Common Questions and Controversies in the Management of Acne in Women

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Bethanee J. Schlosser, MD, PhD

S016: Common Questions and Controversies in the Management of Acne in Women

Author: UpToDate®

Advisory Board: Allergan, UCB, Beiersdorf

Speaker: Allergan

Off-label use of medication will be discussed.
Outline

• Combined oral contraceptives for acne
  – Comparison of COC formulations
  – COC vs oral antibiotic

• Spironolactone for acne
  – Predictors of response
  – Serum potassium monitoring
When Should I Consider Prescribing Combined Oral Contraceptives for Acne?
<table>
<thead>
<tr>
<th></th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Choice</strong></td>
<td>Topical Retinoid</td>
<td>Topical Retinoid + Topical Antimicrobial</td>
<td>Oral Antibiotic + Topical Retinoid +/- BPO</td>
</tr>
<tr>
<td><strong>Alternatives</strong></td>
<td>Alt. Topical Retinoid or Azelaic acid* or</td>
<td>Alt. Topical Antimicrobial Agent + Alt.</td>
<td>Oral Isotretinoin or High Dose Oral</td>
</tr>
<tr>
<td></td>
<td>Salicylic acid</td>
<td>Topical Retinoid or Azelaic Acid*</td>
<td>Antibiotic + Topical Retinoid +/- BPO/Azelaic Acid*</td>
</tr>
<tr>
<td><strong>Alternatives</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>for Females</strong></td>
<td>See 1st Choice</td>
<td>See 1st Choice</td>
<td></td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>Topical Retinoid</td>
<td>Topical Retinoid +/- BPO</td>
<td></td>
</tr>
</tbody>
</table>

1. Consider physical removal of comedones; 2. With small nodules (>0.5 - 1 cm); 3. Second course in case of relapse; 4. For pregnancy, see text; 5. See text

*There was not consensus on this alternative recommendation, however, in some countries Azelaic acid prescribing is appropriate practice.

FDA Indication for Combined 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
Combined OCPs: Noncontraceptive Health Benefits

1960
- Dysmenorrhea
- Menorrhagia

1970
- Bone cysts
- Ovarian cysts

1980
- Benign breast disease
- Endometrial cancer

1990
- Fibroids
- Colon cancer

2000
- Acne

2010
- PMDD

How Young Is Too Young For Combined Oral Contraceptive Use in Acne?
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\(^1\)
  - COC anti-gonadotropin effect ↓ ovarian estradiol production
- 20-30mcg EE COCs interfere with peak BMD acquisition\(^2\)
- Initiate ≥ 1 year after menarche

How Effective Are Combined Oral Contraceptives for Acne?
Combined Oral Contraceptives

• Ethinyl estradiol
  – 1960s: 50-150µg per pill
  – 2010s: 10-30µg per pill

• Progestin androgenicity varies

• Ethinyl estradiol + any COC progestin = anti-androgenic

<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>
</tbody>
</table>
- 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 Oral Contraceptive is “Best” for Acne?
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.
Hormonal Contraceptives: Patient Assessment of Acne

- Retrospective study of 2147 F on hormonal contraceptive at initial teledermatology assessment for acne

<table>
<thead>
<tr>
<th>Contraceptive Type</th>
<th>N (%)</th>
<th>Mean Age (years)</th>
<th>Age Range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined oral contraceptives</td>
<td>1237 (57)</td>
<td>24.3</td>
<td>15-51</td>
</tr>
<tr>
<td>Intrauterine device</td>
<td>493 (23)</td>
<td>26.8</td>
<td>17-47</td>
</tr>
<tr>
<td>Subdermal implant</td>
<td>159 (7)</td>
<td>23.5</td>
<td>16-32</td>
</tr>
<tr>
<td>Vaginal ring</td>
<td>111 (5)</td>
<td>25.1</td>
<td>18-46</td>
</tr>
<tr>
<td>Depot injection</td>
<td>96 (4)</td>
<td>23.5</td>
<td>15-44</td>
</tr>
<tr>
<td>Other</td>
<td>51 (2)</td>
<td>25.0</td>
<td>17-41</td>
</tr>
<tr>
<td>All</td>
<td>2147</td>
<td>24.9</td>
<td>15-51</td>
</tr>
</tbody>
</table>

Combined OCPs: Patient Assessment of Effect on Acne
Is Pelvic Examination Required Prior to Starting a Combined Oral Contraceptive?
OCPs and Health Screening

- Pelvic examination and Pap smear are not required for initiation of hormonal contraception in most women\(^1\)

- Pelvic examination “…is not necessary prior to initiating oral contraceptives in teenagers”\(^2\)

- PMH, family history
- Blood pressure measurement
- Pregnancy test

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## WHO Combined OCP Use: Medical Suitability

<table>
<thead>
<tr>
<th>NOT RECOMMENDED</th>
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<tbody>
<tr>
<td>Pregnancy</td>
<td>Breastfeeding (6wk – 6mo postpartum)</td>
</tr>
<tr>
<td>Current breast cancer</td>
<td>Postpartum (&lt; 21 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>Previous hypertension (including pregnancy)</td>
</tr>
<tr>
<td>Hypertension (SBP ≥ 160, DBP ≥ 100)</td>
<td>Hypertension (SBP 140-159, DBP 90-99)</td>
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<tr>
<td>Diabetes with end-organ damage</td>
<td>Migraine w/o aura &lt; 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>
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<tr>
<td>Previous CVA</td>
<td>Mild compensated cirrhosis</td>
</tr>
<tr>
<td>Migraine w/ focal neurologic sx, w/o aura if ≥ 35yr</td>
<td>History of cholestasis related to OCP use</td>
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<td>Concurrent drug use affecting liver enzymes</td>
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<td>Severe decompensated cirrhosis</td>
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<td>Liver tumor (benign or malignant)</td>
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What is the Risk of VTE with Combined OCP Use?
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OCPs and VTE: What We Know

• VTE incidence is higher in OCPs 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 30mcg¹

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

• 30-35µg EES + desogestrel, drospirenone, gestodene, or CYPA had RR 50-80% higher than OCP containing levonorgestrel

de Bastos M et al. The Cochrane Database of Systematic Reviews 2014; CD010813.
## VTE Risk in Women:

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<th>Annual Incidence of VTE</th>
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<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>10-15/10,000</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>
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The American College of Obstetricians and Gynecologists Committee opinion 540. [http://www.acog.org](http://www.acog.org)

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.
When Should I Consider Prescribing Spironolactone for Acne?
When to Consider Spironolactone for Acne

- Patients on combined OCP but inadequate control of acne
- Patients with contraindications to combined OCP
  - Patients with known hypercoagulability
  - 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
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, FIFA, Olympics, etc.**
Spironolactone for Acne: Combination Therapy

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

How Do I Dose Spironolactone for Acne?
Spironolactone for Acne: Level of Evidence

- Cochrane review for acne and/or hirsutism
  - Only 1 study addressed acne as outcome
  - No evidence for effectiveness for the treatment of acne vulgaris

- Hybrid systematic review of 10 RCT, 21 case series
  - All at ‘high risk’ of bias, quality of evidence was low/very low
  - Crossover trial demonstrated superiority of spironolactone 200mg/day vs placebo for inflammatory acne
  - Limited quality evidence to support use at ≤ 100mg/day

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
Which Patients Are Most Likely to Respond to Spironolactone?
Predicting Response to Spironolactone

- Retrospective, 70 F ≥ 20yo (mean 31.3yo) with facial acne
- Spironolactone ≤ 150mg/day x median 6 months
- Remission = ≤ 5 comedones, ≤ 2 inflammatory
- 75% prior OCP; 56% prior isotretinoin

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<th>Factor</th>
<th>OR (95% CI)</th>
<th>p value</th>
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<td>High # inflammatory lesions at inclusion</td>
<td>1.08 (1.03-1.13)</td>
<td>0.001</td>
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<td>Relapse with previous isotretinoin</td>
<td>2.46 (1.09-5.54)</td>
<td>0.029</td>
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<td>OCP containing 1st or 2nd generation progestin</td>
<td>2.77 (1.35-5.71)</td>
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Do I Need to Monitor Serum [K] in Patients on Spironolactone for Acne?
Monitor serum potassium within 1 week of initiation or titration of ALDACTONE and regularly thereafter. More frequent monitoring may be needed when ALDACTONE is given with other drugs that cause hyperkalemia or in patients with impaired renal function.

- CHF
- HTN
- Edema
- Primary hyperaldosteronism
Serum [K]: No Need to Monitor in Healthy Young Acne Patients

- 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

Serum [K]: Monitor in Older Acne Patients

- Retrospective study, 2006-2016
- 618 women ages 18-65yo prescribed spironolactone for acne
- 124 serum [K] at baseline and at follow-up within 12 months
  - No comorbidities of interest (HTN, DM, renal failure)
  - Mean age at spironolactone initiation = 32yo (18-57yo)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N</th>
<th>Rate of Incident Hyperkalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-45yo</td>
<td>112</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>46-65yo</td>
<td>12</td>
<td>2 (16.7%)</td>
</tr>
</tbody>
</table>

- p = 0.0245

Serum [K] Monitoring Guidelines

• Renal function, electrolytes
  – Older patients (>45yo)
  – Higher doses of spironolactone (200mg/day)
  – History of renal or cardiac disease
  – Concomitants medications which may influence renal function or serum [K]

• ROS: dizziness, lethargy, abnormal thirst, muscle cramps, ↑ HR, ↓ urination
Does Spironolactone Exposure Increase the Risk of Malignancy?
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)

- Breast adenomas
- Hepatocellular adenomas
- Benign adenomas of testes
- Benign uterine endometrial stromal polyps
- Thyroid follicular cell adenomas, carcinomas
Spironolactone: Breast Cancer

- 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\(^4\)

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\(^3\) 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

How Do Hormonal Treatments Compare to Oral Antibiotics in Acne?
Meta-Analysis: COC vs Oral Antibiotics

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

<table>
<thead>
<tr>
<th>Total Lesion Percent Reduction</th>
<th>3Abx</th>
<th>3OCP</th>
<th>3Plac</th>
<th>6Abx</th>
<th>6OCP</th>
<th>6Plac</th>
</tr>
</thead>
<tbody>
<tr>
<td># Studies</td>
<td>19</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td># ITT Subjects</td>
<td>1325</td>
<td>731</td>
<td>777</td>
<td>42</td>
<td>3383</td>
<td>1502</td>
</tr>
<tr>
<td>Weighted Mean of Percent Reduction (%)</td>
<td>48.0</td>
<td>37.3</td>
<td>24.5</td>
<td>52.8</td>
<td>55.0</td>
<td>28.6</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>43.6-52.4</td>
<td>33.1-41.5</td>
<td>20.5-28.5</td>
<td>51.5-54.1</td>
<td>47.9-62.1</td>
<td>20.8-36.4</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>9.9</td>
<td>4.8</td>
<td>4.6</td>
<td>0.9</td>
<td>12.6</td>
<td>13.7</td>
</tr>
</tbody>
</table>

Meta-Analysis: COC vs Oral Antibiotics

Drug Usage Survival of Spironolactone vs Oral Antibiotics for Acne

- Retrospective database, 11838 females 12-40yo
- Duration of treatment (≥ 12 months)
- Spironolactone vs oral antibiotics: HR = 0.74 (0.71-0.77)

Hormonal Management of Acne

• There are no significant differences between different formulations of combined OCPs for acne treatment.

• Combined OCPs are as effective as oral antibiotics for the chronic treatment of acne.

• Serum potassium monitoring should be considered in older women taking spironolactone for acne.

• Spironolactone does not increase risk of malignancy in women.
Dermatology Foundation
SHAPING THE FUTURE OF DERMATOLOGY