**Hormonal Therapies and Beyond: What’s New in Treating Acne in Women**

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**Disclosure of Relationships with Industry**

Bethanee J. Schlosser, MD, PhD
S007: Women’s Health Therapeutic Hotline
Hormonal Therapy and Beyond
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.

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**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

**Hormonal Therapy for Acne**

<table>
<thead>
<tr>
<th>Anti-Androgens (receptor)</th>
<th>Androgen Inhibitors (synthesis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestins</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>Progestins</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Flutamide</td>
</tr>
</tbody>
</table>

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### Strength of Evidence for Hormonal Therapy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined oral contraceptives</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>B</td>
<td>II, III</td>
</tr>
<tr>
<td>Flutamide</td>
<td>C</td>
<td>III</td>
</tr>
</tbody>
</table>

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  


### Combined Oral Contraceptives

- **Ethinyl estradiol**  
  - 1960s: 50-150µg per pill  
  - 2010s: 10-30µg per pill  
- **Androgenicity varies by progestin**  
- **Overall net effect is antiandrogenic due to estrogen impact**  
- **Reduce androgens via:**  
  - Reduces GnRH pulsatility → ↓ LH production  
  - ↑ sex hormone binding globulin synthesis

### Combined OCPs: Progestins

- **10 different progestins**  
  - 1st-3rd generation: derived from 19-nortestosterone  
  - 4th generation (drospirenone): derived from 17α-spironolactone  
- **Bind androgen receptor → variable activation**  
  - Drospirenone → competitive inhibition  
- **Reduce GnRH pulsatility → ↓ LH production**

### 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 (drospirenone)</td>
<td>Norethindrone</td>
<td>Norgestrel</td>
</tr>
<tr>
<td>Cypionate acetate</td>
<td>Norgestimate (norethindrone acetate)</td>
<td>Norethindrone acetate</td>
<td>Medroxyprogesterone acetate</td>
</tr>
<tr>
<td>Gestodene</td>
<td>Ethynodiol diacetate</td>
<td>Desogestrel (drospirenone)</td>
<td>Levonorgestrel</td>
</tr>
</tbody>
</table>

### Which Patients Are (or Are Not) Candidates for Combined OCP Therapy?

- **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
**WHO Combined OCP Use Eligibility**

<table>
<thead>
<tr>
<th>CONTRAINDED</th>
<th>CAUTION OR SPECIAL MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Breastfeeding (6wk – 6mo postpartum)</td>
</tr>
<tr>
<td>Current breast cancer</td>
<td>Postpartum (&lt;31 days)</td>
</tr>
<tr>
<td>Breastfeeding &lt; 6wk postpartum</td>
<td>Age ≥ 35 and light smoker (&lt;15 cigarettes/day)</td>
</tr>
<tr>
<td>Age ≥ 35yr and heavy smoker (≥ 15 cigarettes/day)</td>
<td>Hypertension (SBP ≥ 160, DBP ≥ 100)</td>
</tr>
<tr>
<td>Hypertension (SBP ≥ 140, DBP ≥ 90)</td>
<td>Hypertension (SBP 140-159, DBP 90-99)</td>
</tr>
<tr>
<td>Diabetes w/ end-organ damage</td>
<td>Migraine w/o aura &lt; 35yr</td>
</tr>
<tr>
<td>Diabetes ≥ 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>History of breast cancer ≥ 5 years of no disease</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>Migraine w/ focal neurologic sx, w/o aura if ≥ 35yr</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>
</tbody>
</table>

**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

**How Well Do Combined OCPs Work for Acne as Monotherapy?**

- 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

**Which Combined OCPs Are Most Effective for Treating Acne?**

- 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 DLQI 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

Arowojolu AO et al. The Cochrane Database of Systematic Reviews 2012; CD004425.

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 mos of use
  - Normalizes by 3rd month after discontinuation
- Tobacco use increases risk
- Higher estrogen doses increase risk
  - 2-fold increase: 50mcg vs 30mcg

Gomes MPV and Batcher SR. Arch Intern Med 2004; 164: 1905.

Combined OCP Progestins: Meta-Analysis

- 26 studies reviewed
- All combined OCP use increases risk of VTE vs non-use
  - 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

de Bastos MF et al. The Cochrane Database of Systematic Reviews 2014; CD010813.

VTE Risk in Women:

<table>
<thead>
<tr>
<th></th>
<th>Annual Incidence of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40 years</td>
<td>1-5/10,000</td>
</tr>
<tr>
<td>Combined OCP use</td>
<td>3-9/10,000</td>
</tr>
<tr>
<td>DSP, desogestrel, CYP use</td>
<td>10-13/10,000</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>5-20/10,000</td>
</tr>
<tr>
<td>Postpartum (≤12 wks)</td>
<td>40-65/10,000</td>
</tr>
</tbody>
</table>


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.

How Do Combined OCPs Compare to Oral Antibiotics for the Treatment of Acne?
Spironolactone

- Aldosterone antagonist \(\rightarrow\) diuresis
- Competitive inhibitor at the androgen receptor
- High doses \(\downarrow\) androgen synthesis via P450 inhibition
- Inhibits 5α-reductase
- ↑ hepatic SHBG synthesis
- Some affinity for progesterone receptor

Meta-Analysis: Combined OCPs vs Oral Antibiotics


Spironolactone

- Not approved by the FDA for dermatologic indications
- Acne vulgaris
  - Reduces sebum (dose-dependent)
- Female hirsutism
- Female androgenetic alopecia
- Dose: 50-200mg

When to Consider Spironolactone for Acne

- 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 with hypertension and acne
- Patients unable to take/access/afford other acne medications

Spironolactone: Contraindications

- Renal insufficiency
- Hyperkalemia
  - ACEIs, ARBs, KCl, NSAIDs
- Pregnancy Category C
  - Feminization of male fetus
- Abnormal uterine bleeding (evaluate first)

**Banned substance for NCAA, Olympics, etc.**

Spironolactone for Acne

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

Spironolactone for Acne: Combination Therapy

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

Spironolactone: In My Clinical Practice

- Starting dose: 50mg to 100mg
  - Drospirenone 3mg = 25mg spironolactone
- Once daily dosing until 100mg po BID
  - BID dosing may minimize adverse effects
- Better bioavailability if taken with food
- Assess initial impact in 2 to 3 months
- Dose increase by 25mg or 50mg depending on response
- Once well-controlled for 6 months, consider taper

Spironolactone: Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic effect</td>
<td>29%</td>
</tr>
<tr>
<td>Menstrual irregularities (any)</td>
<td>22%</td>
</tr>
<tr>
<td>Spotting</td>
<td>12%</td>
</tr>
<tr>
<td>Change in flow (↑↓)</td>
<td>0% - 6%</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>17%</td>
</tr>
<tr>
<td>Breast enlargement</td>
<td>4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18%</td>
</tr>
<tr>
<td>Headache</td>
<td>13%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12%</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>11%</td>
</tr>
</tbody>
</table>

Spironolactone: Black Box Warning

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

Monitoring Guidelines

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

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

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.
Spironolactone: Long-Term Safety

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


Isotretinoin Use in Females with Acne

- 35 million visits for acne between 1990-1997
  - Women had 1.4X # of visits for acne vs men
  - Men were 1.7X more likely to receive isotretinoin at a visit
- Duration of time elapsed prior to isotretinoin
  - Retrospective chart review 2005-2014, 137 patients met criteria
  - Mean age isotretinoin: M 18.4yr, F 21.2yr (p = 0.006)
  - M = 124.8 days, F = 199.3 days (NS)


Topical Acne Treatment Response by Sex

- Dapsone 7.5% gel QD, phase 3, pooled subgroup analysis
- Moderate inflammatory acne

<table>
<thead>
<tr>
<th>Vehicle Female</th>
<th>Vehicle Male</th>
<th>Dapsone 7.5% Female</th>
<th>Dapsone 7.5% Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean reduction – Total lesion counts</td>
<td>45.8%</td>
<td>39.7%</td>
<td>53.4%</td>
</tr>
<tr>
<td>Mean reduction – Noninflammatory</td>
<td>37.1%</td>
<td>41.8%</td>
<td>49.8%</td>
</tr>
<tr>
<td>Mean reduction – inflammatory</td>
<td>44.3%</td>
<td>51.5%</td>
<td>49.7%</td>
</tr>
<tr>
<td>Clear/almost clear</td>
<td>23.2%</td>
<td>18.3%</td>
<td>33.9%</td>
</tr>
</tbody>
</table>

### Topical Acne Treatment Response by Sex

- Post hoc analysis of phase 3 RCT, mod to severe acne
- Clindamycin 1.2%/BP 3.75% gel QD vs vehicle

<table>
<thead>
<tr>
<th></th>
<th>Vehicle Female</th>
<th>Vehicle Male</th>
<th>Clinda/BPO Female</th>
<th>Clinda/BPO Male</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean reduction - Inflammatory</td>
<td>30.9%</td>
<td>32.3%</td>
<td>65.3%</td>
<td>55.8%</td>
<td>0.049</td>
</tr>
<tr>
<td>Mean reduction - Noninflammatory</td>
<td>30.2%</td>
<td>25.2%</td>
<td>55.7%</td>
<td>48.1%</td>
<td>0.064</td>
</tr>
<tr>
<td>≥ 2 grades Improvement</td>
<td>20.5%</td>
<td>13.6%</td>
<td>42.5%</td>
<td>28.2%</td>
<td>0.049</td>
</tr>
</tbody>
</table>