Contraception and the dermatologist

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Contraceptives are pertinent to dermatologists in 3 major instances: (1) prescribing combined oral contraceptives for the treatment of acne; (2) ensuring that women being treated with potential teratogens are on adequate contraception; and (3) counseling female patients regarding contraceptives that can worsen acne. Most modern combined oral contraceptives will benefit acne; however, there are some agents that may be more effective than others, primarily because of the progestin used in the agent. Long-acting reversible contraceptives should be first line for women on teratogenic medications, but some of these agents can worsen acne because they release progestins. (J Am Acad Dermatol 2013;68:1022-9.)

Key words: acne; combined oral contraceptives; contraception; depot medroxyprogesterone acetate; etonogestrel implant; intrauterine device; nickel hypersensitivity.

Contraceptive methods are of particular interest to the dermatologist for a variety of reasons. Oral contraceptives are a well-known treatment option for acne and hirsutism, whereas other contraceptive methods, such as medroxyprogesterone acetate (Depo-Provera, Pfizer Inc, New York, NY), implantable etonogestrel (Nexplanon, Merck & Co, Inc, Whitehouse Station, NJ), and the levonorgestrel intrauterine device (IUD) (Mirena, Bayer HealthCare, Montville, NJ) can cause acne to flare. In addition, the dermatologist should be familiar with the various methods of contraception and the side effects, contraindications, and effectiveness of each, especially when prescribing potentially teratogenic medications to women of childbearing age.

Abbreviations used:

COC:	combined oral contraceptive
EE:	ethinyl estradiol
FDA:	Food and Drug Administration
IUD:	intrauterine device
SMART:	system to manage Accutane-related teratogenicity

CONTRACEPTIVE EFFICACY

Half of pregnancies in the United States are unplanned, and more than half of the women with unplanned pregnancies are on contraception at the time of conception.[1] In light of this, there has been a re-examination of contraceptive methods, which are now grouped based on effectiveness rather than type.[1] First-tier contraceptives, including vasectomy, sterilization, IUDs, and subcutaneous implants, are the most effective, easy to use, and have a pregnancy rate of less than 2 per 100 women in the first year of use.[1] By increasing the use of first-tier methods, physicians can decrease the number of unintended pregnancies for women on contraception. A list of currently available contraceptive methods and of the efficacy and tier classification of each is outlined in Table I.[1-3]

The most recent studies on contraception, such as one recently published in the *New England Journal of Medicine*, have highlighted the first-tier long-acting reversible contraceptive methods, such as IUDs and subcutaneous implants, in reducing the number of unintended pregnancies.[4] In addition, a 2002 survey conducted by the Guttmacher Institute showed that the discontinuation rates for short-acting contraceptive methods in the first year was as high as 57% for male condoms, 33% for oral contraceptives, and 44% for injectables (eg, Depo-Provera, Pfizer Inc),[5] which further highlights the need for increased use of first-tier contraceptives.

Contraception is commonly prescribed by dermatologists when initiating therapy with the teratogen isotretinoin. The iPledge program was implemented in 2006 with the goal of reducing fetal exposure to

From the Division of Dermatology, Ohio State University.
Funding sources: None.
Disclosure: Dr Zirwas has acted as a consultant for Smart Practice, Onset, Taro, and Valeant. Dr Tyler has no conflicts of interest to declare.
Accepted for publication November 23, 2012.

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Published online January 21, 2013.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2012.11.018

isotretinoin, but a recent study by Shin et al[6] showed that fetal exposure has not significantly decreased when compared with the previously implemented system to manage Accutane-related teratogenicity (SMART) program. The most common reasons for this failure are patient noncompliance with contraception or contraceptive failure.[6] In fact, a recent study by Steinkellner et al[7] showed that both taking 1 or more category X medications and taking contraception prescribed by a dermatologist were independent risk factors for noncompliance with oral contraception. Given all the recent data, when considering therapy with a potentially teratogenic medication such as oral isotretinoin in a woman of childbearing age who has not undergone sterilization, it is the opinion of the authors that long-acting reversible contraceptive methods should be first line.

CAPSULE SUMMARY

- All combined oral contraceptives treat acne, but some may be more effective because of the particular progestin in the agent. When prescribing oral contraceptives, patients should be screened for contraindications.
- Progestin-only contraceptive methods frequently worsen acne.
- Dermatologists should consider long-acting reversible contraceptives first line for women on teratogenic medications because of high failure rates with other methods.

COMBINED ORAL CONTRACEPTIVES AND ACNE

All combined oral contraceptives (COCs) have the ability to improve acne and hirsutism, although not all have a Food and Drug Administration (FDA)-approved indication to treat these conditions. All COCs suppress luteinizing hormone-driven androgen production and increase sex hormone binding globulin. The result is a decrease in the levels of free androgen, leading to a reduction in excess hair growth and an improvement in acne.[8] Sex hormone binding globulin is produced by the liver and non-oral hormonal methods, such as the vaginal contraceptive ring and the contraceptive patch, bypass the first-pass liver effects that occur with oral ingestion of hormonal agents. This leads to less of an increase in sex hormone binding globulin and subsequently less of an effect on acne and hirsutism.[8]

COCs, by definition, include a combination of a progestin and an estrogen.[9] Older synthetic first-generation progestins, such as the gonane norethindrone, and second-generation estranges, such as levonorgestrel and norgestrel, are derived from progesterone and may activate the androgen receptor, theoretically lessening the beneficial effects of these agents for acne and hirsutism.[10] Desogestrel and norgestimate are newer third-generation gonanes or synthetic progestins that have less activity at the androgen receptor and therefore more benefit in acne and hirsutism.[9] Drospirenone, a fourth-generation progestin and analogue of spironolactone, blocks androgens from binding to the receptor, making it an effective COC for treating acne.[9] For all COCs, however, the effects of the estrogen outweigh the effects of the progesterone, so androgen levels decrease overall.[9] In fact, a recent Cochrane review of 23 trials on the effectiveness of COCs for acne showed that they all reduced noninflammatory and inflammatory facial acne lesions. Some of the trials showed that antiandrogenic progestins such as cyproterone acetate (not available in the United States) and drospirenone were superior, but overall few differences were found between types of COCs.[11]

Despite the fact that all COCs are effective in treating acne, certain COCs have an FDA-approved indication. Ethinyl estradiol (EE) 20/30/35 μg plus norethindrone 1 mg (Estrostep FE, Warner Chilcott, Rockaway, NJ), EE 35 μg plus norgestimate 180/215/250 μg (Ortho Tri-Cylcen, Ortho-McNeil-Janssen, Raritan, NJ), and EE 20 μg plus drospirenone 3 mg (Yaz, Bayer HealthCare) have all been approved for the treatment of moderate acne based on clinical trial evidence.[12]

A multicenter randomized, double-blind, placebo-controlled trial on the effectiveness of EE 35 μg plus norgestimate 180/215/250 μg (Ortho Tri-Cylcen, Ortho-McNeil-Janssen) in treating moderate acne showed a statistically significant mean percent decrease in total lesion count from baseline to cycle 6 of 53.1% (COC) versus 26.8% (placebo).[13] Comparatively, 2 randomized, double-blind, placebo-controlled trials of EE 20 μg plus drospirenone 3 mg (Yaz, Bayer HealthCare) showed statistically significant mean percent decreases in total lesion count from baseline to cycle 6 of 79.9% (COC) versus an unusually high placebo response of 79.8%[14] and 46.3% (COC) versus 30.6% (placebo).[15] Similarly, a multicenter, randomized, double-blind, placebo-controlled trial of 100 μg levonorgestrel/20μg EE (Alesse, Wyeth Ayerst, Madison, NJ) revealed a statistically significant mean percent decrease in total lesion count from baseline to cycle 6 of 39.9% (COC) versus 23.4% (placebo).[16] Finally, pooled data from 2 multicenter placebo-controlled trials of