Safe and Effective Who Are Expecting...

Innovative interventions are dermatologist- and patient-friendly, safe, and reliably effective.

By Joseph Bikowski, MD

While acne is commonly associated with adolescence, dermatologists recognize that the condition can persist well past the early teen years or emerge—and re-emerge—in adulthood. While managing acne in women may present unique challenges to the clinician, it may also present opportunities to establish safe, convenient, and effective regimens that patients welcome. An interesting context for examining treatment options for this population is to consider therapies specifically for those women who wish to avoid pregnancy and options for those women who are pregnant. Relatively recent pharmaceutical developments allow dermatologists to effectively meet the needs of each subset of patients.

Options for the Non-Pregnant Woman

The role of androgens in the pathogenesis of acne is well documented, with androgen surge implicated in the onset of acne at adolescence. Circulating androgens stimulate the sebaceous glands, resulting in excess sebum production. Along with faulty keratinization, *Propionibacterium acnes* colonization, and associated inflammation, this excess sebum production establishes the milieu for development of the comedones, papules, pustules, and nodules of acne vulgaris. Pharmaceutical development in acne largely has sought to normalize keratinization, decrease inflammation, and/or reduce *P. acnes* levels. In addition to helping to normalize keratinization, isotretinoin diminishes sebum production, diminishes *P. acnes* counts, and diminishes inflammation. Otherwise, no other medication developed specifically for acne management is able to modulate sebum production.[1]

Hormone-modulating and anti-androgenic drugs have been shown to provide benefit in the management of acne, presumably through their influence on the sebaceous glands. Studies doc-

Acne Therapy for Women And Those who Aren't

ument the efficacy of oral contraceptive pills (OCs) and spironolactone either individually or in combination for improving acne.[2,3] In fact, Ortho-Tricyclen (norgestimate/ethinyl estradiol, Ortho) was the first oral contraceptive pill to earn an acne indication. In a randomized trial involving 257 women with moderate acne vulgaris, investigator global assessment ranked 93.7 percent of the OC-treated group as improved at the end of the study compared to 65.4 percent of the placebo group.[4] Treated patients had significant improvement in total comedones, open comedones, closed comedones, papules, pustules, and the subject's self-assessment compared with controls.

American Academy of Dermatology guidelines published last year support the use of estrogen-containing oral contraceptive pills for the management of acne vulgaris based on available evidence.[5] Most recent data seem to favor the use of oral contraceptive formulations containing lower doses of estrogen in the 20-35mcg range.[2] Doses of ethinyl estradiol as low as 20 mcg have been associated with lower incidence of side effects, such as breast tenderness, bloating, and nausea compared to higher-dose estrogen formulations.[6]

Reversing Traditional Reservations

Despite data documenting the efficacy of oral contraceptives in acne management, many dermatologists have been reluctant to prescribe these agents. Much of this reluctance may relate to a common misconception in the medical community that patients must undergo a full gynecologic exam including pelvic exam and Papanicolaou (Pap) smear prior to initiation of OC therapy. Furthermore, there may be some confusion regarding the appropriate time within a woman's menstrual cycle to initiate hormonal therapy.[7]

Guidelines published in 2006 clarify that a Pap smear is not required prior to initiation of hormonal contraceptive therapy.[7] While patients should be encouraged to regularly undergo this cervical cancer screening, it has "minimal bearing on initiating contraception."[7] Assessment of the patient's medical history, including cardiovascular risk factors, concurrent medications, allergies, smoking history, and current and past health problems, as well as height, weight, and blood pressure will determine whether the patient is an appropriate candidate for oral contraceptive therapy.[7]

The practice of initiating oral contraceptives only at the start of menses has been widespread and likely derived from concerns about potential fetal exposure to hormones if a woman does not know she is pregnant upon therapy initiation. However, data show that hormonal exposure poses no risks to the fetus, therefore, therapy may be initiated between menses.[7] Urine pregnancy tests prior to therapy initiation and use of back-up contraception during the first week of hormonal therapy may reassure patients.[7]

Assessing a Newer Option

Recognizing that traditional barriers to the use of oral contraceptives have been removed and that the dermatology community has determined that contraceptive formulations containing low-dose estrogen can safely and effectively manage acne, dermatologists in practice should become familiar with available therapeutic options that may be appropriate for a woman who chooses oral contraception either for contraceptive purposes or for regulation of menses and would additionally benefit from the beneficial effects on acne. A new 20mcg low-dose ethinyl estradiol formulation containing drospirenone (EE/DRSP, Yaz, Bayer Healthcare) is the newest oral contraceptive to receive an acne indication. In fact, the formulation has three indications: for oral contraception, improvement of acne, and management of symptoms of premenstrual dysphoric disorder (PMDD, see sidebar). Its unique formulation makes it a suitable choice for a wide range of women with acne. DRSP is an analog of spironolactone that confers antimineralocorticoid and antiandrogenic activity.[8] The combination of DRSP with ethinyl estradiol has been shown to have similar efficacy and safety compared to other low-dose oral contraceptives and may offer improved tolerability (decreased rates of weight gain, mood changes, acne, and improvement in premenstrual dysphoric disorder).[8]

In double-blind trials, EE/DRSP has been shown to provide 99 percent contraceptive protection over one year, and the agent improved moderate acne over the course of six treatment cycles.[9] Studies found that EE/DRSP is at least as effec-

tive as the combination of ethinyl estradiol and cyproterone acetate (not marketed in the US but available worldwide), with dermatologists, gynecologists, and subjects themselves subjectively rating the improvement of facial acne with treatment as excellent or good.[10]

In a randomized trial, 568 women were treated with EE/DRSP and 586 were treated with norgestimate (NGM)/EE over six treatment cycles.[11] While both treatments provided a similar decrease in inflammatory lesions, EE/DRSP-treated patients had greater reductions in total lesion counts and higher scores for investigators' assessment of therapeutic effect on facial acne. Subjects' assessments were consistent with those of investigators. In a recent, small trial involving 27 women, the addition of spironolactone 100mg/day to EE/DRSP was shown to be effective (85 percent of patients were entirely clear or had excellent results) with no significant side effects or elevations of serum potassium.[12]

In addition to its efficacy against acne, combination EE/DRSP appears safe. The risk of thromboembolism among therapy initiators was low and similar to that for other oral contraceptives.[13] EE/DRSP has the potential to induce potassium retention, leading to hyperkalemia, therefore patients should be monitored when concomitantly using potassium-sparing drugs (including NSAIDs, diuretics, and potassium chloride).[14]

OCPs as a Dermatologic Therapy

Oral contraceptive pills containing estrogen are effective for acne management as demonstrated by various studies and clinical practice. Their use is supported by acne treatment guidelines from the AAD. For a woman with acne who is interested in the use of hormonal therapies for contraception or regulation of menses, the relatively new combination formulation of ethinyl estradiol and drospirenone is a suitable acne therapeutic option that demonstrates superiority over other oral contraceptive formulations marketed in the US and has an improved safety profile compared to older, high-dose estrogen formulations.

Newly published guidelines clarify the level of patient evaluation necessary for initiation of OC therapy; A pelvic exam is not required. Therefore, for the female acne patient

Summary of Guidelines for Initiating Oral Hormonal Contraception[7]

- **To rule out contraindications, assess:**

Thorough medical history, including cardiovascular risk factors, smoking, concurrent medications, allergies, history of thromboemboli.

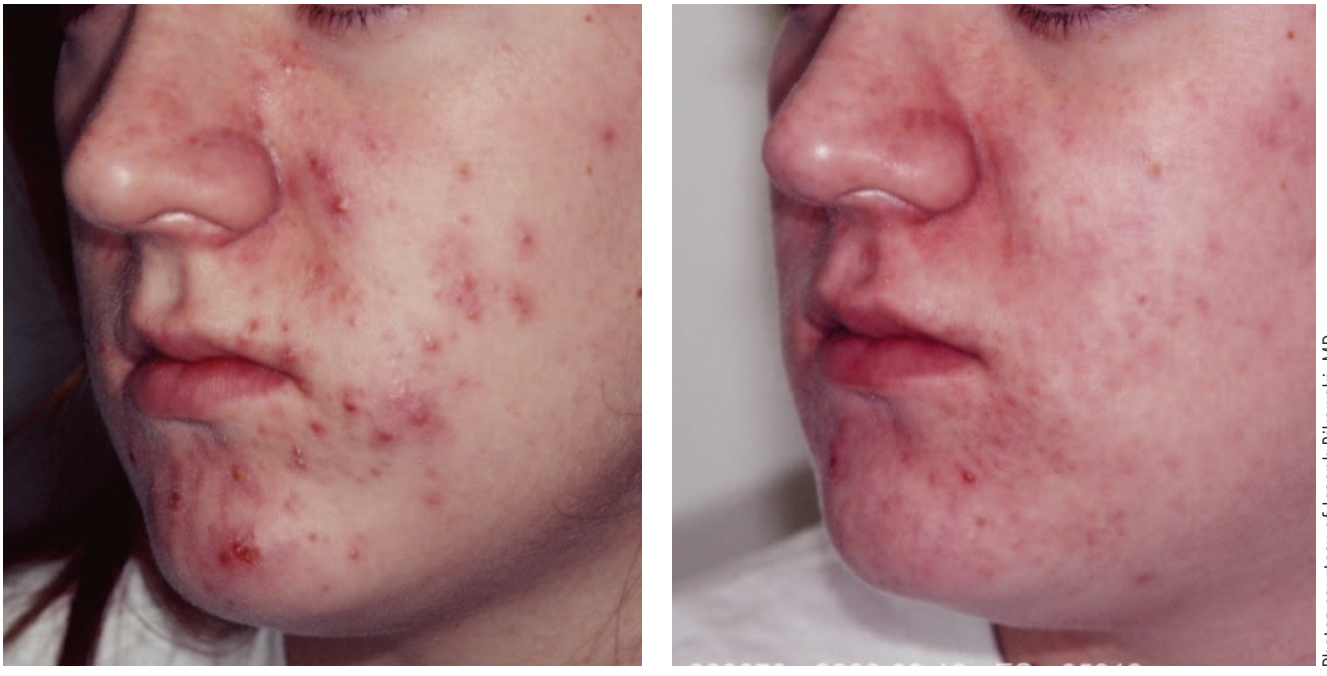
- **Pap smear is not required.** Though it is an important screening tool, initiation or renewal of oral contraception does not increase risk of cervical neoplasia.

- **Immediate initiation of OCs is associated with better compliance and long-term adherence.**

- **Hormonal therapy may be started at any point during menstrual cycle.**
  - If last menstrual period was fewer than five days ago, institute OCs immediately. Patients may be advised to use back-up barrier contraceptive method (such as condoms) for one week, if desired.
  - If last menstrual period was more than five days ago or patient has had unprotected sex, but urine* pregnancy test is negative:
    1. Advise patient that negative urine test is not conclusive but hormonal therapy will not harm fetus.
    2. Patient may institute OCs immediately, if desired. Patients may be advised to use back-up barrier contraceptive method (such as condoms) for one week, if desired. Obtain second test at two weeks.
    3. OR Patient may choose to receive prescription to initiate therapy on first day of menses, if desired.

* Serum pregnancy test is a more reliable testing option that may be considered.

For more information, download "Initiating Hormonal Contraception" from www.aafp.org/afp.



Photos courtesy of Joseph Bikowski, MD

The patient above is shown before (left) and after 12 weeks of twice-daily application of azelaic acid gel 15%.

interested in the use of OCs for their contraceptive effect or regulation of menses, dermatologists can feel comfortable instituting OC therapy for its dual anti-acne and contraceptive activity.

Acne in Pregnancy

Because of individual variability in hormonal changes, skin type, and other factors, the effect of pregnancy on susceptibility to acne is not entirely predictable. It is fairly common for women who previously suffered from acne to have it clear completely on becoming pregnant. But acne during pregnancy is also common, especially during the first trimester, when androgen levels typically increase over pre-pregnancy levels.

Treatment options for acne in pregnancy are limited. Despite recent doubts about their teratogenicity, particularly in the low-estrogen formulations, all OCPs are still classified as pregnancy category X by the FDA and are therefore off limits for use as an acne treatment for pregnant women. The other sebum-reducing agent, isotretinoin, has been well documented to cause severe birth defects in the first trimester. Tetracyline, a category D drug, should not be taken after the 16th week of gestation or during lactation because of its potential for suppressing fetal and neonatal calcification and bone growth. Among commonly prescribed oral antibiotics, clindamycin and erythromycin are considered relatively safe (category B), and may be the only option for treating severe inflammatory acne, though their effectiveness may decrease over time due to antibiotic resistance.

Topical agents are treatment of choice for pregnant women, being less likely to enter the maternal bloodstream in amounts sufficient to harm the fetus. But less potential for harm can also mean less effectiveness. One of the most effective topical agents, the retinoids, are largely avoided, because their effect on the fetus traditionally has been suspected to be similar to if less severe than that of oral

What is PMDD?

Premenstrual dysphoric disorder (PMDD) is a DSM-IV diagnosis. The condition is characterized by markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability; decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating, and weight gain. Symptoms are associated with onset of menses.

— Arch Womens Ment Health (2003) 6:203–209

iPledge, Isotretinoin, and the Dermatologist

Now in its second year, the iPledge program has become a familiar part of daily dermatology practice. Of course, one element of the program is ensuring that female patients of childbearing potential actively employ two forms of birth control. Women of childbearing potential accounted for 45 percent of all iPledge enrollees during the program's first year.

Interestingly, recently released data on the first 12 months of iPledge show that nearly half (49.1 percent) of the women who did not become pregnant (122 pregnancies were exposed to isotretinoin) say that their isotretinoin prescriber referred them to another healthcare provider for birth control counseling. Given the importance of contraception during isotretinoin therapy, dermatologists have a responsibility to at least be familiar with the options available to their female patients. Recognizing that implementation of hormonal therapy does not require a pelvic exam, dermatologists can feel comfortable prescribing oral contraceptives to their female patients who are candidates for isotretinoin. This would be a convenience to patients, may enhance compliance, and could ensure better outcomes with isotretinoin therapy.

It is interesting to note that of the 122 pregnancies reported during the first year of iPledge, 18 percent were in women who chose abstinence as their primary method of pregnancy avoidance, while 72 percent occurred in women who chose oral contraception plus condom use. Failure to use two forms of contraception ranked as the most commonly-cited reason for pregnancy. These findings suggest that:

1. Since the rate of pregnancy was significantly lower with abstinence, we can confidently embrace this method of avoidance for iPledge enrollees who chose to pursue it and can effectively counter any challenges to abstinence, whether from colleagues, program administrators, or outside observers.

2. Lack of compliance with contraceptive measures contributed to contraceptive failure. Anything dermatologists can do to promote compliance and increase convenience of and comfort with hormonal therapy among enrollees who elect to use it may help to limit fetal exposure to isotretinoin.

retinoids. Interestingly, two trials have demonstrated that exposure to topical tretinoin is not associated with negative effects on the fetus.[15,16] One study found no difference in the rate of malformations between exposed and nonexposed pregnancies.[15] In another study, the prevalence of major anomalies among babies born to 215 tretinoin-exposed women was 1.9 percent, lower than the 2.6 percent rate of anomalies among babies born to 430 age-matched nonexposed women.[16] Topical tretinoin and adapalene are rated pregnancy Category C, while topical tazarotene is rated Category X. Though high doses of salicylic acid in its oral form have been associated with birth defects[17] many dermatologists consider topical salicylic acid to be perfectly safe for acne treatment in pregnant women. Benzoyl peroxide, another Category C drug, is likewise avoided by some but freely prescribed by others. Topical erythromycin and clindamycin are at least as safe as their oral counterparts (Category B) but even more prone to bacterial resistance.[18,19]

A Natural, Safe Option for Pregnant Women

Since many medications address only one or two of the four recognized pathogenetic factors in acne—microbial colonization, abnormal keratinization, inflammatory response, and increased sebum production—combinations of therapies that address several factors at once are often considered more effective than monotherapy. The general rule in pregnancy, on the other hand, is to keep the number of prescribed medications to the minimum.

Azelaic acid (AzA) offers a number of attractive features as an acne medication for pregnant women. It is a naturally occurring substance, with no known fetal effects (Category B), that exhibits antimicrobial, anti-inflammatory, and antikeratinizing properties. It lacks only the ability to reduce sebum production. Its approved form for use in acne treatment in the US is the 20% cream formulation. But the 15% gel formulation (Finacea, Intendis), indicated in the US for treatment of rosacea, is approved in many European countries to treat acne.

The polyacrylic-acid-based aqueous gel offers several advantages over the 20% cream formulation, specifically improved drug release and absorption. In in vitro studies, 25.3 percent of the azelaic acid in the gel vehicle penetrated into viable skin as compared with only 3.4 percent in the cream vehicle. The gel is also less acidic: its pH of approximately 4.8 is optimal for maintaining formulation consistency and does not interfere with the skin acid mantle.[20]

Controlled clinical trials in Europe have found AzA 15% gel to be as effective as benzoyl peroxide and topical clin-

damycin in reducing facial papules and pustules and significantly more effective than clindamycin in reducing closed and open comedones (P=0.031).[21] Patient evaluations of efficacy showed similar results for all three drugs, and all were well tolerated.

A one-year European observational study involving 1,243 patients recorded both physician and patient assessment of the effectiveness of AzA 15% gel, both as monotherapy and in combination with other drugs, in relieving acne symptoms. Most of the physicians (81.9 percent) documented symptom improvement after an average 34.6 days of treatment, with 93.9 percent reporting improvement after an average of 73.1 days. Most patients (74 percent) reported themselves as being "very satisfied" with the treatment, in contrast to previous treatments, for which 71 percent rated their satisfaction as 5 or less on a scale of 0 to 10. AzA 15% gel was reported to be well tolerated by 95.7 percent of patients, and 86.5 percent continued to use it as maintenance therapy after the observational period.[21]

AzA is bacteriostatic against *S. epidermidis* and *P. acnes*, produces a marked inhibition of protein synthesis in these pathogens, and unlike oral or topical antibiotics does not appear to promote bacterial resistance.[21] It decreases the generation of reactive oxygen species by neutrophils, suggesting antioxidant and anti-inflammatory effects.[21] Its efficacy has been shown to be comparable to that of erythromycin, benzoyl peroxide, and oral tetracycline in reducing comedonal and papulopustular lesions of acne.[21]

A Proven Option

Studies conducted in Europe have established the general effectiveness of AzA 15% gel as an acne treatment, and it is approved for this use there. When treating a pregnant woman with acne, dermatologists in the US might well consider prescribing twice-daily application of AzA 15% gel off-label as an alternative to other topical treatments. Data support the safety of AzA in pregnant women. A saturated dicarboxylic acid found naturally in wheat, rye, and barley, it is present in foods—including Rice Krispies and Corn Flakes—consumed by women and children everyday.

Its multiple mechanisms of action and effectiveness in treating both papulopustular and comedonal acne, its acceptance by patients, its tolerability and sustained efficacy both alone and in combination with other agents, and its lack of adverse maternal or fetal effects, make AzA a particularly useful addition to the limited range of options available for treating acne in pregnant women. ■

Dr. Bikowski is a consultant and serves on the Speakers Bureau for Ortho-Neutrogena and Intendis. He has relationships with Galderma, Coria, Allergan, and Medicis.

1. Clarke SB, Nelson AM, George RE, Thiboutot DM. Pharmacologic modulation of sebaceous gland activity: mechanisms and clinical applications. Dermatol Clin. 2007 Apr;25(2):137-46

2. Huber J, Walch K. Treating acne with oral contraceptives: use of lower doses. Contraception. 2006 Jan;73(1):23-9.

3. Zouboulis CC, Piquero-Martin J. Update and future of systemic acne treatment. Dermatology. 2003;206(1):37-53.

4. Lucky AW, Henderson TA, Olson WH, Robisch DM, Lebwohl M, Swinyer LJ. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. J Am Acad Dermatol. 1997 Nov;37(5 Pt 1):746-54.

5. Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, Siegfried EC, Thiboutot DM, Van Voorhees AS, Beutner KA, Sieck CK, Bhushan R; American Academy of Dermatology/American Academy of Dermatology Association. Guidelines of care for acne vulgaris management. J Am Acad Dermatol. 2007 Apr;56(4):651-63.

6. Williams JK. Rationale for new oral contraceptive dosing. Int J Fertil Womens Med. 2004 Jan-Feb;49(1):30-5.

7. Lesnewski R, Prine L. Initiating hormonal contraception. Am Fam Physician. 2006 Jul 1;74(1):105-12.

8. Rapkin AJ, Winer SA. Drospirenone: a novel progestin. Expert Opin Pharmacother. 2007 May;8(7):989-99.

9. Fenton C, Wellington K, Moen MD, Robinson DM. Drospirenone/ethinylestradiol 3mg/20microg (24/4 day regimen): a review of its use in contraception, premenstrual dysphoric disorder and moderate acne vulgaris. Drugs. 2007;67(12):1749-65.

10. van Vloten WA, van Haselen CW, van Zuuren EJ, Gerlinger C, Heithecker R. The effect of 2 combined oral Contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. Cutis. 2002 Apr;69(4 Suppl):2-15.

11. Thorneycroft H, Gollnick H, Schellschmidt I. Superiority of a combined contraceptive containing drospirenone to a triphasic preparation containing norgestimate in acne treatment. Cutis. 2004 Aug;74(2):123-30.

12. Krunic A, Ciurea A, Scheman A. Efficacy and tolerance of acne treatment using both spironolactone and a combined contraceptive containing drospirenone. J Am Acad Dermatol. 2008 Jan;58(1):60-2.

13. Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. Obstet Gynecol. 2007 Sep;110(3):587-93.

14. McAdams M, Staffa JA, Dal Pan GJ. The concomitant prescribing of ethinyl estradiol/drospirenone and potentially interacting drugs. Contraception. 2007 Oct;76(4):278-81.

15. Shapiro L, Pastuszak A, Curto G, Koren G. Safety of first-trimester exposure to topical tretinoin: prospective cohort study. Lancet. 1997 Oct 18;350(9085):1143-4.

16. Jick SS, Terris BZ, Jick H. First trimester topical tretinoin and congenital disorders. Lancet. 1993 May 8;341(8854):1181-2.

17. Joschko MA, Dreosti IE, Tulsi RS. The teratogenic effects of salicylic acid on the developing nervous system in rats in vitro. Teratology. 1993 Aug;48(2):105-14.

18. Simonart T, Dramaix M. Treatment of acne with topical antibiotics: lessons from clinical studies. Br J Dermatol. 2005 Aug;153(2):395-403.

19. Ross JI, Snelling AM, Carnegie E, Coates P, Cunliffe WJ, Bettoli V, Tosti G, Katsambas A, Galvan Peréz Del Pulgar JI, Rollman O, Török L, Eady EA, Cove JH. Antibiotic-resistant acne: lessons from Europe. Br J Dermatol. 2003 Mar;148(3):467-78.

20. Draelos ZD. What's in a formulation? Cos Derm. 2003;16:56-58

21. Thiboutot D. J Drugs Dermatol. 2008;7:6-9