

## Contraception and its impact on acne

Understanding the effects is imperative for patient satisfaction

by FRANCES E. CASEY, MD, MPH

**C**ounseling patients about contraceptive methods requires shared decision-making. Patients may have concerns about adverse effects from methods or have conditions for which they are hoping certain contraceptive options may offer a noncontraceptive benefit. Acne can be a devastating condition causing anxiety and social isolation and potentially leading to permanent skin scarring. Acne affects 85% of adolescents and young adults aged 12 to 25 years but continues to affect 5% to 12% of the adult female population.<sup>1,2</sup> Understanding the ways contraception will and won't affect this condition is imperative for user satisfaction.

Pilosebaceous units, consisting of a hair shaft, hair follicle, sebaceous gland,

and erector pili muscle, are found in almost all regions of the skin. Inflammatory acne is thought to occur with follicular hyperkeratinization trapping sebum and bacteria, blocking this pilosebaceous unit, leading to a cytokine cascade resulting in recruitment of immune cells furthering development of papules, pustules, and nodules.<sup>3</sup> Noninflammatory acne, trapped dead keratinocytes and sebum, includes open (blackheads) and closed (whiteheads) comedones. Androgen receptors are present in pilosebaceous duct keratinocytes and follicles. Thus, androgens are thought to regulate sebaceous glands and hair growth. Androgens stimulate sebum production along with growth and accumulation of skin cells in the hair follicle.

Androgen production takes place

primarily in the adrenal cortex and ovaries and includes both strong (testosterone) and weaker (androstenedione and dehydroepiandrosterone) types. Peripheral tissues (adipose, muscle, and skin) convert weaker androgens to testosterone. During puberty, the enzymes within the pilosebaceous unit (primarily 5 $\alpha$ -reductase) can convert testosterone precursors to dihydrotestosterone (DHT). DHT, a potent androgen, can then bind to the androgen receptor in target tissues. Transient rises in peptide factors during puberty trigger a chain of events at the activated androgen receptor, leading to an excess production of keratinocytes and sebum.<sup>1</sup> These mechanisms for androgen production can be affected by exogenous hormones.

Medical conditions causing a high



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androgen state, such as polycystic ovarian syndrome (PCOS) or congenital adrenal hyperplasia, can worsen acne. As many as 70% to 80% of PCOS patients experience cutaneous manifestations.<sup>4</sup> However, most patients with acne have normal circulating androgen levels. In these patients, a hypersensitivity of the sebaceous glands to androgens causes an increase in sebum production.

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Acne treatments have primarily relied on topical and systemic antibiotics, spironolactone, and isotretinoin but result in treatment failure in a large percentage of patients. Antibiotics, spironolactone, and retinoid-based therapies carry teratogenic potential. Hormonal therapies allow a wider range of treatment options, less risk to a developing fetus, and a potentially improved adverse effect profile over systemic antibiotics, and are at least equally effective. Combined oral contraceptives (COCs) are a treatment option for all types of acne: noninflammatory (comedones) and inflammatory (papulopustular and nodulocystic).<sup>5</sup> A meta-analysis of close to 5000 patients comparing treatment effectiveness at 6 months showed a 55% lesion reduction with combined hormonal methods, a 52% reduction with systemic antibiotics, and a 29% reduction with placebo.<sup>6</sup>

### Combined hormonal contraceptives

The estrogen component, typically ethinyl estradiol, in a combined hormonal method of contraception drives a reduction in acne through several mechanisms. First, estrogen works directly to decrease both the size of the sebaceous gland and sebum production. Second, estrogen increases liver production of sex hormone binding globulin (SHBG). SHBG binds avidly to dihydrotestosterone and testosterone, reducing the unbound fractions available for binding to androgen receptors. Third, increased levels of estrogen provide feedback at the levels of the anterior pituitary and hypothalamus, decreasing luteinizing hormone (LH) and follicular stimulating hormone (FSH) release and ovarian production of testosterone in turn.

A Cochrane review evaluating 31 randomized controlled trials comparing COCs to other pills, acne treatments, or placebo show that COCs consistently reduced acne lesion counts, severity grades, and self-assessed acne.<sup>7</sup> Authors were not able to determine effectiveness of individual COC types with respect to acne improvement. Three oral contraceptive pills hold US Food and Drug Administration (FDA) approval for acne treatment: norgestimate/ethinyl estradiol (Ortho Tri-Cyclen; Janssen Pharmaceuticals); norethindrone/ethinyl estradiol (Estrostep; Allergan); and drospirenone/ethinyl estradiol (Yaz; Bayer).

A similar systemic effect would be expected with the contraceptive patch and vaginal ring. Even though these methods have not been reviewed extensively with respect to acne reduction, a Cochrane review comparing the vaginal ring or the contraceptive patch to COCs showed that ring users reported less

**Table. Androgenic Activity by Progestin Type<sup>9,10</sup>**

Progestin type	Androgenic activity
Levonorgestrel	High
Norgestrel	High
Norethindrone	Medium
Norethindrone acetate	Medium
Ethinodiol diacetate	Low
Norgestimate	Very low
Desogestrel	Very low
Drospirenone	Anti

acne than COC users.<sup>8</sup>

Progestins have variable intrinsic androgenic activity (**Table**).<sup>9,10</sup> 19-nortestosterone progestins (derived from testosterone) include estranes and gonanes. The ethyl substitution at the 13-carbon position in gonanes confers less androgenic activity. Progestins derived from progesterone include pregnanes and norpregnanes. The absence of a methyl group at the 10-carbon position gives norpregnanes strong progestational activity with no androgenic, estrogenic, or glucocorticoid activity. Drospirenone, an analogue of spironolactone, has antiandrogenic and antiminerlocorticoid activity. Cyproterone acetate, also an antiandrogenic progesterone, is approved for acne treatment in Europe and Canada but not the United States.<sup>11</sup> Clinically, the androgenic activity of progestins in combined oral contraceptives is negligible given the low dose of current formulations.<sup>12</sup> However, a 2016 retrospective review of over 2147 patients at initial consult for acne reported drospirenone-based

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combined contraceptives to be most helpful for acne > norgestimate and desogestrel > levonorgestrel and norethindrone ( $P \leq .035$  for all pairwise comparisons).<sup>13</sup>

### Progesterone methods

Because of comorbid medical conditions, a patient may not be a good candidate for a combination contraceptive method containing estrogen. As the ethinyl estradiol in a combined method is responsible for the increase in SHBG improving acne, a progesterone-only method would not be expected to have this effect. Both estrogen and progesterone, though, lower the levels of adrenocorticotropic hormone inhibiting adrenal androgenesis.<sup>14</sup> In addition, progestins block  $5\alpha$ -reductase activity, the enzyme responsible for testosterone conversion to DHT and decrease testosterone receptor expression and gonadotrophin (FSH, LH) synthesis.<sup>15</sup> Progesterone may have potential to increase sebum production, but this has not been well demonstrated in reproductive-age patients.<sup>16</sup> The degree to which exogenous progestins affect the sebaceous gland have been disputed. Often these reports are based on retrospective reviews and do not account for acne severity at baseline or method change.

### Progestin-only pills

There are no isolated trials evaluating progestin-only pills (POPs) compared with other methods for acne suppression. It would be assumed that a

progestin-only pill would not have the extent of androgen suppression of a combined hormonal contraceptive given the lack of estrogen effect, but progestin types can have varying effects on androgen levels. The progestin-only pill most widely available in the United States, norethindrone, is an estrane derived from testosterone with high-binding affinity for the androgen receptor. In a trial evaluating adverse effects over a year, over half of the users of a POP (levonorgestrel 30 mcg not available in the United States) reported acne at 9 and 12 months compared with COC and copper intrauterine system users.<sup>17</sup> Drospirenone, derived from  $17\alpha$ -spironolactone, with antiandrogenic properties, carries an FDA approval for acne treatment in combined hormonal therapy with ethinyl estradiol and has been shown in a retrospective review to be more beneficial for acne treatment than a norethindrone combined method.<sup>13</sup>

### Depo-Provera

Depot medroxyprogesterone acetate (DMPA) can be given as an intramuscular or subcutaneous injection every 12 to 14 weeks. Because of the suppression of ovarian estradiol production, DMPA primarily causes unscheduled bleeding and amenorrhea. Minor adverse effects of this estrogen reduced state may include hair loss and acne, but these are infrequently reported.<sup>18</sup>

### Contraceptive implants

Contraceptive implants include Jadelle,

(2 rods each containing 75 mg of levonorgestrel for a total of 150 mg) and Nexplanon (a single rod containing 68 mg of etonogestrel, the active metabolite of desogestrel). Acne is the most common skin complaint among contraceptive implant users. Levonorgestrel causes a decrease in SHBG, directly leading to an increase in free testosterone. Even though etonogestrel is less androgenic, acne is among the adverse effects for which etonogestrel implant users discontinue.<sup>19</sup> A 3-year randomized trial assessing adverse effects showed reports of acne to be equivalent between etonogestrel and levonorgestrel implant users but higher compared with copper intrauterine system users.<sup>20</sup> Combined hormonal contraception, sometimes used to decrease unscheduled bleeding in implant users, could be expected to improve acne and could be considered.<sup>21</sup>

### Hormonal intrauterine system

The hormone-releasing intrauterine systems (IUSs) include 52 mg levonorgestrel (LNG) devices, a 19.5-mg LNG device, and a 13.5-LNG device. Circulating plasma levels of levonorgestrel in users of the 52 mg-LNG IUS system are one-half those in contraceptive implant users and 10 times less than those in progestin-only pill users.<sup>22,23</sup> The androgenic activity of LNG may affect some users even though the circulating levels of LNG in IUS users do not suppress SHBG.<sup>24</sup>

Studies have shown some patients

will experience a flare of their acne vulgaris within 1 to 3 months following placement of the LNG IUS.<sup>25,26</sup> However, the rates of combined oral contraceptive discontinuation immediately prior to use of the LNG IUS and a baseline evaluation of acne severity prior to LNG IUS use have not been consistently reported. Because of this, it is difficult to know if this flare is due to the removal of suppressive effects of combined hormonal methods, primarily a decline in SHBG allowing an increase in circulating androgens, or due to the hormones of the LNG IUS itself.

Some studies have reported as high as a 1% removal rate specifically for acne vulgaris among LNG IUS users. Method cessation because of acne concerns is reported to be higher among LNG IUS users compared with users of the copper intrauterine device (IUD) and combined hormonal methods.<sup>13, 27,28</sup>

### Copper intrauterine system

Reports of acne for users of the copper intrauterine system are higher than for users of combined contraceptive methods.<sup>17</sup> This is because of the comparative effect of an estrogen benefit suppressing androgens in combined methods rather than any physiologic effect of the copper IUS contributing to acne. As the copper IUS is nonhormonal, it would not be expected to alter acne.

### Discussion

Acne can have a debilitating effect, causing loss of productivity and social isolation. Combined hormonal methods can be an effective treatment with multiple studies demonstrating lesion reduction.<sup>7</sup> Acne improvement may be a sole indication for combined method use or may be seen as a noncontraceptive benefit in patients seeking pregnancy



prevention. It is likely that the estrogenic component is primarily responsible for driving acne improvement, but it is possible that progestins with less androgenic effects have additional benefit in patients for whom acne is a primary concern.

Method initiation, whether transitioning from no prior method or to a different method, provides an excellent opportunity for patient-centered counseling. A patient transitioning from a combined estrogen and progesterone-based method to a progesterone-only or nonhormonal method may experience an acne flare or worsening over time because of the rapid dissolution of estrogen-based androgen suppression. A recognition of this effect prior to its occurrence may foster a trusting relationship such that a patient feels comfortable seeking additional support for bothersome adverse effects rather than method discontinuation. For patients who are not estrogen candidates and who have concerns regarding acne worsening or development, an evidence-based discussion regarding progesterone-only or nonhormonal methods is appropriate.

Studies have clearly demonstrated a direct correlation between patient-centered counseling and successful contraceptive use and continuation.<sup>29</sup> Patient-centered counseling involves trust building, including an evaluation of a patient's concerns, and an evidence-based response regarding adverse effect correlation to contraceptive method choice. Some studies have demonstrated that patients may doubt a provider's willingness to discuss negative aspects of contraceptive use.<sup>30,31</sup> Other studies have demonstrated provider refusal to honor patient requests for intrauterine device or contraceptive implant removal because of adverse effects.<sup>32</sup> Using open-ended communication encouraging patients to voice concerns, questions, and/or preferences for method choice and honoring method discontinuation when requested can build a trusting relationship and facilitate contraceptive method initiation and continuation. ■

FOR REFERENCES VISIT  
[contemporaryobgyn.net/contraception-acne](http://contemporaryobgyn.net/contraception-acne)

