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Hormonal therapies for acne

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Abstract Acne is a common, worldwide problem that is usually multifactorial in etiology, but androgens may play a pivotal role in the development and severity of acne. Endocrinopathies, such as polycystic ovarian syndrome, ovarian tumors, or adrenal hyperplasia or tumors, may be detected in some patients with acne, especially if acne is sudden in onset, associated with hirsutism or menstrual irregularities, or associated with cushingoid facies, acanthosis nigricans, patterned hair loss, or deepened voice. In these instances, serum-free and total testosterone, dehydroepiandrosterone, luteinizing hormone, and follicle stimulating hormone should be tested. Appropriate referral and long-term follow-up is warranted in patients diagnosed with an endocrinopathy. Hormonal therapies for acne include systemic medications with various mechanisms: androgen receptor blockers, adrenal androgen production blockers, or ovarian androgen production blockers. Androgen receptor blockers include spironolactone, cyproterone acetate, chlormadinone, and flutamide; adrenal androgen production blockers include glucocorticoids; and ovarian production blockers include gonadotropin-releasing agonists and oral contraceptives. Practical guidelines are shared for the practicing physician treating hormonally related acne.

Epidemiology

Acne affects individuals worldwide, with a variable prevalence depending on population studied, from 17% in Basra, Iraq, to 4-8% in China, Germany, and Egypt, to as low as <1% in Tanzania.[1] The peak age range is 16-20 years old.[1] Although in younger and post-pubertal age groups, acne is more common in women, the prevalence in men increases until puberty and tends to be more severe.[1]

Hormonal contributions to acne

Acne is multifactorial, and hormonal considerations are complex. Both sex hormones and metabolic hormones seem to play a role in the development and severity of acne. For instance, elevated dehydroepiandrosterone (DHEAS), dihydrotestosterone (DHT), and insulin-like growth factor 1 (IGF-1) positively correlate with increasing acne lesion counts in women and androstenedione and DHEAS in men.[2] Metabolic and sex hormones may have a reciprocal or complementary relationship, as the effect of androgens on acne lesion counts is reliant upon the presence of IGF-1.[2] Additionally, postadolescent men with acne had a higher incidence of insulin resistance than age-matched controls, although the diagnosis of metabolic syndrome was not associated with a degree of statistical significance.[3] In another study examining 401 women with suspected polycystic ovarian syndrome (PCOS), a syndrome increasingly recognized as linked to metabolic syndrome, 61% of those that met diagnostic criteria for PCOS exhibited acne ($P = 0.004$).[4] Despite the increased prevalence of acne, there was not a difference in lesion count or distribution, and acne was not a reliable marker for elevated androgen levels.[4]

The various hormones possibly implicated in acne and their proposed mechanisms are summarized below. A detailed description is beyond the scope of this text.[5]

- *Androgens* (testosterone, DHT, DHEAS) increase the size and secretion of sebaceous glands. Sources of circulating androgens include the adrenal gland, ovary, or

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testes. Androgens can also be produced locally within the sebaceous gland; for example, testosterone can be converted to DHT by the type 1 5-alpha-reductase of the sebaceous gland.
- *Estrogens* counter the action of androgens by three potential mechanisms: direct opposition locally, inhibition of androgen production in the gonads via feedback loop, or by gene regulation.
- *Growth hormone and growth factors* – growth hormone stimulates production of growth factors such as IGF-1, both of which are secreted in high levels during puberty, when acne is at its peak incidence. In some tissues, possibly including sebaceous glands, the action of IGF-1 is influenced by androgens.
- *Melanocortins* (melanocyte-stimulating hormone, adrenocorticotrophic hormone [ACTH]) regulate sebum production through unknown mechanism.

The remainder of this contribution will focus on the hormonal influences and therapies for acne in women because, at the present, the treatment of acne in men is the same regardless of hormonal factors.

The majority of patients with acne will not have an associated endocrine disorder[5]; however, recognition of endocrinopathy in an acne patient is important. Whether a woman's acne is hormonally related may be indicated by historical clues: for example, acne worsens before menstruation; persistence of acne despite conventional therapy (topical retinoid, topical benzoyl peroxide, and topical or systemic antibiotic); or acne is sudden in onset.[6] Indications to pursue an endocrine work-up include[6] the following:

- Acne of sudden onset, in particular if no prior history of acne;
- Acne with associated hirsutism;
- Acne with associated irregular menstrual cycles; and
- Acne with associated signs of hyperandrogenism, such as cushingoid facies, increased libido, new acanthosis nigricans, deepened voice, insulin resistance, or patterned hair loss.

Once an endocrinopathy is suspected, the next step is to delineate the source of androgen excess: adrenal tumor, congenital adrenal hyperplasia, ovarian tumor, or PCOS.[6] A concise panel of blood work can be helpful and includes DHEAS, total and free testosterone, and ratio of luteinizing hormone (LH) to follicle stimulating hormone (FSH). DHEAS is specific for adrenal source of androgens, and LH and FSH are specific for ovaries, whereas testosterone may be converted from within the adrenal glands and ovaries. Parameters are summarized as follows:

- DHEAS >8000 ng/mL suggestive of adrenal tumor
- DHEAS 4000-8000 ng/mL suggestive of congenital adrenal hyperplasia (like 11- or 21-hydroxylase deficiency)
- Total testosterone >150-200 ng/dL suggestive of ovarian tumor.
- Total testosterone mildly elevated suggestive of PCOS
- LH/FHS ratio >2.5-3 suggestive of PCOS.[6]

Of note, oral contraceptives should be held for 4-6 weeks before performing these tests, as oral contraceptive therapy may result in falsely reassuring values.[6] If endocrinopathy is diagnosed or suggested by test results, evaluation and treatment with a specialist should be sought. Identification and appropriate long-term surveillance are important because of the increased risk of diabetes and cardiovascular disease.

Treatment

Broadly speaking, the currently available treatment options for hormonal acne may be categorized as androgen receptor blockers, adrenal androgen production blockers, or ovarian androgen production blockers.[6] Androgen receptor blockers include spironolactone, cyproterone acetate, chlormadinone, and flutamide. Adrenal androgen production blockers include glucocorticoids, whereas ovarian production blockers include gonadotropin-releasing agonists and oral contraceptives.[6]

Androgen receptor blockers

Spironolactone

Spironolactone is the most commonly utilized antiandrogen therapy in the United States.[6] Spironolactone blocks androgen receptors and inhibits 5-α-reductase. Spironolactone may reduce the severity of acne when dosed 50-200 mg/d over a 3-month period,[7] but generally, much lower doses are required to treat acne, such as 25-100 mg/d (25 mg/d, 25 mg bid, or 50 mg bid), in contrast to the higher doses needed to treat androgenetic alopecia or hirsutism.[6] Most acne patients experience clinically significant improvement by 3 months of therapy.[8] Adequate contraception is recommended during spironolactone therapy, as studies in rats have demonstrated feminization of male fetuses.[9] In otherwise healthy women, these doses are well tolerated, and recent data do not support the laboratory monitoring of potassium, as the rate of hyperkalemia was the same as baseline population.[10] Of note, this is not a generalization for women with other medical conditions including cardiovascular disease, renal failure, or concomitant use of medications affecting the renin-angiotensin-aldosterone system. Side effects of spironolactone tend to be transient and include menstrual irregularities in as many as half of treated patients. Usually, this is oligomenorrhea or irregular menstrual bleeding but may less often manifest as hypermenorrhea. Often, these side effects resolved within 2-3 months of continued therapy.[8] Additional side effects include nausea, dizziness, or polyuria, which may resolve in 1-2 weeks of continued