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Hormonal Therapy for Acne

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Acne affects more than 40 million people, of which more than half are women older than 25 years of age. These women frequently fail traditional therapy and have high relapse rates even after isotretinoin. Recent advances in research have helped to delineate the important role hormones play in the pathogenesis of acne. Androgens such as dihydrotestosterone and testosterone, the adrenal precursor dehydroepiandrosterone sulfate, estrogens, growth hormone, and insulin-like growth factors may all contribute to the development of acne. Hormonal therapy remains an important part of the arsenal of acne treatments available to the clinician. Women dealing with acne, even those without increased serum androgens, may benefit from hormonal treatments. The mainstays of hormonal therapy include oral contraceptives and antiandrogens such as spironolactone, cyproterone acetate, or flutamide. In this article, we discuss the effects of hormones on the pathogenesis of acne, evaluation of women with suspected endocrine abnormalities, and the myriad of treatment options available.

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Acne is a common condition, affecting 40 to 50 million people in the United States each year. Although acne is thought to affect mainly adolescents, a significant number of adults continue to struggle with acne or develop new-onset acne after the teenage years, with women being affected more frequently than men.¹ Treatment failures with traditional acne therapies are common in women. As many as 81% of women report failures with systemic antibiotics, and failures with isotretinoin range from 15% to 30%.^{2,3} Although there is still much to learn, research continues to delineate the important role of hormones in the pathogenesis of acne. This translates clinically into new therapies or the addition of hormonal therapies to traditional acne therapies that can greatly enhance the efficacy of treatment and patient satisfaction in selected women. Our goal in this article is to discuss the hormonal influence on the pathogenesis of acne, the clinical evaluation of a patient with suspected hormonal acne, and the available therapeutic options.

Acne is a disease of the pilosebaceous unit with a complex pathophysiology. Four main pathogenic factors are known to lead to the development of acne: (1) follicular epidermal hyperproliferation; (2) excess sebum production; (3) inflammation; and (4) the presence and activity of *Propionibacterium acnes*. With the onset of puberty, androgen-mediated stimulation of the sebaceous gland results in increased sebum pro-

duction. Follicular hyperkeratinization and increased keratinocyte adhesion subsequently result in follicular plugging and comedone formation. These events combine to create an environment favorable to colonization by the Gram-positive bacteria *Propionibacterium acnes*, which subsequently secretes various inflammatory mediators and chemotactic factors that initiate and propagate the inflammatory response. Hormones have been suggested to play a role in the follicular hyperkeratinization seen in follicles affected with acne⁴ but are best known for their effect on the sebaceous gland.

Androgens

Sebaceous glands are found all over the human body, with the exception of the palms and soles, and are most numerous on the scalp and the face. Together with the hair follicles, they comprise the pilosebaceous unit. During the first 6 months to 1 year of life sebum production is high but then remains quiescent until puberty, when sebaceous activity increases dramatically. Clinical and experimental evidence confirm the importance of androgens in sebaceous gland function. In women, it is well known that a hyperandrogenic states, such as polycystic ovarian syndrome (PCOS), can be associated with acne as well as hirsutism and female pattern hair loss. One recent study reported 63% of women have a 25% premenstrual increase in the number of inflammatory acne lesions.⁵ Although most women with acne have plasma androgen levels within the normal range, their levels are significantly increased compared with those women without acne.⁶ Other studies have shown that the onset of acne in the

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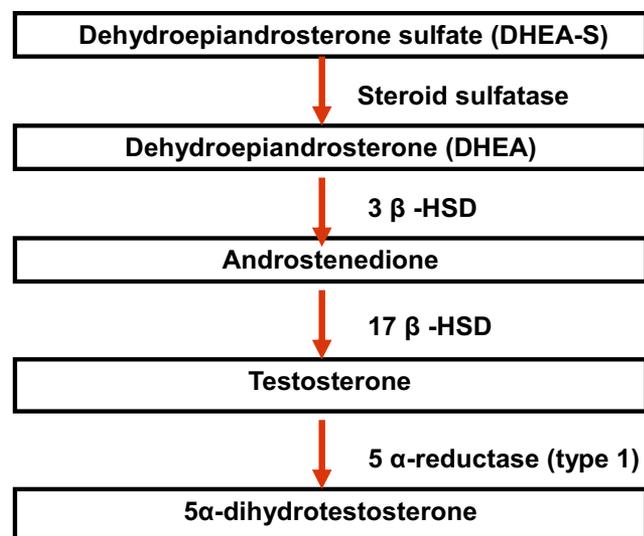


Figure 1 Steroid hormone metabolism in the sebaceous gland.

prepubertal period is associated with increased levels of dehydroepiandrosterone sulfate (DHEAS).^{7,8}

Many patients report that their acne flares during periods of stress. Although objective data are limited, stress is known to increase the output of adrenal steroids, which may affect the sebaceous gland. It has been shown that patients with acne have a greater increase in urinary glucocorticoid levels after corticotropin administration.

A majority of circulating androgens are produced by the zona reticularis of the adrenal gland and the gonads, but can also be produced within the sebaceous gland from DHEAS, an adrenal precursor hormone (Fig. 1). Functional androgen receptors are also required for sebum production because those men without functional androgen receptors do not develop acne.⁹ Androgen receptors are expressed in the basal layer of sebaceous glands and in the outer root sheath keratinocytes of the hair follicle.^{10,11} Three predominant isozymes of steroid metabolizing enzymes are expressed in sebaceous glands: (1) 3β -hydroxysteroid dehydrogenase; (2) 17β -hydroxysteroid dehydrogenase; and (3) 5α -reductase. 3β -hydroxysteroid dehydrogenase, which is proven to localize in the sebaceous gland, acts on dehydroepiandrosterone (DHEA) to convert it to androstenedione.¹² DHEA is the produced from the adrenal hormone DHEAS by steroid sulfatase.

There are 2 forms of 3β -hydroxysteroid dehydrogenase. Type I is active in the skin, placenta, and mammary tissue, whereas type II is concentrated in the gonads and adrenal glands.¹³ The reversible enzyme 17β -hydroxysteroid dehydrogenase is responsible for converting androstenedione to testosterone. There are 11 isozymes of 17β -hydroxysteroid dehydrogenase, which vary in their tissue localization and ability to reduce or oxidize androgens and estrogens. This may represent a regulatory point in androgen and estrogen metabolism as the type 2 isozyme appears to be the most active in the sebaceous gland, where it prefers to oxidize testosterone back to androstenedione.¹⁴ Testosterone is then taken up by the cell and rapidly converted by type 1 5α -

reductase to 5α -dihydrotestosterone (DHT). Interestingly, 17β -hydroxysteroid dehydrogenase and 5α -reductase have different activity based on location, with acne-prone skin having greater activity of type 1 5α -reductase and nonacne-prone skin having greater activity of 17β -hydroxysteroid dehydrogenase the activity.^{15,16} DHT has 5 to 10 times more affinity for the androgen receptor than testosterone. Once DHT or testosterone has bound to the androgen receptor it is translocated to the nucleus, where it initiates transcription of androgen-responsive genes. The exact genes are unknown, but candidates include enzymes involved in lipogenesis.

Estrogen

The role of estrogens in the development of acne remains unclear. It is known that estrogen given in sufficient amounts will suppress sebum production. Some women will respond to lower doses of estrogen, but others require greater doses to reduce sebum production.¹⁷ Some women experience an exacerbation of acne during high estrogen states like pregnancy and the expression of estrogen receptors in the sebaceous gland is not well defined. Estradiol, the major active estrogen, is produced from testosterone by aromatase. It can also be converted to the less potent estrone by the action of 17β -hydroxysteroid dehydrogenase. It is hypothesized that estrogens may impact sebum secretion by one of several mechanisms, including (1) direct opposition of androgens within the sebaceous gland, (2) inhibition of androgen production by the gonads through a negative feedback loop on gonadotrophin release, or (3) regulation of genes involved in sebaceous gland growth or lipid production.

Growth Hormone

Growth hormone is also hypothesized to play a role in the development of acne.¹⁸ Growth hormone is secreted by the pituitary gland and acts on the liver and peripheral tissues to produce insulin-like growth factors (IGFs), of which IGF-1 is the most prevalent. During adolescence, growth hormone is maximally secreted, and serum levels of IGF-1 are at their highest. IGF-1 can be produced in the skin where it can interact with receptors on the sebaceous gland to stimulate growth. This is supported clinically by the development of acne and seborrhea in conditions of growth hormone excess like acromegaly.

Melanocortins

Melanocortins include melanocyte-stimulating hormone and adrenocorticotrophic hormone and play an important role in regulating feeding behaviors, body weight, immune function, and pigmentation. Mice lacking the melanocortin-5 receptor exhibit decreased sebum production.^{19,20} The melanocortin-5 receptor is localized in human sebaceous glands, epidermis, and hair follicles, but the significance of this finding is still unknown.²¹ Melanocortin-5 receptor variants were studied in patients with acne, hidradenitis suppurativa, and several sebaceous gland neoplasms and no association be-

Table 1 Endocrine Evaluation

Laboratory Test	Hormone Level (ng/dL)	Suspected Diagnosis
DHEAS	>8000 4000 to 8000	Adrenal tumor Congenital adrenal hyperplasia
Total testosterone	>200 >150	Ovarian androgen-secreting tumor PCOS
Free testosterone	Elevation from normal range	Hyperandrogenism
LH:FSH ratio	>2/3	PCOS
17-hydroxyprogesterone	Elevated >200	Late-onset congenital adrenal hyperplasia

tween genetic variations of the receptor and clinical characteristics was detected.²²

When to Suspect an Endocrine Disorder

Hormones will certainly influence acne, but an overwhelming majority of acne patients do not have an endocrine disorder. The development of sudden-onset acne, acne associated with hirsutism or irregular menses, or treatment-resistant acne may be associated with hyperandrogenism from several different causes. The most common of which are PCOS and congenital adrenal hyperplasia; however, the possibility of an ovarian or adrenal tumor must be considered. Other clinical signs of hyperandrogenism include cushingoid features, increased libido, acanthosis nigricans, deepening of the voice, female pattern hair loss, or clitoromegaly. It is important to note that women with hyperandrogenic states may also have insulin resistance, which puts them at increased risk of developing cardiovascular disease and diabetes. These women should be referred to an endocrinologist or gynecologist to help manage their condition.

If an endocrine abnormality is suspected, screening tests can help to delineate the source of excess androgens (Table 1), including DHEAS, total testosterone, free testosterone, and luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio. If DHEAS is increased, the source of excess androgens is the adrenal gland. If the level is >8000 ng/dL, the patient may have an adrenal tumor and should be sent to an endocrinologist for further workup. Levels in the 4000-8000 ng/dL range can be associated with congenital adrenal hyperplasia. Testing for 17-hydroxyprogesterone can be added. Increased levels are indicative of late-onset congenital adrenal hyperplasia (CAH). CAH is an autosomal-recessive condition in which enzymes necessary for cortisol synthesis and sometimes aldosterone production are deficient. The excess precursors are subsequently shunted toward androgen production resulting in virilization (Fig. 2). The most common enzyme deficiency is 21-hydroxylase, which is present in 95% of cases. Other possible causes include deficiencies in 17- α hydroxylase, 11- β hydroxylase, and 3- β hydroxysteroid dehydrogenase.

An ovarian source of androgens is possible when serum total testosterone levels are increased. When serum testosterone levels are >150-200 ng/dL, an ovarian tumor may be the source, with mild increases seen in PCOS. Finally, an in-

creased LH/FSH ratio (greater than 2-3) can confirm a diagnosis of PCOS. The optimal time for checking these laboratory values is during the luteal phase of the menstrual cycle, just before the onset of menses. It is important to have patient stop oral contraceptive pills at least 1 month before testing because underlying hyperandrogenism would be masked. Any abnormalities should be confirmed with repeat testing before proceeding with therapy. Even when all of the levels are normal, there may still be a role for hormonal therapy in women with acne, in particular those women with menstrual flares as well as in women with acne located along the mandible and the chin (Fig. 3).

Hormonal Therapy

Drugs used for hormonal therapy can be divided into four main groups (Table 2):

- Androgen receptor blockers (spironolactone, cyproterone acetate, and flutamide);
- adrenal androgen production blockers (glucocorticoids);
- ovarian androgen blockers (oral contraceptives); and
- enzyme inhibitors (dutasteride);

The main goal of these therapies is to oppose the effects of androgens on the sebaceous gland.

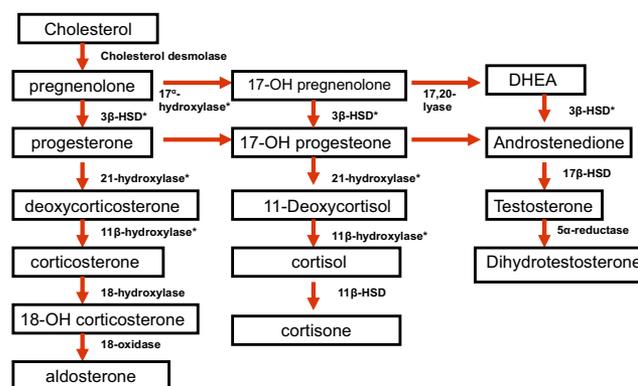


Figure 2 Adrenal steroidogenesis; HSD, hydroxysteroid dehydrogenase.



Figure. 3 Typical adult female acne.

Androgen Receptor Blockers

Spironolactone

Spironolactone, although not approved by the Food and Drug Administration (FDA), has been used to treat acne and hirsutism for more than 20 years. Its main mechanism of action is as a steroidal androgen receptor blocker, which competes with testosterone and dihydrotestosterone for androgen receptors and decreases androgen-stimulated sebocyte proliferation.²³ It is also known to inhibit androgen biosynthesis by decreasing type II 17 β -hydroxysteroid dehydrogenase, therefore halting the conversion of androstenedione to testosterone.²⁴ Other proposed actions of spironolactone include inhibition of 5 α -reductase and increased steroid-hormone binding globulin.²⁵ Together, this results in a 30-50% reduction in sebum excretion.²⁶

The efficacy of spironolactone has been established by several studies showing improvement in 50-100% of those women treated.²⁷⁻³⁰ Dosages in those studies ranged from

100 to 200 mg daily; however, lower doses of 50 to 100 mg daily often produce good clinical results and have the advantage of reduced side effects.³¹ In this study, 85 women receiving spironolactone as a sole agent or in combination with other treatments were followed over the course of 2 years. A total of 33% of patients cleared, 33% of patients noted significant improvement, 27.4% improved somewhat, and 7% showed no response. In our experience, great clinical results can be seen with doses as low as 25 mg once or twice daily.

Side effects of spironolactone are dose dependent and include menstrual irregularities (metrorrhagia, amenorrhea, break-through bleeding), breast tenderness and enlargement, central nervous system symptoms (lethargy, headache, lightheadedness, dizziness), orthostatic hypotension, hyperkalemia, and reduced libido. Although most patients who take spironolactone experience at least one side effect,^{32,33} they are generally not severe enough to discontinue therapy and can be tempered by concomitant use of oral contraceptives.³⁴ Hyperkalemia is one of the most-feared consequences of therapy. Although approximately 13.7% of patients will experience minimal increases in serum potassium levels, this is not considered clinically significant in young, healthy women. Laboratory monitoring of potassium is optional but is recommended in older women with multiple medical problems or cardiac disease or patients receiving combination therapy with oral contraceptives containing the progestin drospirenone. Interestingly, one recent report evaluated women on both spironolactone and a combined oral contraceptive containing 30 μ g ethinyl estradiol and 3 mg drospirenone (Yasmin®). Patients' serum potassium was measured at baseline and 4 to 6 weeks after starting therapy. No significant increases were found in any of the 27 patients, and 85% noticed clearing or excellent improvement in their acne after 6 months.³⁵ Another potentially serious side effect of spironolactone therapy is risk of hypospadias and feminization of the male fetus with prenatal exposure. Because of the

Table 2 Hormonal Treatments for Acne

Drug	Mechanism of Action	Standard Dose	Side Effects
Spironolactone	Androgen receptor blocker	25 to 200 mg daily	Menstrual irregularities, breast tenderness, hyperkalemia, hypotension, birth defects
Cyproteroneacetate*	Androgen receptor blocker	50 to 100 mg daily on days 5 to 14 of menstrual cycle or 2 mg combined with 35 μ g of ethinylestradiol	Breast tenderness, headache, nausea, and breakthrough bleeding, hepatotoxicity, birth defects
Flutamide	Androgen receptor blocker	250 to 500 mg daily	Hepatotoxicity, breast tenderness, gastrointestinal upset, hot flashes, and decreased libido, birth defects
Oral contraceptives	Ovarian androgen blocker	Depends on specific pill	Menstrual irregularities, breast tenderness, gastrointestinal upset, weight gain (see text for contraindications)
Glucocorticoids	Adrenal androgen production blocker	2.5 to 5 mg of prednisone at bedtime	Adrenal suppression (higher risk with dexamethasone)

*Not approved for use in the United States.

risk of birth defects and the reduction of side effects, it is prudent to use spironolactone in conjunction with an oral contraceptive in most cases.

It is important to note that early concerns about the potential risk for breast cancer have not been verified. There have been no documented cases of breast carcinomas and case controls have not shown an overall increase risk for breast carcinoma.³⁶

Cyproterone Acetate

Cyproterone is used outside the United States for the treatment of refractory acne. It is a synthetic derivative of 17-hydroxyprogesterone that works as an androgen receptor-blocker. It has also been shown to decrease the production of adrenal androgens by inhibiting the conversion of dehydroepiandrosterone to androstenedione by 3 β -hydroxysteroid dehydrogenase/ Δ^{5-4} isomerase.^{37,38} Several studies have confirmed the efficacy of cyproterone acetate, with overall improvements of 75-90%.^{39,40} Its effectiveness in the treatment of acne is thought to be related to its ability to reduce sebum production and comedogenesis.⁴¹ It has also been shown to decrease testosterone, gonadotropin, and androstenedione, as well as improve acne and seborrhea in as little as 3 months.⁴²⁻⁴⁴ As a sole agent, it is used in doses of 50 to 100 mg daily given on days 5 to 14 of the menstrual cycle; however, it is more commonly incorporated into oral contraceptive pills in doses of 2 mg combined with 35 μ g of ethinyl estradiol (Diane-35TM and DianetteTM). The most common side effects are breast tenderness, headache, nausea, and breakthrough bleeding, which tend to resolve by the second cycle.⁴⁵ The most serious reported side effect is hepatotoxicity, but it appears to be dose dependent.⁴⁶ There has also been much debate about whether the use of cyproterone acetate as the progestin component of oral contraceptive pills increases the risk of thromboembolism, but the risks are no more common than with the use of other combined oral contraceptives.⁴⁷ As with all androgen receptor blockers, use with caution in women of child-bearing potential because of the risk of feminization of the male fetus.

Flutamide

Flutamide is a nonsteroidal androgen receptor blocker approved by the FDA for use in the treatment of prostate cancer but also is effective in treating hirsutism and acne in women. It is converted to its highly potent metabolite, 2-hydroflutamide, which acts to selectively inhibit the binding of dihydrotestosterone to the androgen receptor. Because flutamide has less affinity for the androgen receptor than spironolactone, greater doses are usually needed.⁴⁸ Earlier studies used doses of 500 mg/d⁴⁹; however, lower doses (250 mg/d) are also effective.⁵⁰ In a comparison study of flutamide 250 mg twice daily and spironolactone 50 mg twice daily 80% of subjects receiving flutamide improved versus 40% of those treated with spironolactone.⁵¹ Some researchers report even lower doses (62.5 mg/d) of flutamide to be safe and effective in the treatment of hirsutism.⁵² Monitoring of liver function with flutamide is necessary as cases of fatal hepatitis have been reported.^{53,54} Hepatotoxicity seems to be dose and age related.⁵⁵ Side effects are comparable with the other andro-

gen receptor blockers and include breast tenderness, gastrointestinal upset, hot flashes, and decreased libido. Addition of an oral contraceptive pill and use of lower doses can reduce these side effects⁵⁶ and decrease concerns over pregnancy risk.

Adrenal Androgen-Production Blockers

Glucocorticoids

Androgen production can be blocked by the administration of low dose glucocorticoids. This treatment is usually reserved for those patients with late-onset CAH. CAH is caused by an inherent defect in the enzymes 21-hydroxylase or less commonly 11-hydroxylase, resulting in buildup of androgen precursors. Patients typically have increased DHEAS in the range of 4000 to 8000 ng/dL, as well as increased 17-hydroxy progesterone. Prednisone or dexamethasone may be used, but dexamethasone carries a greater risk of adrenal suppression. Typical doses are 2.5 to 5 mg/d of prednisone taken at bedtime. Serum DHEAS levels can be monitored and should decrease or normalize with therapy. An ACTH stimulation test may be necessary to check for adrenal suppression. ACTH is injected with subsequent blood monitoring of cortisol levels 30 minutes later. An increase in plasma cortisol indicates the adrenal gland is functioning properly.

Ovarian Androgen Blockers

Gonadotropin-Releasing Agonists

Agents such as busarelin, nafarelin, and leuprolide are effective in the treatment of acne and hirsutism in women with and without endocrine abnormalities.⁵⁷ They work by blocking androgen production by the ovary. These gonadotropin releasing agonists disrupt the cyclic release of FSH and LH from the pituitary, therefore blocking ovulation. These agents are available as a nasal spray or an injection. Because these drugs also suppress the production of estrogens patients can develop menopausal symptoms, headaches, and bone loss which may limit the use of this medication for acne.

Oral Contraceptives

Oral contraceptives contain an estrogen (usually ethinyl estradiol) and a progestin to decrease the risk of endometrial cancer associated with unopposed estrogens. The first combination pills had high concentrations of estrogen in the 100- to 150- μ g range, and carried a high risk of thromboembolic disease, stroke, and myocardial infarction.⁵⁸ Therefore, newer formulations contain estrogen doses ranging from 20 to 35 μ g of ethinyl estradiol (EE). With the use of lower estrogen doses the risk of myocardial infarction is improved and the risk for ischemic stroke approaches that of the general population, except in heavy smokers.⁵⁹

Oral contraceptives reduce the production of androgens and sebum by inhibiting LH and FSH, thereby suppressing ovulation and ovarian androgen production. In addition, circulating levels of testosterone are decreased by the estrogen induced increase in steroid hormone binding globulin.

The second component in oral contraceptives is progestin. Many progestins have the inherent ability to interact with

androgen receptors, aggravating acne, hirsutism, and androgenic alopecia; however, the newer third-generation progestins, desogestrel, norgestimate, and gestodene, have the lowest intrinsic androgenic activity.⁶⁰ One of the most promising recent developments is the novel progestin drospirenone. Drospirenone is a 17- α -spironolactone derivative that possesses both antiandrogenic and antimineralocorticoid activity. A 3-mg dose of drospirenone is equivalent to 25 mg of spironolactone. This has the added benefit of off-setting the estrogen-related fluid retention and weight gain associated with some oral contraceptives.⁶¹

Oral Contraceptives Studied in Acne

It is commonly accepted that all oral contraceptives will inhibit serum androgen levels, increase sex hormone-binding globulin, and improve acne regardless of the type of progestin or concentration of estrogen, however, several oral contraceptives have been studied specifically for their effects on acne (Table 3). These contraceptive agents include those containing EE in combination with: cyproterone acetate (Diane®, Dianette®), levonorgestrel (Triphasil®, Alesse®), norgestimate (Ortho Tri-Cyclen), desogestrel (Desogen®), drospirenone (Yasmin®, Yaz®), and ethynodiol diacetate (Demulen®). Only 3 oral contraceptives (Ortho Tri-Cyclen®, Estrostep®, Yaz®) are approved by the FDA for the treatment of acne in the United States.

As previously mentioned, cyproterone acetate can be used alone or as the progestin in the oral contraceptives, Diane and Dianette. When used in combination with EE, reductions in inflammatory lesions range from 50% to 75%.^{44,62} The results of a study in which the authors examined acne treatment with the oral contraceptive containing ethinyl estradiol and levonorgestrel (Triphasil®) showed a 75% reduction in comedones as well as a 50% decrease in inflammatory lesions.⁶³

The oral contraceptive EE/norgestimate (Ortho Tri-Cyclen®) demonstrated improvement in 2 large studies with large numbers of women. A 50-60% percent reduction in inflammatory lesions was noted, as well as reductions in total lesion

counts, increased sex hormone-binding globulin, and better global assessment scores after 6 months of therapy.^{63,64}

A low-dose estrogen oral contraceptive containing ethinyl estradiol 20 μ g and levonorgestrel 100 μ g (Alesse®) was evaluated in 2 placebo-controlled randomized clinical trials involving 350 and 371 women, respectively. Patients with moderate-to-severe facial acne were followed over the course of 6 months. In both studies, the women participating demonstrated significantly reduced acne lesion counts compared with placebo with reductions of inflammatory lesions between 32% and 47%, noninflammatory lesions by 13% and 25%, and total reductions of 23% and 40%.^{65,66}

Two large placebo-controlled trials involving 593 women showed improvement in total lesion counts, quality of life, global assessment, and inflammatory lesions with the use of the triphasic oral contraceptive containing 20-35 μ g of ethinyl estradiol and 1 mg of norethindrone acetate (Estrostep®). In these studies, inflammatory lesions were reduced by approximately 47%.⁶⁷

The incidence rates of both acne and seborrhea were also reduced with a monophasic oral contraceptive containing desogestrel (30 μ g EE/150 μ g desogestrel; Desogen®).⁶⁷ After 6 cycles of treatment, preexisting acne had disappeared in >80% of the 1021 women who had acne at baseline.⁶⁸

The use of the newer oral contraceptive pills containing the progestin drospirenone has also been studied. The efficacy of EE 30 μ g/drospirenone (Yasmin®) was directly compared with the ethinyl estradiol 35 μ g/cyproterone acetate pill (Diane-35®) in a randomized controlled study during a 9-month period. Both treatments reduced total facial acne by 60% and also decreased sebum production and increased sex-hormone binding globulin levels.⁴⁴ The safety of Yasmin® has been compared with other oral contraceptive pills in a large multinational observational study with no increased risk of adverse cardiovascular or other serious events in users of drospirenone containing oral contraceptives versus those using other oral contraceptive pills.⁶⁹ Other studies of the use of Yasmin® in hyperandrogenic states such as PCOS have demonstrated lowered testosterone, free testosterone, DHEAS, androstenedione levels as well as increased sex hormone-binding globulin levels.^{70,71}

The newest oral contraceptive to hit the market is Yaz®, which combines 20 μ g of EE and 3 mg of drospirenone in a 24/4 active/inert regimen. It was approved by the FDA for the treatment of moderate acne in January 2007 based on two multicenter, double-blinded, randomized, placebo-controlled trials. These trials followed 889 subjects over 6 cycles. Both showed similar results, with a 42-46% reduction in total lesion counts.⁷²⁻⁷⁴ As mentioned previously, when oral contraceptives containing the progestin drospirenone are used in addition to spironolactone, potassium levels should be monitored at baseline and 4 to 6 weeks after starting therapy.

Prescribing Oral Contraceptive Pills

Not all physicians are comfortable prescribing oral contraceptive pills. If that is the case, patients can be referred to their gynecologist for treatment. If you do decide to prescribe

Table 3 Oral Contraceptives Used for Acne Treatment

Drug Name	Estrogen (μ g)	Progesterone (mg)
Ortho Tri-Cyclen*	Ethinylestradiol 35	Norgestimate 0.18/0.215/0.25
Estrostep*	Ethinylestradiol 20/30/35	Norethindrone 1
Yaz*	Ethinylestradiol 20	Drospirenone 3
Yasmin	Ethinylestradiol 30	Drospirenone 3
Alesse	Ethinylestradiol 20	Levonorgestrel 0.1
Mircette	Ethinylestradiol 20/10	Desogestrel 0.15
Triphasil	Ethinylestradiol 30/40/30	Levonorgestrel 0.5/0.75/0.125
Desogen	Ethinylestradiol 30	Desogestrel 0.15
Ortho Cyclen	Ethinylestradiol 35	Norgestimate 0.25

Limited to those studied in acne and available in the United States.

*FDA-approved for use in the treatment of acne.

oral contraceptives, it is important to choose the right patient and counsel them on the potential risks and benefits of oral contraceptive use.

Patients are typically directed to start taking oral contraceptives on the Sunday after their normal menstrual period begins. By using this method, patients have the potential of having bleeding-free weekends; however, a recent study showed that only 47% of patients achieve the desired result.⁷⁵ The other standard method has patients begin pills with the start of their period. The advantage to this method is that there is no need for back-up birth control. A novel prescribing method recommends starting the pill on the same day it is prescribed. Called the "quick start" method, patients need a negative pregnancy test before start and use of back-up contraception for 1 to 3 weeks. The advantages to the quick start method include increased compliance without an increased side effect profile.⁷⁶⁻⁷⁸

Common side effects of therapy include nausea, vomiting, breakthrough bleeding, weight gain, and breast tenderness. These minor side effects tend to resolve after the first 2-3 cycles as the body adjusts to the medicine. Other side effects can include mood changes, melasma, and decreased sexual desire. As newer formulations of the drugs are developed the side effect profiles have become more favorable. As a class oral contraceptive pills have some potentially serious complications and are generally accepted to be contraindicated in the following patients:

- Preexisting cardiovascular disease, elevated blood pressure (160/100 mm Hg), angina pectoris, complicated valvular heart disease;
- a history of thromboembolic disorders or a familial tendency to form blood clots, or major surgery with prolonged immobilization;
- severe obesity and/or hypercholesterolemia;
- smokers older than the age of 35;
- known or suspected breast cancer, endometrial cancer, hepatic adenomas or carcinomas, or other estrogen dependent neoplasm;
- undiagnosed abnormal uterine bleeding;
- a history of cholestatic jaundice of pregnancy or jaundice with prior pill use;
- pregnancy or lactation (<6 weeks' postpartum);
- hypersensitivity to any component;
- migraines without focal neurologic symptoms at age 35 years or migraines with focal neurologic symptoms at any age;
- diabetes with evidence of nephropathy, retinopathy, neuropathy, vascular disease, or >20 years' duration; and
- severe (decompensated) cirrhosis.

Oral contraceptives are safe and effective, but popular press has reported on some potential complications that have heightened patient concerns. Two of the most prominent concerns are related breast cancer risk and decreased efficacy with concomitant antibiotic use. In 1996, the Collaborative Group on Hormonal Factors in Breast Cancer released results of a meta-analysis of 54 worldwide studies, including 53,297

subjects with breast cancer and 100,239 controls. The report generated 2 important conclusions. First, it supported a modest increase in breast cancer risk during use and in the first 10 years after stopping therapy. Second, the authors found no increase in risk of breast carcinoma 10 or more years after discontinuation. Cancers detected in users of oral contraceptives were less advanced than in those women never using oral contraceptive pills.⁷⁹ The authors concluded that the increased risk observed during and immediately after discontinuation may be caused by increased screening in that population while they are receiving therapy. In a 2004 review, authors evaluated 51 epidemiologic studies and concluded that transient increases in rates of breast carcinoma during or near the time of combined oral contraceptive use do not contribute significantly to increased rates of breast cancer.⁸⁰

There is a theoretical concern about antibiotics reducing the efficacy of oral contraceptive pills. By altering the bacterial flora estrogen absorption can be impaired; however, pharmacokinetic studies suggest estrogen levels are unaffected by antibiotics such as tetracycline or doxycycline.^{81,82} Several case reports, however, have linked antibiotics to pregnancy. Existing reports focused on tetracycline with an incidence of 1.2 to 1.4 pregnancies/100 woman-years. The pregnancy rate was no greater than the failure rate reported for oral contraceptives.^{83,84} However, we counsel our patients that are taking both a tetracycline antibiotic and a birth control pill that a back-up form of birth control may be necessary to prevent pregnancy. Unlike the tetracycline family of antibiotics, rifampin will most certainly alter the efficacy of oral contraceptive pills. Patients must be counseled to use a backup method of birth control while taking rifampin.

Enzyme Inhibitors

Because certain enzymes in the skin can contribute to local androgen production, theoretically treatments that block enzymatic activity may be useful in the treatment of acne.⁶ Because DHT is the most potent androgen known to directly influence acne, enzymes that synthesize DHT could be targeted, however blocking these enzymes may also block key steps in the synthesis of other steroid hormones. A safer alternative would be to target the downstream enzymes like 5 α -reductase. Testosterone binds with a greater affinity to type I 5 α -reductase (found in the skin) than the type II enzyme, therefore higher doses of inhibitor may be required to affect the skin, as is the case with dutasteride, a dual enzyme inhibitor.⁸⁵ Because the type II 5 α -reductase enzymes are not found in the skin, inhibitors of these enzymes (such as finasteride) are unlikely to be useful as a treatment options. The 5 α -reductase inhibitors are well known for the treatment of androgenetic alopecia in males, however due to their risk of teratogenicity they are not recommended for use in females and are not studied as a treatment for acne. In the future it is possible that locally acting enzyme inhibitors could be developed that will be effective for both men and women with acne.

Conclusion

Hormonal therapy is an important addition to our traditional armamentarium of acne therapies, especially in those women not responding to conventional therapy. It is important to be able to recognize clinical signs of hyperandrogenism and then perform an appropriate workup consisting of DHEAS, total and free-testosterone levels, and an LH/FSH ratio. Even without laboratory abnormalities, many women will respond to hormonal therapy.

We are fortunate to have a myriad of treatment options. Hormonal therapy choices include androgen-receptor blockers, androgen-production blockers, and possible enzyme inhibitors in the future. Spironolactone and combined oral contraceptive pills remain the mainstay of treatment and in the right patients can be extremely safe and effective.

Research on the effects of hormones and acne continues to flourish and as mechanisms by which they exert their effects on the sebaceous gland and skin are uncovered, the potential for the development for new therapies aimed at the hormonal aspects of acne is possible.

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