Hormonal Therapy for Acne: Pros and Controversies

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Disclosure of Relationships with Industry
Bethanee J. Schlosser, MD, PhD
S004: Acne and Rosacea
Hormonal Therapy: Pros and Controversies
Elorac, Galderma, Novan: Investigator, Fees to Institution
Decision Support in Medicine, UpToDate®: Author, Honoraria
Novan, Allergan: Advisory Board, Honoraria
Off-label use of medication will be discussed.

Strength of Evidence for Hormonal Therapy

<table>
<thead>
<tr>
<th>Recommendation</th>
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A/I = Recommendation based on consistent and good-quality patient-oriented evidence
B/II = Recommendation based on inconsistent or limited quality patient-oriented evidence
C/III = Recommendation based on consensus, opinion, case studies or disease-oriented evidence


When to Consider Hormonal Therapy

- Hyperandrogenism
- Late-onset or persistent (>25yo)
- Prominence of acne at lower face, neck
- Perimenstrual flare
- Comedonal acne with seborrhea
- Resistant to “conventional” therapies
- Alternative to repeat isotretinoin
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Combined Oral Contraceptives

- Ethinyl estradiol
  - 1960s: 50-150µg per pill
  - 2010s: 10-30µg per pill
- Androgenic activity of progestins varies
- Overall net effect is antiandrogenic due to estrogen impact
- Reduce androgens via:
  - Reduces GnRH pulsatility $\rightarrow$ ↓ LH production
  - ↑ sex hormone binding globulin synthesis

Androgenic Index of Progestins

<table>
<thead>
<tr>
<th>NONE</th>
<th>LOW</th>
<th>MODERATE</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drospirenone</td>
<td>Desogestrel</td>
<td>Norethindrone</td>
<td>Norgestrel</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>Norgestimate</td>
<td>Norethindrone acetate</td>
<td>Medroxyprogesterone acetate</td>
</tr>
<tr>
<td>Gestodene</td>
<td>Ethynodiol diacetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desogestrel</td>
<td>Levonorgestrel</td>
<td></td>
<td></td>
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</table>

Spironolactone

- Aldosterone antagonist $\rightarrow$ diuresis
- Competitive inhibition at the androgen receptor
- High doses $\rightarrow$ ↓ androgen synthesis via P450 inhibition
- Inhibits 5α-reductase
- ↑ hepatic SHBG synthesis
- Not approved by FDA for dermatologic indications

When to Consider Spironolactone Specifically

- Patients on combined OCP but inadequate control of acne
- Patients with contraindications to combined OCP
  - Patients with LAR hormonal contraceptive devices and acne
  - Patients on progestin-only oral contraceptive pill, nursing
- Patients unable to take/access/afford other acne medications

HORMONAL THERAPY FOR ACNE: PROS
• Moderate facial acne
• 20mcg EE/3mg DSP (n=266) vs placebo (n=268)
• % reduction greater for treatment group across all lesion types (p<0.0001)
• OR clear/almost clear = 4.31
  At least 3 cycles of use prior to judging efficacy


• Moderate inflammatory truncal acne, 18-45yo
• 20mcg EE/3mg DSP 24/4 regimen (n=16) vs placebo (n=14)
• % reduction greater for treatment group across all lesion types, mean DLOI score
• Significant reductions seen as early as week 12 (3 cycles)

Meta-Analysis: Combined OCPs for Acne

• 24 randomized trials
  – 9 compared combined OCP vs placebo
  – 17 compared different OCPs
  – 1 compared combined OCP (EE/CYP) vs oral antibiotic (MCN)
• Combined OCPs outperformed placebo
• No consistent differences in acne reduction between different combined OCPs


Meta-Analysis: Combined OCPs vs Oral Antibiotics

• 32 RCT met criteria (of 226 total pubs)
• At least 6 months of data
• Acne lesions counts, excluded PCOS, etc.

Spironolactone for Acne

- 116 Asian females
- 64 completed 20wks
- 53% excellent response
- 47% good response


Spironolactone for Acne

- 85 adult women → 73 evaluable
- 79% failed oral antibiotic
- 14% failed isotretinoin
- 50-100mg/day
- Mean duration = 10 months


Spironolactone for Acne

- Retrospective review of 110 women, mean follow-up 17 mo
- Overall 87% improved, 60% cleared
- CASS score reduction: face 73.1%, chest 75.9%, back 77.6%


Cost of Medications

- Spironolactone 50mg $0.32 per pill
- Doxycycline hyclate 100mg $0.84 per pill
- Doxycycline monohydrate 100mg $0.74 per pill
- Minocycline 100mg $2.81 per pill
- Isotretinoin 40mg $5.23 per pill

FDA Indication for OCP Use in Acne

- Moderate inflammatory acne
- At least 15 years old
- Has achieved menarche
- Desires contraception
- Plans to take OCP for at least 6 months
- Has failed to respond to topical anti-acne medications

Data obtained from Pharmacychecker.com for zip code 60091 on July 26, 2017.

Data obtained from Pharmacychecker.com for zip code 60091 on July 26, 2017.
OCPs and Health Screening

- Pelvic examination and Pap smear are not required for initiation of hormonal contraception in most women.
- Pelvic examination “…is not necessary prior to initiating oral contraceptives in teenagers.”
- History (PMH, family, social)
- Blood pressure measurement
- Pregnancy test


WHO Combined OCP Use Eligibility

<table>
<thead>
<tr>
<th>NOT RECOMMENDED</th>
<th>CAUTION OR SPECIAL MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Breastfeeding (F&lt;6wk postpartum)</td>
</tr>
<tr>
<td>Current breast cancer</td>
<td>P&lt;21 days</td>
</tr>
<tr>
<td>Breastfeeding &lt;6wk postpartum</td>
<td>Age ≥ 25 and light smoker (&lt;15 cigarettes/day)</td>
</tr>
<tr>
<td>Age ≥ 25yr and heavy smoker (≥15 cigarettes/day)</td>
<td>Previous hypertension (including pregnancy)</td>
</tr>
<tr>
<td>Hypertension (SBP ≥ 160, DBP ≥ 100)</td>
<td>Hypertension (SBP 140-159, DBP 90-99)</td>
</tr>
<tr>
<td>Diabetes with end-organ damage</td>
<td>Migraine w/o aura ≥ 35yr</td>
</tr>
<tr>
<td>Diabetes &gt;20 years duration</td>
<td>Known hyperlipidemia should be assessed</td>
</tr>
<tr>
<td>Current or previous DVT or PE</td>
<td>History of breast cancer ≥ 5 years of no disease</td>
</tr>
<tr>
<td>Major surgery with prolonged immobilization</td>
<td>Biliary tract disease</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>Mild compensated cirrhosis</td>
</tr>
<tr>
<td>Migraine w/focal neurologic sx, w/o aura F ≥ 35yr</td>
<td>History of cholestasis related to OCP use</td>
</tr>
<tr>
<td>Active viral hepatitis</td>
<td>Concurrent drug use affecting liver enzymes</td>
</tr>
<tr>
<td>Severe decompensated cirrhosis</td>
<td>Liver tumor (benign or malignant)</td>
</tr>
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WHO Combined OCP Use Eligibility

Combined OCP Progestins: VTE Risk

- 1st prospective, international active surveillance study
- 85,109 new OCP users followed 2-6yr → 206,296 woman-years
- DSP24d, DSP21d, non-DSP, LNG combined OCP
- All outcomes of interest were validated

Combined OCP Progestins: Meta-Analysis

- 26 studies reviewed
- All combined OCP use increases risk of VTE vs non-use with RR 3.5 (95% CI 2.9-4.3)
- Dose of ethinyl estradiol, individual progestin
- OCP 30-35µg EES + gestodene, desogestrel, drospirenone, or CYP A had RR 50-80% higher than for OCP containing levonorgestrel


OCPs and VTE: What We Know

- VTE incidence is higher in OCP users 40-49yo vs younger users
- VTE risk is higher in first 6-12 months of use – Normalizes by 3rd month after discontinuation
- Tobacco use increases risk
- Higher estrogen doses increase risk – 2-fold increase: 50mcg vs 30mcg


VTE Risk in Women:

<table>
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<tr>
<th>Annual Incidence of VTE</th>
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<tbody>
<tr>
<td>20-40 years</td>
</tr>
<tr>
<td>Combined OCP use</td>
</tr>
<tr>
<td>DSP, desogestrel, CYP use</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Postpartum (≤12 wks)</td>
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Combined OCP and VTE

- American Society for Reproductive Medicine
  - There is fair evidence that preparations of COCs with drospirenone or third-generation progestins have only a slightly higher risk of VTE compared with those containing norethindrone or levonorgestrel. (Grade B)
  - In the patient in whom combined hormonal contraception is appropriate, it is reasonable to use any currently available preparation.

How Young Is Too Young? Combined OCP and Bone Mineral Density

- COC + effect on BMD in perimenopause
- COC + or neutral effect on BMD in women > 30yo
- Bone mass ↑ by 25-40% during puberty → 90-95% of final bone mass achieved on average 3-4yrs after menarche
  - COC anti-gonadotropin effect ↓ ovarian estradiol production
- 20-30mcg EE COCs interfere with peak BMD acquisition

Spironolactone: Contraindications

- Renal insufficiency
- Hyperkalemia
  - ACEIs, ARBs, KCl, NSAIDs
- Pregnancy Category C
  - Feminization of male fetus
- Abnormal uterine bleeding (evaluate first)
**Banned substance list for NCAA, Olympics, etc.

Serum K: To Monitor or Not?

- Retrospective study, 2000-2014
- 967 healthy women, 18-45yr
- Mean age = 27.5yr and 26.2yr
- Baseline ↑ [K] = 0.76%
- +Spironolactone ↑ [K] = 0.72% (13/1802)
- Dose, duration of spironolactone

Monitoring Guidelines

- Renal function, electrolytes
  - Older patients
  - History of renal or cardiac disease
  - Concomitants medications which may influence renal function or serum [K]
  - Higher doses of spironolactone (200mg/day)
- ROS: thirst, weakness, lethargy, muscle cramps, dizziness, ↑ HR, ↓ urination
- Contraception, pregnancy testing
Spironolactone and Thrombosis

- Aldosterone is PROthrombotic\(^1\)
  - Arterial and venous thrombosis models
  - Endothelial dysfunction (↓ nitric oxide)
  - Fibrinolytic disorders (↑ PAI-1)
- Spironolactone improves this profile\(^1\)
  - Hepatic vein thrombosis, protein C deficiency\(^2\)
  - Portal vein thrombosis in HepB cirrhosis\(^3\)

\(^3\) M Kumar et al. Eur J Gastro Hepatol 2011; 23: 617.

Spironolactone: Black Box Warning

**WARNING**
Aldactone has been shown to be a tumorigen in chronic toxicity studies in rats (see Precautions). Aldactone should be used only in those conditions described under Indications and Usage. Unnecessary use of this drug should be avoided.

- 25 to 150 times usual human dose (by weight)
- Benign adenomas of testes
- Hepatocellular adenomas
- Thyroid follicular cell adenomas, carcinomas
- Benign uterine endometrial stromal polyps
- Breast adenomas

Spironolactone: Long-Term Safety

- 506 person-years (70.6mos) → 7 abnormal mammograms → no breast carcinoma\(^1\)
- 461 person-years (3yrs follow-up) → no cases of breast carcinoma\(^2\)
- 1475 women x 3.7yrs → 9 cases reported, age-specific rate of 8.3 cases\(^3\)
- 5 case control studies → no evidence for causality\(^4\)

\(^3\) Friedman GD, Ury HK. J Natl Cancer Inst 1980; 65: 723.

Spironolactone and Malignancies in Women

- Retrospective cohort study of Danish national prescription drug registry
- 2.3 million women, ≥20yo, 1995-2010
- 28.8 million woman-years


Treating Acne with Hormonal Therapy

- Take a thorough history, select patients appropriately.
- No significant differences between combined OCPs for acne treatment.
- Spironolactone has distinct differences compared to OCPs.
- The risk/benefit ratio of hormonal therapies may be favorable for many women with acne.