —Cerebrovascular accident (history or high risk)
  - —Deep venous thrombosis (history or high risk)
  - —Gallbladder disease
  - —Heart disease
  - —Hypertension or diabetes mellitus with vascular changes (history)
  - —Liver disease
  - —Migraine with aura
  - —Pulmonary embolism (history or high risk)
  - —Smoking (especially in patients age >35 y)

RICH: In some patients, acne worsens with OC use, but the acne may have been even worse had they not taken an OC.

THIBOUTOT: For the patients in whom acne persists, I usually do hormone screening.

HARPER: The acne that seems to occur in older women is more nodular than comedonal. And that is more difficult to treat.

Managing Patients With Diabetes Mellitus

SONDHEIMER: In the young patient with type 1 diabetes mellitus, an OC may change insulin requirements, but there is no evidence that it will increase her risk of vascular and arterial events. As a woman with diabetes gets older, however, her risk increases because the main long-term risks of diabetes are vascular and arterial. Clearly, when a young patient with diabetes is being prescribed OCs, she should be urged to discuss this intervention with her endocrinologist.

HARPER: I think it's important for the dermatologist to know if there are issues related to changes in the insulin requirement. I'm not at all comfortable dealing with these issues, so if a young patient with diabetes and acne comes in, I definitely send her back to her endocrinologist to discuss the OC issue.

SONDHEIMER: I think dermatologists will discover how comfortable most gynecologists are in prescribing OCs to young women with diabetes.

Managing Patients With Migraine

O'CONNELL: Many young patients with acne have a history of migraine. One thing relatively new to OB/GYNs who prescribe OCs is that migraines alone are not a contraindication—it is migraines with aura that preclude OC use. However, trying to get a history of aura may not be that simple. It's a question of the neurologic symptoms that occur before the pain actually starts, not just photophobia. And it is important to determine if the patient is actually seeing flashes of light and wavy lines or experiencing auditory sensations. These symptoms resolve before the headache begins and comprise the classic aura. If you're having difficulty establishing a history of aura in a patient with a history of migraine, it may be worth referring her to an internist or a neurologist to get clearance for OC use. It's migraine with aura that puts the patient at increased risk for stroke with or without an OC, but the OC compounds the risk.

Headaches that occur just before the menses are known as menstrual migraines. With modern OCs, some patients find that they have fewer headaches. Patients who use a calendar to document their headaches, including their frequency and severity, usually find that their headaches become less frequent after starting OCs.

THIBOUTOT: That is true. It does help when patients document their headaches and other problems. Having the documentation facilitates getting another opinion from their OB/GYN or neurologist, when necessary.

Mood and Libido

SONDHEIMER: What about the mood and libido alterations associated with OCs?

O'CONNELL: In the same way that patients complain about headaches and nausea, they also report mood changes while taking OCs or placebo. Of course, mood changes and libido may improve when a patient is taking an OC and is in a contented healthy relationship. If the relationship is not good, things may head in the opposite direction. There are no data that the pill causes mood or libido shifts in either direction. Overall, the pill does not affect mood or libido.

RICH: To what extent are androgens helpful for libido? Can testosterone increase libido?

O'CONNELL: This is controversial. Testosterone levels vary widely over the course of a month. Even women with androgenic signs of acne or hirsutism can have normal testosterone levels. Some data suggest that use of testosterone may improve libido in some women, especially older women who have had surgical menopause.

SONDHEIMER: I think it is very unlikely that androgens play a major role in a woman's libido and orgasm, because there are many psychosocial and health-related factors affecting how a woman feels sexually. Given its multifactorial nature, the issue has not been studied much.

O'CONNELL: You can't discount the number of messages that women receive about OCs—from partners, friends, and mothers. The media also have a considerable influence on perceptions of OCs and their safety. When premenstrual dysphoric disorder improved in women who were given ethinyl estradiol 20 μg/drospirenone 3 mg (Yaz), this alone should have made the front page of every newspaper, but

we only occasionally see articles about how OC use improves acne. For the most part, we seldom hear about the benefits of OCs.

RICH: That negative press about OCs is what a mother reads and then calls to tell her daughter about, before telling her to stop taking the pills.

O'CONNELL: Right, and the boyfriend is afraid she's going to get fat because she's on the pill. So, the amount of negative messaging takes its toll. Consequently, when anything negative happens to a woman who is taking the pill, she automatically blames the pill.

Weight Gain and OCs

O'CONNELL: Some women complain about gaining weight while on the pill. Weight changes usually occur over a long time. In fact, most women gain weight over time. Does the pill make that happen? No, the cause is usually lifestyle. The evidence behind all this was provided in a review by Gallo et al.[3] The several randomized trials examining weight gain with OCs or the patch showed little if any connection. As part of my thesis, I reviewed all observational studies demonstrating a similar potential of the pill to make women lose or gain weight. The real culprits are eating and not exercising—it is not routinely the pill.

SONDHEIMER: I have done a lot of research on premenstrual syndrome, particularly with regard to bloating. This of course does not manifest as actual weight gain, but I think that when a woman feels bloated, she becomes more sensitive to whatever weight change she has. Somehow, it becomes more bothersome and noticeable.

We know that progestins have the potential to slow down gastrointestinal motility and make people feel bloated. So even though there is no weight gain, I think there may be degrees of feeling bloated.

Archer[4] studied gastrointestinal motility and changes over the normal menstrual cycle. Of course, some patients also experience water-retention changes related to the effects of progesterone and aldosterone.

RICH: What about breast enlargement and tenderness?

O'CONNELL: There are anecdotal reports, and I have heard women say that their breasts have become a full cup size larger. But breast enlargement, and enlargement in other areas, such as the hips and abdomen, is probably just part of overall weight gain.

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CME TEST

Oral Contraception and Acne

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1. **Though the initiating factor for acne is still unclear, there are a number of pathogenic factors, including:**
   a. Sebum overproduction
   b. Follicular hyperkeratinization
   c. *Propionibacterium acnes* colonization
   d. Inflammation
   e. All of the above

2. **Antibiotic use for the treatment of acne has decreased, due in part to concerns about resistance.**
   a. True
   b. False

3. **The contribution of oral contraceptives to acne treatment is through:**
   a. Increased testosterone production by ovaries, adrenal glands, and peripheral sources
   b. Reduced adrenal production of dehydroepiandrosterone sulfate and androstenedione
   c. Increased 3α-androsterone glucuronide
   d. a & b

4. **Serum markers and clinical outcomes are closely linked across the spectrum of markers; thus, these markers can be utilized to track a patient's clinical course.**
   a. True
   b. False

5. **Good candidates for acne treatment with low-dose oral contraceptives include:**
   a. Women who have acne and want contraception
   b. Men
   c. Women older than 35 who are smokers
   d. a & c

6. **Free testosterone is the primary androgen associated with acne.**
   a. True
   b. False

7. **The most serious risks associated with modern oral contraceptives include:**
   a. Medication interactions
   b. Liver disease
   c. Vascular events
   d. b & c

8. **To date, rifampin is the only antibiotic shown to decrease the effectiveness of oral contraceptives.**
   a. True
   b. False

9. **Individualized patient care for acne will include:**
   a. Patient counseling
   b. Potential combination therapy use
   c. Follow-up patient visits
   d. All of the above

10. **Oral contraceptives should be considered as a first-line treatment option for acne.**
    a. True
    b. False

Oral Contraception and Acne

ANSWER SHEET

Record your answers here by circling the appropriate letter:

1.	a	b	c	d	e	6.	a	b	
2.	a	b				7.	a	b	c	d
3.	a	b	c	d		8.	a	b	
4.	a	b				9.	a	b	c	d
5.	a	b	c	d		10.	a	b	

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PROGRAM EVALUATION:

Fill in the appropriate circle on each line:

	High				Avg.	Low
How did this compare to other educational events in which you have participated?	❍	❍	❍	❍	❍	
Please evaluate the educational level of this CME activity:	❍	❍	❍	❍	❍	
Please evaluate the educational format for this subject:	❍	❍	❍	❍	❍	
Upon completion of this activity, the degree to which I can better:						
• Describe the female patients most likely to benefit from acne management with such hormonal treatments as oral contraceptives (OCs).	❍	❍	❍	❍	❍	
• Discuss the relationships between sex hormone–binding globulin, androgenicity, and acne.	❍	❍	❍	❍	❍	
• Explain the mechanism of action of OCs in acne management.	❍	❍	❍	❍	❍	
• Recall how to dose OCs for optimal safety and efficacy in acne management.	❍	❍	❍	❍	❍	
• Recognize the need to collaborate with OB/GYNs in promoting adherence among women seeking both acne management and contraceptive protection.	❍	❍	❍	❍	❍	

	High		Avg.		Low
Based on content, how effective was the activity in meeting your expectations and objectives?	❍	❍	❍	❍	❍
Evaluate how relevant this information is to your practice:	❍	❍	❍	❍	❍
The likelihood you will make even small changes in your practice based on the information presented in this activity is:	❍	❍	❍	❍	❍
In terms of delivery of the presentation, please rate the effectiveness of the activity:	❍	❍	❍	❍	❍

Do you believe that the subject matter was presented objectively and with fair balance? ❍ Yes ❍ No

PRACTICAL IMPLICATIONS:

Please list areas you might change in your practice as a result of this activity:

_____

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What other related clinical areas and topics would you like offered as CME activities in the future?

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