Practical Approach to Challenging Acne for the General Dermatologist

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Acne vulgaris is a common reason why women present to dermatologists and is often challenging to treat. Management of acne in an adult female patient may require distinct diagnostic and therapeutic considerations, including a workup for endocrine disorders and use of hormonal therapy. Hormonal therapy is safe and effective for the treatment of acne in women, even those with normal androgen levels. It may require more long-term treatment; understanding patient preferences and setting expectations for treatment are paramount. The use of oral contraceptive pills and spironolactone present therapeutic opportunities in acne management that should be in every dermatologist's toolbox. This session will cover a practical approach to prescribing hormonal acne therapy and is relevant to any dermatology provider who sees adult female patients with acne.

Treatment of acne in adult female patients:
- All of the central tenets of acne management are true
- Women over age 25 have high rate of treatment failure: 82% fail multiple courses of systemic antibiotics, 32% relapse after isotretinoin

Principles of hormonal therapy:
- May need long-term systemic treatment
- Hormonal therapy is safe and effective even in women with normal androgen levels (age>14, post-menarchal)
- One of the goals of hormonal treatment is to reduce sebum production
- Need close monitoring for side effects, for underlying endocrine disease

Prescribing oral contraceptive pills (OCPs): Key points
- How they work:
  - Estrogen provides the most benefit
  - Stimulates SHBG synthesis (liver): decrease free testosterone, DHEA-S, also reduces sebum production
  - Inhibit 5a-reductase: decreases peripheral conversion of testosterone
  - Decrease production of ovarian and adrenal androgens
  - Lesion count reduction: 40-70%
- Pick progesterone with low androgenic activity: norgestimate, desogestrel (3rd gen progestins)
- FDA-approved for acne (caution: norethindrone has strong androgenic properties)
  - Ortho Tri-Cyclen (norgestimate 180/215/250mcg + 35mcg ethinyl estradiol)
  - EstroStep: norethindrone acetate 1 mg + EE 20/30/35 mcg + 7 day hormone-free interval or ferrous fumarate
  - Yaz: drospirenone 3mg + EE 20 mcg + 4 day hormone-free interval

FAQs about OCPs

<table>
<thead>
<tr>
<th>Questions</th>
<th>Answers</th>
</tr>
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<tbody>
<tr>
<td>Am I required to perform a pelvic exam, Pap smear first?</td>
<td>WHO, ACOG, Planned Parenthood: No.</td>
</tr>
<tr>
<td>How do I counsel patients about clotting risks?</td>
<td>Risk of DVT @ baseline: 1/10,000 woman-years</td>
</tr>
<tr>
<td>Risk of DVT @ 1 year: 3.4/10,000 woman-years</td>
<td></td>
</tr>
<tr>
<td>Risk of DVT in pregnancy: 5-12/10,000 pregnancies</td>
<td></td>
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<tr>
<td>How do I counsel patients about CV risks?</td>
<td>Smoking, hypertension, diabetes increase risk</td>
</tr>
<tr>
<td>How do I counsel patients about breast cancer risks?</td>
<td>WHO study: RR 1.24 Not dose nor duration related Endometrial, ovarian cancer risk is reduced</td>
</tr>
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<td>How do I counsel patients about weight gain?</td>
<td>1-2 kg occurs in 30% patients, fluid retention</td>
</tr>
<tr>
<td>What are the most common side effects?</td>
<td>Unscheduled bleeding, nausea, breast tenderness Decreased with lower estrogen dose (except bleeding)</td>
</tr>
<tr>
<td>What are rare side effects?</td>
<td>Decreased libido, melasma, mood changes</td>
</tr>
<tr>
<td>Can I use OCPs and systemic antibiotics?</td>
<td>Yes, except 3A4 inducers (rifampin), 76% of reported cases Likely safe: tetracyclines, no difference in pregnancy rate</td>
</tr>
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OCP contraindications: Pregnancy or breastfeeding <6 month postpartum; History of stroke, VTE, MI; Smoking (any amount) + age >35; Uncontrolled hypertension (SBP >160, DBP >100); History of migraine with focal symptoms/ aura; History of migraine + age >35; Current or past history of breast CA; Hypercholesterolemia (LDL >160); Diabetes + age >35 or end-organ damage; Viral hepatitis or cirrhosis; Liver tumor (any); Major surgery with prolonged immobilization
Prescribing spironolactone: Key points

- How it works:
  - 25 mg/day blocks aldosterone (K+ sparing diuretic)
  - 50-100mg/day blocks androgen (at receptor level)

- Effective: non-FDA approved, no placebo-controlled trials
  - Dose spironolactone alone or with OCP (50-200 mg/day)
  - Expect 33-85% reduction in acne, also seborrhea
  - Dose dependent: low-dose study (50-100mg/day): 33% improvement -> 100mg + drospirenone: 85% improvement
  - Improves subjective reports of hirsutism in 9 studies

- Safe (8 year safety study: no serious complications), but has side effects:
  - Breast tenderness (17%), menstrual irregularities (22%, esp at higher doses, no OCP), headache (13%), fatigue (15%)
  - Hyperkalemia (minimal rise in K+ in 13%, no sequelae
  - Consider: checking K+ @ baseline, 4 weeks if woman >50 years, cardiac/renal disease, or also on drospirenone
  - Diuretic (take in AM) with blood pressure reduction: mean 5mmHg SBP, 2.6mmHg DBP
  - Teratogen: Category D. Hypospadias, feminization
  - Black box warning: benign breast, thyroid tumors in animal studies. No known risk in humans.

Additional therapies to consider: both effective in women with hirsutism and acne

- Cyproterone acetate (CPA) is a 17-hydroxyprogesterone derivative (not available in the US) with potent androgen blockade
  - may have up to 75-90% efficacy in acne
  - Yasmin versus Diane (CPA): equal efficacy (62% versus 59%)

- Flutamide is a non-steroidal androgen-receptor blocker used in prostate cancer (doses: 250-500mg/day)
  - side effects: hepatotoxicity, GI upset, hot flashes, decreased libido

- Corticosterone 17\(\alpha\) propionate 1% cream (on the horizon) tested in men only, with modest efficacy (*BJD, 2011, 165: 177-183*)

How to prescribe hormonal therapy:

- OCP alone is 40-70% effective
- Adding androgen blockade in those who do NOT respond to OCP: 50-80% effective
- Spironolactone 50-100mg/day (best tolerated)
- Consider spironolactone alone (in select patients only). Caution: increased side effects
- Combining hormonal + all other standard acne therapies is acceptable

Key differential diagnosis of hyperandrogenism:

- Polycystic ovary syndrome (PCOS) = MOST COMMON
- Androgen-secreting neoplasm (adrenal, ovary)
- Non-classical congenital adrenal hyperplasia
- HAIR-AN (Hyperandrogenism, insulin resistance, acanthosis nigricans)
- Hyperandrogenism and hirsutism
- Exogenous steroids

Diagnostic evaluation for acne and hyperandrogenism (HA)

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Diagnosis</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (total)</td>
<td>Elevated</td>
<td>&gt;200 Ovarian tumor</td>
<td>Essential</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;150 HA (ie, PCOS)</td>
<td></td>
</tr>
<tr>
<td>Testosterone (free)</td>
<td>Elevated</td>
<td>HA (ie, PCOS)</td>
<td>Essential</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>Elevated</td>
<td>&gt;8000 (Adrenal tumor) 4000-8000 (CAH)</td>
<td>Essential</td>
</tr>
<tr>
<td>17-hydroxyprogesterone</td>
<td>Elevated</td>
<td>Congenital adrenal hyperplasia (late-onset)</td>
<td>Essential</td>
</tr>
<tr>
<td>LH:FSH</td>
<td>3:1 suggestive</td>
<td>PCOS</td>
<td>Helpful</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Elevated</td>
<td>Pituitary tumor</td>
<td>Helpful</td>
</tr>
<tr>
<td>TSH</td>
<td>Abnormal</td>
<td>Thyroid disease is common cause of menstrual irregularity</td>
<td>Helpful</td>
</tr>
<tr>
<td>Transvaginal ultrasound to assess ovarian volume and follicle count (also r/o presence of tumor)</td>
<td>Increased volume/ count</td>
<td>PCOS</td>
<td>Essential</td>
</tr>
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Rotterdam criteria for Polycystic Ovary Syndrome (PCOS): must fulfill 2 of 3. Remember that PCOS spectrum is broad.

- Amenorrhea or oligomenorrhea (<8 menstrual cycles per year)
- Clinical or biochemical evidence (ie, labs) of hyperandrogenism
- Ultrasound findings consistent with PCOS