

Mini-Reviews

Adolescent Female Acne: Etiology and Management

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Abstract. Acne vulgaris, a multifactorial condition often conferring significant psychosocial morbidity, affects an estimated 40 million people in the United States. The majority of these individuals are adolescents and young adults. The pathophysiology of the condition is still not fully known, but it is believed to be related in part to excess sebum production, follicular hyperkeratinization, microbial colonization by *P. acnes*, and inflammation. Prior to initiating treatment in a female patient, a hyperandrogenic state must be considered and ruled out through history, physical exam, and laboratory evaluation if necessary. Treatment options are vast and include hormonal therapy among others. Hormonal therapies have long been noted to reduce acne lesions and offer a valuable adjuvant to standard therapy. Hormonal agents are thought to improve acne by blocking the androgen receptor and/or decreasing circulating androgens which leads to decreased sebum production. Hormonal treatment options include spironolactone, other antiandrogens, and oral contraceptives. The use of these agents to effectively treat acne has been demonstrated in several randomized, placebo-controlled clinical trials. Optimal results are often achieved with combination therapy with the goal of targeting multiple pathogenic pathways in acne development.

Key Words. Acne—Acne vulgaris—Antiandrogen therapy—Drospirenone—Ethinyl estradiol—Levonorgestrel—Norethindrone—Norgestimate—Oral contraceptives—Spironolactone

Introduction

Affecting an estimated 40 to 50 million people in the United States,¹ acne vulgaris is a multifactorial disorder most prevalent in adolescents and young adults. Some reports estimate that as many as 90% of all

teenagers are affected by acne, with virtually 100% of teenagers experiencing some degree of comedone formation.² Acne has transcended historical understanding as a mere nuisance of adolescence to its current perception among dermatologists as a pathological condition often conferring significant psychosocial morbidity. The economic burden of acne to society is unknown, but is postulated to be high.³ As the most common dermatological condition treated in the outpatient setting, management of this condition by non-dermatologists is growing. Left untreated, permanent scarring and psychological morbidity may occur. Treatment options are vast and include topical retinoids, topical and systemic antibiotics, oral isotretinoin, and hormonal treatments for women.

This article discusses the pathophysiologic basis for hormonal manipulation for acne vulgaris in females and reviews the best evidence supporting its efficacy. We provide an overview of existing hormonal agents and offer insight to guide appropriate integration of hormonal therapy into a successful therapeutic regimen.

Pathophysiology of Acne

Acne vulgaris has long been understood as a chronic inflammatory disorder of the pilosebaceous follicles. Characterized by open and closed comedones, papules, pustules, and nodules, the development of acne lesions occurs by a still unclear sequence of pathophysiological events.⁴ The inciting event is believed to be stimulation of the pilosebaceous units by circulating androgens. Sebum production leads to retention hyperkeratosis which blocks and dilates the follicular infundibulum resulting in a formation of a comedone. The follicular plugging, along with bacterial colonization of the follicle by *Propionibacterium acnes*, causes inflammatory mediators to be released into the skin. Inflammatory lesions including papules, pustules, and nodules develop as a result of accumulation of

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neutrophils, lymphocytes, and foreign body giant cells within and around the affected pilosebaceous unit. Acne tends to appear at puberty, coinciding with the increase in sex hormones during this period. Acne patients often present with a variety of lesions in various stages along with post-inflammatory acne scars and hyperpigmentation.⁴ Other potential factors that may contribute to acne development and severity include genetics,⁵ stress,⁶ and exogenous exposure to comedogenic substances including tars, polyvinyl chloride, and medications (corticosteroids, androgens, halogens).⁷ Positive association with acne and milk intake (both whole and skim) in women has been recently noted as well.⁸

Androgens are thought to play a crucial role in the pathogenesis of acne. This notion is supported by clinical observation of acne onset around puberty and flare during menstruation or hyperandrogenic states. Several small studies have shown a statistically significant increase in circulating androgen levels in women with acne compared to appropriate controls (although still within normal limits).^{9,10} The clinical significance of these findings is unknown because the direct relationship between androgen levels and acne severity is yet to be established.

It is important to keep in mind that the majority of female patients with acne will have androgen levels within normal limits and will not have an underlying endocrinopathy. Nonetheless, the possibility of a hyperandrogenic state in female patients with acne in certain clinical settings must be excluded. Suspicion should be high in women with signs of virilization and irregular menses. The most commonly considered endocrinopathies in this setting are polycystic ovary syndrome (PCOS), late-onset adrenal hyperplasia (LOAH), or a virilizing tumor (adrenal or ovarian).

Diagnosis and Workup of Female Acne

Clinical

Acne lesions are frequently distributed on the face, chest, upper back, and upper arms. Lesions include open or closed comedones, papules, pustules, nodules, and scars. Patients frequently present with various lesions in differing stages of formation and resolution. Acne is often graded on a scale from mild-to-moderate inflammation, featuring predominantly comedones, erythematous papules to papulo-pustules, to moderate-to-severe papulo-nodular, nodulo-cystic and scarring inflammatory states. Generally, the diagnosis of acne is straightforward with differential diagnoses including rosacea (which lacks comedones), perioral dermatitis, folliculitis, and drug-induced acneiform eruptions.

In our clinical experience, females who present with varying acneiform lesions along the mandible and chin or “beard area” (Fig. 1) tend to have a type



Fig 1. Mandibular distribution of hormonally influenced acne in a 15-year-old patient.

of acne that typically flares during certain portions of the menstrual cycle and responds to hormonal therapy. These patients are not in a hyperandrogenic state but hormonal manipulation will be beneficial adjunctive therapy. However, in the setting of hirsutism, or increased hair growth in females in male pattern, this clinical presentation of acne is frequently associated with underlying endocrinopathy.

History, together with physical examination of the female patient with acne, determines the need to pursue workup for an underlying endocrinopathy. The history and physical should focus on signs and symptoms of androgen excess, including: menstrual irregularity, infertility, hirsutism, truncal obesity, polycystic ovaries (on sonogram), recalcitrant acne, infrequent menses, female-pattern or the rarer male-pattern alopecia in the female patient, deepening voice, and clitoromegaly. Cutaneous finding of acanthosis nigricans combined with any of above is another marker of probable hormonal abnormalities.⁴ This is referred to as HAIR-AN syndrome (hyperandrogenicity insulin resistance and acanthosis nigricans).⁴ Suspicion of an endocrinopathy should also be higher in patients with type II diabetes mellitus.

History can also elucidate iatrogenic causes of acne. Certain medications can induce or worsen acne, including corticosteroids, bromides, iodides, lithium and vitamin B₁₂.⁷ Use of exogenous androgens that are known to exacerbate acne including depo-provera, anabolic steroids, and progestin-containing intra-uterine devices should be ruled out.¹¹⁻¹³

Laboratory Assays

Guidelines from the American Academy of Dermatology discourage routine endocrinologic evaluation as a screening measure in all acne patients.¹⁴ The majority of patients will have a negative history and exam,

thus requiring no further workup. Endocrinologic testing is indicated in the presence of acne and evidence of androgen excess, or when patients show no abnormal signs and symptoms but have recalcitrant acne when hormonal manipulation is unsuccessful.

Normal total testosterone and dehydroepiandrosterone sulfate (DHEAS) obtained 2 weeks prior to the onset of menses, along with imaging may exclude an androgen secreting tumor of the adrenals or ovaries. DHEAS levels may be normal in late-onset congenital adrenal hyperplasia and highly elevated (> 8000 ng/mL) in adrenal tumors.⁴ Testosterone levels may be high (> 200 ng/dL) in patients with ovarian tumors.⁴ Measurement of leutinizing (LH) and follicular-stimulating hormone (FSH) and free testosterone may add to clinical suspicion of PCOS.⁴ Testosterone levels may be high (150–200 ng/dL) in patients with PCOS with an associated increased LH/FSH ratio (> 3).⁴ LOAH is typically associated with elevation in 17-hydroxyprogesterone.⁴ Sex hormone binding globulin (SHBG) can be measured and is increased with oral contraceptive pills. Hyperprolactinemia is not uncommon in hyperandrogenic patients and must be excluded prior to diagnosis of PCOS.¹⁵ Positive assays, along with clinical suspicion for an endocrinopathy, warrant referral to an endocrinologist or gynecologic endocrinologist.¹⁴

Principles of Successful Acne Treatment

Acne treatment options are vast and include a number of non-hormonal and hormonal therapies. When deciding on the acne treatment regimen, one should take into account individual patient factors including disease state (predominant lesion type and severity), pre-existing medical conditions, desired treatment mode (topical vs. oral), and endocrine history. If the patient reports that acne tends to fluctuate with menstrual cycle and/or physical exam supports hormonal distribution of acne lesions, hormonal therapy in addition to standard non-hormonal options should be considered even if no hyperandrogenic state is suspected or identified. Successful treatment is often achieved by targeting more than one of the known mechanisms involved in the pathogenesis of acne with combination therapy.¹⁶ Patients are typically evaluated on a quarterly basis and regimen is adjusted based on the clinical response.

Non-Hormonal Treatment Options

Non-hormonal acne treatments are often combined with hormonal agents for a synergistic effect. Non-hormonal treatments include topical and systemic retinoids (specifically isotretinoin) as well as topical and systemic antibiotics (usually doxycycline and minocycline). Topical treatments are considered standard of care and form the mainstay of acne treatment.

Studies and our clinical experience have shown that simultaneous use of a topical retinoid with an antibiotic is more effective than either agent alone.^{17–19} Moreover, a combination of benzoyl peroxide with another topical antibiotic is more effective than either medication alone.²⁰ Typically, mild comedonal acne responds well to a combination of a topical retinoid (tretinoin, adapalene, tazarotene) and an antibiotic in a form of a wash or a cream. Systemic antibiotics (doxycycline, minocycline, amoxicillin) are reserved for treatment of moderate-to-severe inflammatory acne. Topical retinoids are usually combined with systemic antibiotics.

Systemic retinoid, isotretinoin, is highly effective in treatment of severe inflammatory, nodulocystic acne. Due to its known teratogenic effects, females of child-bearing potential require two forms of contraception during treatment as well as for 1 month following completion of the treatment with this retinoid. All females prescribed isotretinoin (along with the prescribers of the medication) need to discontinue all tetracycline-based medications and are required by the FDA to register and comply with the iPLEDGE system.

Hormonal Treatment

Spirolactone, a synthetic steroid, acts by blocking peripheral androgen receptors at high doses,²¹ inhibiting the activity of 5α -reductase, and reducing androgen synthesis. In randomized, placebo-controlled trials each examining skin improvement over 12 weeks of therapy, spironolactone was shown to significantly reduce acne inflammatory lesion counts. Therapy was shown to confer both a subjective and objective improvement. Clinical response is dose dependent; maximum response is seen at doses of 100–200 mg/day.^{21,22} Reported side effects of spironolactone therapy include hyperkalemia, breast tenderness, and irregular menses.^{14,22}

Flutamide, a non-steroidal antiandrogen, which prevents androgen action at the tissue level, has been tried in treatment of moderate-to-severe acne in females in hyperandrogenic state (defined as mean levels of unbound testosterone of 11 pmol/l; androstenedione 12 nmol/l and DHEAS 8 μ mol/l) at doses of 250 mg/day.²³ Acne score reductions by 60% were noted in 75% of the patients in this study.²³ However, the potential for hepatotoxicity, which can lead to liver failure, limits this agent's widespread use.¹⁴

Cyproterone acetate (CPA), an antiandrogen, has shown to be effective in treating acne when used in combination with ethinyl estradiol in females in hyperandrogenic state.²³ It appears that both low (2 mg) and high-dose (50 mg) CPA is effective at reducing acne lesion scores by 70–77% in 83–92% of patients.²³ This agent is not approved for use in the U.S. Currently, there is no evidence to support the use of finasteride,

cimetidine, ketoconazole and other therapies with anti-androgenic effects in the treatment of acne.¹⁴

The effectiveness of oral contraceptives (OC) in acne treatment is believed to be mediated by their ability to decrease free testosterone levels by as much as 50% via suppression of luteinizing hormone which normally stimulates androgen synthesis.^{24,25} OCs also increase sex hormone-binding globulin thereby reducing bioavailable testosterone. Furthermore, OCs prevent conversion of free testosterone to dihydrotestosterone by blocking androgen receptors and inhibiting 5-alpha-reductase activity.²⁵ It appears that the progestin portion of the OCs plays a key role in all these events and studies have shown that different progestins produce distinctive effects on SHBG and testosterone.^{24,26} The overall result of these processes is reduced sebum production,²⁵ which, as we discussed in the pathophysiology portion of this review, is felt to be the inciting event in acne formation.

Numerous studies demonstrating the efficacy of oral combinations of estrogen and progestins in treating acne date back to the 1980s. More recently, a number of randomized, placebo-controlled, double-blinded trials have strengthened the evidence for use of hormonal therapies in the treatment of acne vulgaris. These studies have attempted to control for the often large “placebo effect” seen in previous open-label and comparative trials.

Separate placebo-controlled trials of 35 µg ethinyl estradiol/triphasic 180-250 µg norgestimate (Ortho Tri-Cyclen/Tri-Cilest) combination have shown a significant mean decrease in inflammatory lesion counts

of 51–62% compared to placebo arm of 34–38% over the course of six cycles (6 months). Mean total lesion count was reduced by 46–53% vs 26–33% in placebo groups ($P = 0.001$ and $P = 0.0001$, respectively).^{27,28} Free testosterone decreased and SHBG increased significantly in the OC arm while both measures remained unchanged in placebo group.²⁷ Triphasic 20-30-35 µg ethinyl estradiol /1 mg norethindrone (Estrostep) combination, has also been shown to significantly reduce mean inflammatory (50% vs 39% placebo) and total lesion counts (43% vs 31% placebo) over six cycles ($P = 0.0004$ & $P < 0.0001$ respectively).^{29,30}

Similarly, 20µg ethinyl estradiol /100µg levonorgestrel (Alesse/Loette) combination demonstrated significant reduction in both mean inflammatory (46% vs 32% placebo, $P = 0.027$; 31% vs 22% placebo, $P = 0.044$) and total acne lesions (39% vs 23% placebo, $P = 0.004$; 22% vs 9% placebo, $P = 0.017$) when compared to placebo at cycle 6.^{30–32}

Meticulous skin care, physician encouragement, and patient optimism have been theorized to account for the large placebo effect (9–39% reduction from baseline of total or inflammatory lesions in placebo group compared to 22–62% reduction in treatment group) seen in these trials.³⁰ Thus, these factors may be essential components of patient education, along with hormonal and non-hormonal therapies, when counseling patients about acne treatment. Most recently, Drospirenone, a novel progesterone with antiandrogenic and antimineralocorticoid properties, has emerged as a novel progestin that when combined

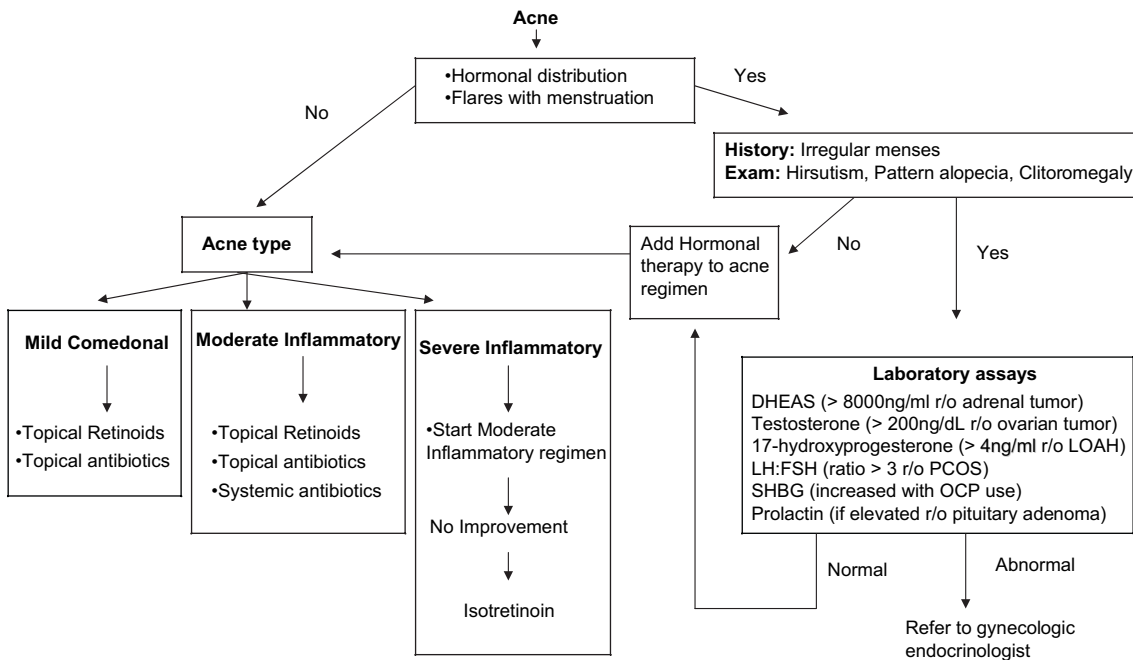


Fig 2. Diagnostic and treatment algorithm for adolescent female acne.

with ethinyl estradiol is effective as an oral contraceptive.³³ A randomized, double-blind, head-to-head comparison trial of 30µg ethinyl estradiol/3 mg drospirenone (Yasmin) vs 35 µg ethinyl estradiol/triphasic 180–250 µg norgestimate (Ortho Tri-Cyclen) showed that Yasmin was significantly superior to Ortho Tri-Cyclen in total acne lesion reduction ($P = 0.020$). The two combinations were comparable as to their decreases in inflammatory lesion counts as well as elevation in SHBG and depression in androgen levels.³⁴ A new formulation of drospirenone with lower ethinyl estradiol levels (Yaz 20 µg vs Yasmin 30µg) has been FDA approved in January 2007 for moderate acne treatment. At this time, the actual data from clinical trials of Yaz in acne has not been published.

In summary, several OC formulations, including Ortho Tri-Cyclen, Estrostep and Yaz, have been FDA approved for acne treatment. All of these formulations have been shown to be effective in acne treatment with expected improvement ranging from 40% to over 60%. There is some evidence that formulations containing drospirenone (Yasmin and Yaz) may be most effective in acne but more head-to-head comparison trials are needed.

In our practice we tend to prescribe Ortho Tri-Cyclen, Yaz, or Yasmin as first line hormonal treatments for acne. Prospective randomized studies comparing OCs vs spironolactone vs OCs and spironolactone combination are lacking but there is some evidence that combination therapy is well tolerated with favorable outcomes.³⁵ We usually add spironolactone or start it as a second line treatment alone or in combination with OCs. Some authors encourage the use of spironolactone in combination with OCs to minimize the risk of pregnancy while on spironolactone which can cause feminization of a male fetus.³⁶

Reported side effects of OC therapy include nausea, vomiting, breakthrough bleeding, weight gain, and breast tenderness. More serious complications are infrequent. These include hypertension, thrombophlebitis, and thromboembolic disease. Use of low-dose ethinyl estradiol formulations (20 µg vs 35µg) significantly decreases nausea, bloating, and breast tenderness.³⁷ Patients with contraindication to estrogen therapy including those with history of thromboembolism, coronary artery disease and breast cancer should not be prescribed OCs.³⁸ All patients should be counseled against smoking because that increases OC-related morbidity and mortality.³⁹

The decision to include hormonal therapy in treatment involves the consideration of key factors including the disease state (predominant lesion type, severity, distribution), pre-existing medical conditions (ie PCOS, LOAH), desired treatment mode (topical vs. oral), desire for contraception, and potential compliance when deciding on a therapy. The ideal

candidate for hormonal therapy is a young woman with moderate acne already using one or more topical anti-acne agents who desires birth control. Hormonal therapy generally requires 3–6 months of treatment for visible results.

Conclusions

The use of hormonal agents to prevent and reduce acne lesions is supported by several randomized, placebo-controlled, double-blinded trials. Hormonal agents should be used as a component of combination therapy involving two or more anti-acne agents for treatment in properly selected patients for optimal results (Fig. 2). Choice of hormonal agents should be guided by principles of efficacy and safety. Factors such as acne severity, agent side effect profile, and patient preference can direct selection of specific agents.

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