Hormonal Treatment of Acne and Hidradenitis Suppurativa in Adolescent Patients

Ryan M. Svoboda, MD, MS[a], Nanjiba Nawaz, BA[b], Andrea L. Zaenglein, MD[a,c,*]

KEYWORDS

• Acne • Combined oral contraceptive • Spironolactone • Hormonal therapy • Antiandrogen

KEY POINTS

- Combined oral contraceptives (COCs) are effective in the treatment of adolescent acne in female patients.
- Safe use of COCs requires careful review of medical history for contraindications.
- Consider delaying initiation of COC therapy until 2 years after menarche (or age 14 years) in order to ensure adequate bone acquisition unless clinically indicated.
- Spironolactone is an emerging option for the treatment of adolescent female acne, although data from large, well-controlled trials supporting its efficacy are lacking.
- There is a paucity of data supporting the use of COCs and spironolactone in the treatment of hidradenitis suppurativa, but these agents may be considered adjunctively in combination with other therapies.

INTRODUCTION/HISTORY/DEFINITIONS/BACKGROUND

Hormonal influences play a profound role in maintaining homeostasis of the cutaneous microenvironment, particularly in terms of pilosebaceous unit function.[1,2] In addition to being responsive to hormonal signals released by other organs, such as the adrenal glands and gonads, the pilosebaceous unit has been demonstrated to synthesize androgens both de novo and through metabolism of precursor circulating dehydroepiandrosterone sulfate.[1,3] These cutaneous androgens then play a role in the regulation of sebaceous gland activity by means of an intracrine mechanism.[4]

Beyond being vital to normal cutaneous homeostasis, hormones, particularly androgens, also play a role in the pathogenesis of multiple disorders affecting the pilosebaceous unit, the prototype being acne vulgaris.[5] This is mediated through both increased production of sebum and upregulation of inflammatory cytokines in the local follicular microenvironment.[6] An understanding of the role that androgens play in the pathogenesis of follicular disorders can be leveraged by clinicians treating these conditions. Specifically, hormonal therapy in the form of combined oral contraceptive (COC) pills and the aldosterone receptor antagonist, spironolactone, serves as important therapeutic options for the properly selected patient. This article provides a framework for the use of hormonal therapy for the treatment of dermatologic conditions in the adolescent patient

[a] Penn State/ Hershey Medical Center, Department of Dermatology, 500 University Drive, Hershey, PA 17033, USA; [b] Penn State College of Medicine, 500 University Drive, Hershey, PA 17033, USA; [c] Penn State/ Hershey Medical Center, Departments of Dermatology and Pediatrics, 500 University Drive, Hershey, PA 17033, USA
* Corresponding author. Penn State Milton S. Hershey Medical Center, Department of Dermatology, 500 University Drive, Hershey, PA 17033.
E-mail address: azaenglein@pennstatehealth.psu.edu

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and details important considerations in this specific population.

DISCUSSION

Combined Oral Contraceptive Pills

Mechanism of action

COC are composed of ethinyl estradiol and a variable progestin component. The utility of COC pills in the treatment of acne is achieved through several distinct, but complementary, mechanisms, largely related to the action of the estrogen component. First, COCs exert a negative feedback signal on the hypothalamic-pituitary-gonadal axis, suppressing the production of luteinizing hormone, thereby decreasing endogenous androgen synthesis.[7] Although total serum testosterone is reduced via this mechanism, bioavailable (ie, free) testosterone, which represents the clinically important fraction of total testosterone free to exert its effects on the pilosebaceous unit via binding to the androgen receptor, is further lowered in the setting of COC treatment because of an approximately 4-fold upregulation of sex hormone binding globulin.[8] These mechanisms together lead to an approximately 60% reduction in the levels of circulating free testosterone.[7] Decreased follicular concentrations of free testosterone result in diminished binding to and activation of sebaceous gland androgen receptors, thus reducing sebum production.

The effect of the progestin component of COCs on acne is less well understood. In terms of their function as an active ingredient of COCs, progestins serve to provide a more consistent antiovulatory effect and also prevent adverse effects related to long-term exposure to unopposed estrogen (eg, development of endometrial cancer).[9,10] However, certain progestins also have intrinsic androgenic activity through their ability to cross-react with the androgen receptor and thus could theoretically worsen disorders of the folliculosebaceous unit, such as acne.[11] First generation (estranes), second generation (gonanes), and third generation all are derived from testosterone and thus do have some level of inherent androgenic activity, which could theoretically lead to worsening of acne, although when combined with estrogen derivatives, this has not been a particularly practical concern.[12,13] However, progestin-only methods of contraception have been shown to have a negative effect on acne in some patients.[14] Data do suggest that third-generation progestins have decreased androgenic properties compared with first- and second-generation compounds.[15,16] The novel fourth-generation progestin, drospirenone, is a derivative of spironolactone that demonstrates both antimineralocorticoid and antiandrogenic properties[17]. The results of a comparative in vitro dose-response analysis found that drospirenone and other fourth-generation progestins, nestorone and nomegestrol acetate, have a net antiandrogenic effect and are more similar to natural progesterone than earlier-generation progestins.[18] Currently, 4 COCs are specifically approved by the Food and Drug Administration (FDA) for the treatment of acne. **Table 1** lists select common contraceptives and their components.

Efficacy in acne

Multiple randomized controlled trials (RCTs) have assessed the efficacy of COCs in the treatment of acne. A meta-analysis of 31 trials, accounting for 12,579 patients, found that 9 out of 10 RCTs comparing the efficacy of COCs to a placebo demonstrated a statistically significant improvement in acne in patients treated with COCs.[19] Progestins examined were levonorgestrel, norethindrone acetate, norgestimate, drospirenone, dienogest, and chlormadinone acetate (the latter 2 are not currently available in the United States). Outcomes improved in COC-treated patients included lesion counts (total, inflammatory, and noninflammatory), physician-assessed severity (eg, Investigator Global Assessment), and patient-reported outcomes. Several studies combined in this meta-analysis also directly compared the efficacy of different COC formulations differing in terms of the progestin component. Because of the heterogeneity of the studies and the smaller sample sizes for comparison of the different formulations, definitive conclusions were difficult to draw in terms of comparative effectiveness of different COCs.[19] Despite this, one included study comparing 2 formulations approved by the FDA for the treatment of acne did suggest that the combination of drospirenone/ethinyl estradiol may be more effective than norgestimate/ethinyl estradiol.[20] However, it is difficult to make generalized recommendations for specific formulations in terms of efficacy alone, because of the lack of high-quality comparative data.

A more recent meta-analysis aimed to compare the efficacy of COCs with oral antibiotics in the treatment of acne, given the common use of the latter and the controversies surrounding antibiotic stewardship. This combined study of 32 RCTs found that both COCs and oral antibiotics offered statistically significant reduction in total, inflammatory, and noninflammatory lesion counts compared with placebo after 3 and 6 months of treatment.[21] Patients treated with oral antibiotics

Table 1
Select combined oral contraceptives[68]

Estrogen/Dose(mg)	Progestin/Dose (mg)	Additional Component	Brand[a]	Progestin Generation
Monophasic				
EE/0.02	Drospirenone/3	-	Yaz[b] Yasmin	Fourth
EE/0.03	Desogestrel/0.15		Apri	Second
EE/0.02	Drospirenone/3	Levomefolate, Calcium	Beyaz[b]	Fourth
EE/0.035	Norgestimate/0.25	-	Ortho-Cyclen	Third
EE/0.01	Norethindrone acetate/1	Ferrous fumarate	Lo Loestrin Fe	First
EE/0.02	Norethindrone acetate/1	Ferrous fumarate	Junel FE	First
EE/0.025	Norethindrone acetate/0.8	Ferrous fumarate	Generess FE	First
EE/0.02 0.035 0.03	Norethindrone acetate/1 0.5 1.5	-	Junel 21	First
EE/0.035	Norethindrone acetate/0.5	-	Necon 0.5	First
EE/0.03	Norethindrone acetate/1.5	-	Microgestin 1.5	First
EE/0.02 0.03	Levonorgestrel/0.1 0.15	-	Lessina Aviane Lutera Portia	Second
EE/0.03	Norgestrel/0.3		Low-Ogestrel	Third
EE/0.035	Norgestimate/0.25		Sprintec	Third
Biphasic				
EE/0.035	Norethindrone/0.5/1	-	Necon 10/11	First
EE/0.02/0.01	Desogestrel/0.15/0	-	Kariva	Second
Triphasic				
EE/0.035	Norgestimate/0.18/0.215/0.25	-	Ortho Tri-Cyclen[b] Trinessa	Third
EE/0.025	Norgestimate/0.18/0.215/0.25		Ortho Tri-Cyclen Lo	Third
EE/0.025	Desogestrel/0.1/0.125/0.15	-	Cyclessa	Second
EE/0.035	Norethindrone/0.5/0.75/1	-	Necon 7/7/7	First
EE/0.02/0.03/0.035	Norethindrone 1		Estrostep	First
EE/0.03/0.04/0.03	Levonorgestrel/0.05/0.075/0.125	-	Enpresse	Second
Extended Cycle				
EE/0.03	Levonorgestrel/0.15	-	Jolessa Seasonale	Second
EE/0.03/0.01	Levonorgestrel/0.15/0	-	Seasonique	Second
EE/0.02/0.01	Levonorgestrel/0.1/0	-	LoSeasonique	Second

Abbreviation: EE, ethinyl estradiol.
[a] Numerous generics and brands available; commonly used versions listed.
[b] FDA approved for use in acne vulgaris.

did demonstrate slightly greater reduction in mean inflammatory lesion count at 3 months compared with those treated with COCs (53.2% vs 35.6% reduction), but this comparative benefit was lost by 6 months.[21] Because of the concerns with prolonged antibiotic use for the treatment of acne (eg,

development of antibiotic resistance), the investigators therefore concluded that COCs may be a more appropriate first-line treatment in properly selected female patients who may require long-term therapy.

Efficacy in hidradenitis suppurativa

Hormonal influences also likely play a role in the pathogenesis of hidradenitis suppurativa (HS), as evidenced by variations in disease severity with the menstrual cycle, with up to 44% to 57% of female patients reporting flares during the premenstrual period.[22,23] Similarly, the observations that pregnancy can lead to both remittance and exacerbation of HS activity, and that menopause leads to resolution of symptoms in up to 48% of women, support the notion that sex hormones play a role in the complex pathophysiologic mechanisms underpinning this disease.[24] Despite these observations, however, the evidence supporting the use of COCs in adolescents with HS is mostly anecdotal and has largely been extrapolated from the acne literature.[25] The North American clinical management guidelines for HS, although acknowledging the lack of quality data in this arena, recommend consideration of estrogen-containing combination oral contraceptives in appropriately selected female patients with HS.[26] Based mostly on existing anecdotal data, this expert consensus recommends avoiding contraceptive agents containing progesterone-only because of the potential to worsen the symptoms of HS.

Safety in adolescents—myths and controversies

Several potential adverse effects must be taken into account when considering the use of COCs for the treatment of dermatologic conditions, specifically in the pediatric population. In addition, patients and their parents will occasionally have concerns with initiating treatment, and it is important to elicit these underlying apprehensions and dispel any myths (**Table 2**).

One of the most common misconceptions regarding the use of COCs is that they lead to weight gain. Prior survey studies have found that up to 75% of women believe weight gain to be a side effect of COC use.[27] More concerning, in one study, 68% of respondents reported being counseled by their health care provider on the possibility of weight gain.[28] Despite this common belief of both patients and providers, there is currently a lack of evidence documenting a clear association between COC use and weight gain. In fact, a Cochrane review including 49 trials did not find any evidence to support a major effect on weight in women taking COCs.[29] Because of the fact that only 4 of the included studies involved

Table 2
Combined oral contraceptive pills—myths and controversies

Myth/Controversy	Current Data
"If I start an oral contraceptive pill, I will experience significant weight gain."	• No evidence to support risk of large weight gain in women started on COC therapy[29] • Insufficient data to definitively exclude the possibility of a small change in weight with COC use[29]
"I can't take my doxycycline since I'm on the pill because there is an interaction."	• Rifamycin antibiotics (including rifampin) may reduce the efficacy of COCs because of increased hepatic metabolism of the latter[30] • Nonrifamycin antibiotics (including doxycycline) have not been demonstrated to have an effect on the efficacy or toxicity of COCs[31]
"Oral contraceptives cause cancer."	• COC use has been associated with decreased risk of endometrial and ovarian cancer, with benefits persisting up to 35 y after discontinuation[33,34] • There is a slight increase in incidence of breast and cervical cancer in active COC users, but this risk normalizes 2–5 y after stopping therapy[33,34]
"I smoke cigarettes so I cannot take an oral contraceptive."	• Smoking is an absolute contraindication for COC in patients older than 35 y (≥15 cigarettes per day), but is a precaution in younger patients[69]

the use of either a placebo group or a control group not using contraception, there was insufficient evidence for the investigators to conclude that there is no possibility of a small change in weight with COC use.[29] However, patients should be counseled that there is no strong evidence to support an association with weight gain, and that there more clearly is no significant risk of a large change in weight attributed to the use of COCs. Proper counseling in this regard is imperative to ensure that patient concerns are addressed, in an effort to maximize adherence to the therapeutic regimen.

Another common misunderstanding surrounding the use of COCs is the potential interaction with antibiotics. This is particularly pertinent to consider in patients using hormonal therapy for the treatment of dermatologic conditions, such as acne or HS, as antibiotics often play in important role in the management of these conditions. Although it is commonly thought that antibiotics can reduce the efficacy of hormone-based contraceptives, only rifamycin antibiotics (eg, rifampin and rifabutin), potent inducers of hepatic cytochrome P450 enzymes, have been shown to alter pharmacokinetic outcomes and reduce systemic exposure to the active hormones.[30] Specifically, a systematic review of 29 studies aimed at determining the pharmacokinetic impact of non-rifamycin antibiotics on hormonal contraception did not find any evidence of either decreased efficacy or increased toxicity of either therapy.[31,32] Importantly, two of the studies considered in this review assessed the possible effects of doxycycline in patients on contraception and found none.[31] Because of the clinical significance and importance of these data, the American College of Obstetrics and Gynecology includes these data in their practice bulletin on the use of hormonal contraception in women with coexisting medical conditions.[32]

Because of the hormonal influences on certain cancers of the female reproductive organs, it is not uncommon for adolescent patients or their parents to raise concerns over the potential for an increase in long-term risk of malignancy. However, the existing evidence does not support a link between COC use and an increased long-term risk of cancer. Specifically, the UK Royal College of General Practitioners' Oral Contraception Study, which followed 46,022 women subjects for up to 44 years, found a decrease in the incidence of endometrial (incidence rate ratio 0.66, 99% confidence interval [CI], 0.48–0.89) and ovarian (incidence rate ratio, 0.67; 99% CI, 0.50–0.89) cancer in ever-users compared with never-users of COCs.[33] Although there was a slightly higher incidence of breast and cervical cancers in current and recent users of COCs compared with never-users and those with a remote history of use, the increased risk dissipated after 5 years of discontinuation.[33] A larger study of 256,661 women found similar results, although in this study the slight increase in the odds of developing breast cancer in women treated with COCs (odds ratio, 1.10; 95% CI, 1.03–1.17) was only noted to persist to 2 years out from discontinuation of therapy. Furthermore, the benefit of reduction in endometrial and ovarian cancers was noted to remain statistically significant out to 35 years.[34] Because breast cancer and cervical cancer are not particularly common in the adolescent age group and the slight increase in risk appears to resolve over time, patients can be counseled that use of COCs for the treatment of adolescent acne carries very little tangible risk of malignancy.

Safety in adolescents—considerations

Despite the overall well-tolerated nature of COCs, adverse events do occur, and particular considerations must be taken into account when prescribing these agents for the treatment of dermatologic conditions in adolescents. Common side effects of COCs include headache, nausea, and breast tenderness, although these often resolve with continued use. Intermenstrual bleeding is another commonly reported phenomenon and may possibly be decreased with the use of third-generation progestin-containing formulations, commonly used for acne and HS.[35]

Estrogen is a primary regulator of bone metabolism, and adequate levels of estradiol are required to ensure adequate bone density development during adolescence; if levels are too low, bone resorption results. Although COCs supply exogenous estrogen, mean circulating levels of endogenous estradiol are lower, as the COC prevents the normal midcycle spike in estrogen needed for ovulation. Bone mass acquisition during adolescence is an important predictor of overall bone health as an adult.[36] Therefore, concern has been raised regarding whether the relatively low doses of estrogen in most COC formulations provide for sufficient bone mass acquisition in adolescents.[37] A systematic review sponsored by the National Osteoporosis Foundation found 8 observational studies and no RCT assessing the impact of COCs on bone health in adolescents.[38] Of these, one study of 122 adolescent women revealed that women who were maintained on COCs for more than 2 years demonstrated a trend toward lesser increase in bone mineral density of the lumbar spine compared with those not treated with COCs and those treated for less than 2 years.[39] Another study of 41 COC users and 26

control subjects found that control subjects experienced a significantly greater increase in both bone mineral content and bone mineral density of the lumbar spine over the course of a year.[40] However, the other 6 studies did not reveal a significant difference in bone mass acquisition between COC-treated patients and controls. Overall, the investigators of the National Osteoporosis Foundation study concluded that there is only a low level of evidence (grade D) supporting a negative effect of oral contraceptives on the bone health of adolescent women.[38] An expert consensus statement published in the official journal of the American Academy of Pediatrics does state that owing to concerns regarding bone mass acquisition, consideration can be given to withholding COC use in adolescents until 1 year after the onset of menses (grade C recommendation).[37] Similarly, the American Academy of Dermatology clinical practice guidelines for the treatment of acne recommend avoiding COC use within 2 years of menarche or in patients under the age of 14 years, unless there is a strong clinical indication to start therapy.[12] Additional considerations that may influence the decision to initiate COC therapy include if the patient has heavy or painful menses.

In addition to these overall recommendations, there has been concern regarding the impact of the precise formulation of COCs on bone mass. As bone mass is negatively impacted by lower levels of serum estradiol, low estrogen COC formulations (containing <30 μg ethinyl estradiol), which are associated with lower mean serum estradiol levels than higher estrogen formulations (≥30 μg ethinyl estradiol), may be more detrimental in this regard.[41] Accordingly, data from a large multicenter RCT of more than 1300 adolescents reveal decreased lumbosacral bone mass deposition in subjects randomized to contraception containing 20 μg of ethinyl estradiol compared with those taking a formulation with 30 μg of ethinyl estradiol.[42] Therefore, in terms of reducing risk of future osteopenia, COCs containing 30 μg or more of ethinyl estradiol are preferred.[36]

Venous thromboembolism (VTE) is a potential serious adverse effect of COC treatment and in the past has largely been attributed to the estrogen component of therapy. Indeed, the relative risk of VTE is increased with higher dosages of ethinyl estradiol contained within a COC.[43] For this reason, the concentrations of ethinyl estradiol in commercially available COCs have decreased over time. The contribution of the progestin component of COCs to the risk of VTE has been more hotly debated, although there are data to suggest that formulations containing a third-generation progestin (eg, norgestimate) do portend a slightly higher risk compared with those that include a first- or second-generation agent.[43,44] Furthermore, the second-generation progestin, levonorgestrel, specifically, appears to have the lowest risk of VTE, according to a Cochrane review of 25 publications, although it should be noted that the combination of ethinyl estradiol and levonorgestrel is not currently FDA approved for the treatment of acne in the United States.[45] The results of a more recent meta-analysis suggest that the risk of VTE with fourth-generation (eg, drospirenone) progestin-containing COCs is similar to that of formulations including third-generation progestins, but again, the overall risk was noted to vary only slightly based on progestin class.[46]

The effect of COC use on the risk of arterial thrombosis is less well defined compared with the risk of VTE. The baseline risk of cardiovascular and cerebrovascular insult is relatively low in the adolescent population, and therefore, COC use likely does not lead to a substantial risk of arterial thrombosis in healthy individuals within this group.[47,48] However, a Cochrane review did reveal an overall increase in the risk of myocardial infarction and ischemic stroke in COC users aged 18 to 50 years versus nonusers (Relative Risk, 1.6 and 1.7, respectively).[49] As with the risk of VTE, the incidence of arterial thrombosis does appear directly proportional to the dose of estrogen contained within the COC. However, in contradistinction to the risk of VTE, the incidence of arterial thrombosis does not appear to vary with progestin type.[49] As cigarette smoking, hypertension, and migraine with aura increase the risk of ischemic stroke, COC use for the treatment of acne should be avoided in adolescents with these risk factors.[47] In addition to the risk of ischemic stroke, COC use has also demonstrated an association with a slightly increased risk of hemorrhagic stroke secondary to subarachnoid hemorrhage. This risk is increased in patients taking COCs containing higher concentrations of estrogen and in those with certain comorbidities (ie, current smoking status, hypertension, migraine with aura).[50] Overall, the risk is very low in the adolescent population but must be considered in patients with these coexisting risk factors.

Recommendations

COCs are a valuable option for the treatment of acne in adolescent women and are recommended in the American Academy of Dermatology clinical practice guidelines as an adjunctive treatment consideration for moderate to severe acne (strength of recommendation = A; **Table 3**).[12]

Table 3
Published recommendations for the use of hormonal therapies in the treatment of acne and hidradenitis suppurativa[12,26]

	Acne[a]		Hidradenitis Suppurativa[b]	
Agent	Strength of Recommendation	Level of Evidence	Strength of Recommendation	Level of Evidence
Combined oral contraceptives	A	I	C	II
Spironolactone	B	II	C	III

[a] 2016 American Academy of Dermatology Clinical Practice Guidelines.
[b] 2019 US and Canadian Hidradenitis Suppurativa Foundation Joint Guidelines.

These agents may also be useful in select patients with HS as adjunctive therapy (see **Table 3**). Before initiation, baseline blood pressure should be measured. According to World Health Organization guidelines, COC use is contraindicated in patients with baseline blood pressure ≥160/100 mm Hg and should be initiated cautiously in those with a milder degree of hypertension (140–159/90–99 mm Hg). Other situations in which COC use is not recommended, that may pertain to adolescents, include diabetes with end-organ damage, history of VTE, recent major surgery with prolonged immobilization, history of migraine with focal neurologic deficit (ie, aura), and active viral hepatitis (**Box 1**).[13] It is important to counsel patients that although COCs can be started at any point throughout the menstrual cycle, protection from pregnancy will not be established until after 7 days unless initiated within 5 days of the first day of menses. It is also vital to educate patients that in terms of efficacy, it typically takes approximately 3 months for significant improvement in acne to be seen (and perhaps longer for HS).

Beyond being used for the direct treatment of cutaneous disease, COCs can play an adjunctive role in management as a method of preventing pregnancy in instances where the primary treatment is known to be teratogenic. For example, COCs are often used in adolescent female acne patients being treated with isotretinoin, as the iPledge program requires that all sexually active patients of childbearing potential use 2 forms of birth control. Although it has not been specifically studied, it is mechanistically possible that the addition of a COC to isotretinoin therapy may lead to quicker resolution of acne. It is important to know that estradiol and isotretinoin are both metabolized largely via hepatic cytochrome P450 3A4, and that isotretinoin does lead to a slight potential decrease in plasma concentrations of ethinyl estradiol.[51] Despite this, pharmacodynamic changes have not been noted, but this piece of pharmacokinetic data does suggest the importance of the second method of contraception in patients taking isotretinoin who are heterosexually active.[51]

Box 1
World Health Organization contraindications to combined oral contraceptive therapy

Absolute contraindications
- Current pregnancy
- Current breastfeeding if less than 6 weeks postpartum
- Current breast cancer
- Current smoker (≥15 cigarettes per day) *and* age ≥35 years[a]
- Diabetes greater than 20 years' duration or with end-organ damage
- History of venous thromboembolism
- Hypertension
  - Systolic blood pressure ≥160 mm Hg
  - Diastolic blood pressure ≥100 mm Hg
- Ischemic coronary disease
- Valvular heart disease with complications
- History of stroke
- Migraine with aura (focal neurologic deficit)
- Active viral hepatitis
- Decompensated cirrhosis

Relative contraindications
- Current symptomatic gall bladder disease
- Anticonvulsant therapy
- Migraine without aura *and* age ≥35 years[a]

[a] Not a consideration in adolescent populations.

Similarly, COCs may be helpful as a method of pregnancy prevention in adolescent patients with inflammatory dermatoses who are being treated with other known teratogens, such as methotrexate or mycophenolate mofetil. In cases such as these, the expected benefit of COC use would be solely in terms of birth control.

Spironolactone

Mechanism of action

Spironolactone is a potent mineralocorticoid receptor antagonist that was initially developed as a potassium-sparing diuretic and has played a larger role in the treatment of progressive heart failure and refractory hypertension.[52] In addition to its antimineralocorticoid activity, spironolactone also exhibits antiandrogen effects, through both competitive antagonistic binding to the androgen receptor and decreased testosterone production.[53,54] Furthermore, spironolactone may secondarily inhibit cutaneous 5α-reductase, thus leading to decreased conversion of testosterone to the more potent dihydrotestosterone.[55] Because of these antiandrogenic effects, the use of spironolactone in an "off-label" manner has become commonplace in the treatment of disorders centered on pathology of the pilosebaceous unit.

Efficacy in acne

Several studies have investigated the therapeutic benefit of spironolactone in the treatment of acne. A recent single-center cohort study of 80 adolescent women treated with spironolactone (median dose, 100 mg daily) demonstrated a greater than 50% improvement in acne in 58.8% of subjects, with 22.5% experiencing a complete response.[56] Similarly, a retrospective series of 403 women from a single center revealed a reduction in Comprehensive Acne Severity Scale score in 75.5% of subjects with facial acne treated with spironolactone, although this latter study included only adult women (median age, 26 years).[57] This study did demonstrate similar efficacy of spironolactone in the treatment of truncal acne as well.[57] Despite this, data from large RCT are relatively lacking. A small randomized, double-blind, placebo-controlled crossover study of 21 women did demonstrate a statistically significant improvement in subjective assessment of acne and inflammatory lesion count during treatment with spironolactone.[58] Overall, data supporting the use of spironolactone in the treatment of female acne are promising but not sufficient to draw definitive conclusions, and more studies are needed in this area, particularly in the adolescent population. Despite this, a working group convened by the American Academy of Dermatology, taking into consideration the existing data as well as personal experience and expert opinion, recommends the use of spironolactone in the treatment of acne in select female patients (see **Table 3**).[12]

Efficacy in hidradenitis suppurativa

There are little primary data examining the efficacy of spironolactone in treating this condition. A retrospective study of 20 female patients (including 5 adolescents) demonstrated a reduction in Physician's Global Assessment in 85% of subjects after 3 months of treatment. Of these, 11/20 (55%) achieved complete remission of disease activity. Patients with mild disease were more likely to achieve complete clearance.[59] Overall, the lack of quality data in this arena represents a knowledge gap, and although spironolactone likely represents a low-risk option for women with HS, its use currently receives only a "grade C" recommendation from the North American clinical management guideline working group (see **Table 3**).[26]

Safety in adolescents

Spironolactone has demonstrated an excellent safety record in the long-term treatment of acne. A study of 91 women maintained on spironolactone for a mean of 28.5 months demonstrated no serious adverse effects related to spironolactone over an 8-year follow-up period.[60] This same study did reveal that although side effects are common and dose dependent (occurring in 59% of patients), they only resulted in premature discontinuation of treatment 15% of the time.[60] The most common side effects attributed to spironolactone are slight diuresis and menstrual irregularities, occurring in 29% and 22% of patients, respectively. Menstrual adverse effects are decreased by the concomitant use of COCs, and given the efficacy of the latter in the treatment of acne (and to a lesser degree, HS), the use of these medications together can be an effective strategy.[57] Other common side effects of spironolactone include breast tenderness, breast enlargement, fatigue, headache, and lightheadedness.[60] Importantly, no significant long-term safety concerns were reported in this study, and no patients were diagnosed with breast, ovarian, endometrial, or cervical carcinoma. Because of the largely theoretic risk of undervirilization of the male fetus and the theoretic risk of intrauterine growth retardation, spironolactone is considered FDA pregnancy category C and should be discontinued if pregnancy develops.[61]

Because of the potassium-sparing nature of antimineralocorticoid agents, the potential for the development of hyperkalemia has been a persistent concern of both patients and health care

providers. However, a large study showed no difference in the rate of hyperkalemia in a group of 974 healthy young adult women ages 18 to 45 years (mean age, 27.5 years) prescribed spironolactone for the treatment of acne compared with 1165 healthy control subjects.[62] In addition, studies have not revealed significant hyperkalemia in patients being concomitantly treated with spironolactone and COCs containing the spironolactone analogue, drospirenone.[63] Therefore, in the absence of underlying renal, adrenal, or hepatic disease, routine serum potassium monitoring is not essential for healthy young adult women prescribed spironolactone for the treatment of acne.[62] This recommendation can be extrapolated to healthy adolescents as well.

THE EFFECTS OF OTHER CONTRACEPTIVES ON ACNE AND HIDRADENITIS SUPPURATIVA

A variety of other modalities that contain a hormonal component are used for the purpose of contraception. Because of the varying degrees of the estrogen and progestin components, these agents have varied effects on dermatologic conditions and have been most well studied in acne vulgaris. Although these agents are not usually chosen solely for the indication of treating dermatologic disease, it is important for the clinician to be aware of the possible impact of these other forms of contraception on acne and HS, as multidisciplinary discussion may be required to determine the optimal form of contraception for a given patient. **Table 4** details the effects of alternative forms of hormonal contraception on acne and HS. Further research is needed, particularly in the realm of HS, to better characterize the effects of these alternative forms of contraception on preexisting skin disease.[14,64,65] It is important to emphasize that in individual patients, progesterone-only contraceptives, such as drospirenone, have been self-reported to improve acne and HS, but in a greater proportion of these patients, the net effect appears to be negative.[14,65] Therefore, it is essential to tailor management on a patient-by-patient basis, depending on the possible benefits of a given contraception modality and the severity of preexisting skin disease.

Table 4
Other contraceptive forms and effects on acne and hidradenitis suppurativa[14]

Type	Hormonal Component	Brand[a]	Effect on Acne[14]	Effect on HS[64,65]
Injectable (progestin only)	Depot medroxyprogesterone	Depot-Provera	–	–
Pill (progestin only)	Drospirenone pill Norethindrone pill	Slynd Camila, Errin, Heather, Micronor	N/A[b] –[c]	N/A[b] –[c]
Transdermal contraceptive patch	Norelgestromin and ethinyl estradiol	Xulane, Evra	+[c]	+/–
Combined hormonal vaginal ring	Etonogestrel and ethinyl estradiol	Annovera NuvaRing	+[c]	+/–
Long-acting reversible contraception	Etonogestrel Levonorgestrel	Nexplanon Norplant	– D/C	+/– D/C
Intrauterine device	Levonorgestrel None (copper)	Mirena, Skyla Paragard	– N/A	– N/A

Abbreviations: –, may worsen condition; +, may improve condition; +/–, equivocal effect; D/C, discontinued; N/A, data not available.

[a] Numerous generics and brands available; commonly used versions listed.

[b] Newly approved formulation; package insert lists acne as an adverse event in 3.8% of individuals.[70]

[c] Existing data are not sufficient to draw definitive conclusions; presumed effect based on limited data/extrapolation from data on other contraceptive formulations with similar hormonal components.

New Therapies

Clascoterone 1% cream is a topical androgen receptor inhibitor approved by the FDA in August 2020 for the treatment of acne vulgaris in patients aged 12 and older.[66] Clascoterone is unique in that it will be the first commercially available topical antiandrogen treatment and can safely be used in male patients without significant concern for systemic antiandrogen side effects. Although long-term safety and efficacy data are not yet available, data from phase III clinical trials demonstrate a statistically significant reduction compared with vehicle in inflammatory and noninflammatory lesions from baseline (−19.3 vs −15.5 and −19.4 vs −13.0 for inflammatory and noninflammatory lesions, respectively), in addition to a favorable safety profile.[67] Despite the fact that this trial included patients ranging from age 10 to 58 years, the sample heavily favored the adolescent population (median age, 18). Although postmarket data will be essential, clascoterone cream may be a promising addition to the clinician's arsenal of hormonal agents for the treatment of acne in adolescents.

SUMMARY

Hormonal therapies are increasingly used for the treatment of acne and HS in the adolescent population. COCs have been extensively studied in adolescents with age-specific concerns regarding long-term osteoporosis risk identified. Data on the efficacy of spironolactone in teens with acne and HS are lacking, with support for its use primarily extrapolated from studies in adult women. The safety and efficacy of both COCs and spironolactone in younger adolescent patients need to be further studied.

CLINICS CARE POINTS

- Estrogen-containing combined oral contraceptives are effective in the treatment of adolescent acne in female patients.
- Combined oral contraceptives with estrogen doses of 30 to 35 μg and third- or fourth-generation progestins are recommended for adolescents with acne and hidradenitis suppurativa. Consider delaying initiation of combined oral contraceptive therapy until 2 years after menarche (or age 14), in order to ensure adequate bone mass acquisition.
- Safe use of combined oral contraceptives requires careful review of medical history for contraindications.
- Combined oral contraceptives should be avoided in patients with a history of venous thromboembolism, complicated valvular heart disease (rare among adolescents), and focal neurologic deficit (including migraine with aura).
- Spironolactone appears to be a safe and well-tolerated option for the treatment of adolescent female acne, although data regarding safe use in younger adolescents are particularly lacking.
- There is a paucity of data supporting the use of combined oral contraceptives and spironolactone in the treatment of hidradenitis suppurativa, but these agents may be considered adjunctively in combination with traditional therapies.

DISCLOSURES

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