Hormonal Therapy for Acne

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Disclosure of Relationships with Industry

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S013: Women’s Health Therapeutic Hotline

Hormonal Therapy for Acne

Elorac, Galderma, Novan: Investigator, Fees to Institution

Novan: Advisory Board, Honoraria

Decision Support in Medicine, UpToDate®: Author, Honoraria

Off-label use of medication will be discussed.
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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Triggers to Prompt Endocrinologic Evaluation in Adult Women

- Hirsutism
- Androgenetic alopecia
- Virilization (clitoromegaly, deep voice, muscular habitus)
- Acanthosis nigricans
- Central/abdominal obesity
- Oligomenorrhea/amenorrhea
- Infertility
- Sudden onset, severe acne
- Acne resistant to “conventional” therapy
Endocrinologic Evaluation

• Total, free testosterone
• Dehydroepiandrosterone sulfate (DHEAS)
• 17OH-progesterone

• Follicle-stimulating hormone (FSH)
• Leutinizing hormone (LH)

• Thyroid-stimulating hormone (TSH)
• Prolactin
Endocrinologic Evaluation

• Off combination OCP or other hormonal therapy for 4-6 weeks

• Obtain early in morning (diurnal variation)

• Obtain early in follicular phase (with onset of menses)
  • Avoid mid-cycle evaluation
The diagram illustrates the ovarian cycle, highlighting the stages of growing follicle, ovulation, corpus luteum, and corpus albicans. It also shows the changes in body temperature, anterior pituitary hormones (Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH)), ovarian hormones (Estradiol and Progesterone), and uterine cycle (Menses, Follicular phase, Luteal phase, and Menses).
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• Perimenstrual flare
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• Alternative to repeat isotretinoin
<table>
<thead>
<tr>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comedonal</td>
<td>Papular/pustular</td>
<td>Papular/pustular</td>
</tr>
<tr>
<td>Topical Retinoid</td>
<td>Oral Antibiotic + Topical Retinoid + BPO</td>
<td>Oral Antibiotic + Topical Retinoid + BPO</td>
</tr>
<tr>
<td>1st Choice</td>
<td>Oral Antibiotic + Topical Retinoid +/- BPO</td>
<td>Oral Isotretinoin³</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Oral Isotretinoin or High Dose Oral Antibiotic + Topical Retinoid + BPO</td>
<td></td>
</tr>
<tr>
<td>1st Choice</td>
<td>Oral Antibiotic + Topical Retinoid +/- BPO</td>
<td>Oral Isotretinoin³</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Oral Isotretinoin or High Dose Oral Antibiotic + Topical Retinoid + BPO</td>
<td></td>
</tr>
<tr>
<td>for Females</td>
<td>Oral Isotretinoin or High Dose Oral Antibiotic + Topical Retinoid + BPO</td>
<td></td>
</tr>
<tr>
<td>Maintenance therapy</td>
<td>Topical Retinoid</td>
<td>Topical Retinoid +/- BPO</td>
</tr>
</tbody>
</table>

1. Consider physical removal of comedones. 2. Add oral isotretinoin in case of relapse; 3. For pregnancy, see text; 4. See text. 5. There was not consensus on this alternative recommendation; however, in some countries Azelaic acid prescribing is appropriate practice.

# 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></td>
</tr>
<tr>
<td>Flutamide</td>
<td></td>
</tr>
</tbody>
</table>
# 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
  - 1\textsuperscript{st}-3\textsuperscript{rd} generation: derived from 19-nortestosterone
  - 4\textsuperscript{th} generation (drospirenone): derived from 17α-spironolactone

- Bind androgen receptor $\rightarrow$ variable activation
  - Drospirenone $\rightarrow$ competitive inhibition

- Reduce GnRH pulsatility $\rightarrow$ ↓ 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 (etonogestrel)</td>
<td>Norethindrone</td>
<td>Norgestrel</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>Norgestimate (norelgestromin)</td>
<td>Norethindrone acetate</td>
<td>Medroxyprogesterone acetate</td>
</tr>
<tr>
<td></td>
<td>Gestodene</td>
<td>Ethynodiol diacetate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Desogestrel (etonogestrel)</td>
<td>Levonorgestrel</td>
<td></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>NOT RECOMMENDED</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; 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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Active viral hepatitis</td>
<td>Concurrent drug use affecting liver enzymes</td>
</tr>
<tr>
<td>Severe decompensated cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Liver tumor (benign or malignant)</td>
<td></td>
</tr>
</tbody>
</table>
OCPs and Health Screening

• Pelvic examination and Pap smear are no longer required for initiation of hormonal contraception in most women\(^1\)

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

• 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

<table>
<thead>
<tr>
<th></th>
<th>Inflammatory Lesions</th>
<th>Non-inflammatory Lesions</th>
<th>Total Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage reduction in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inflammatory lesion count from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cycle 1</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>20</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>30</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>40</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>Cycle 5</td>
<td>50</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

• 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)

Which Combined OCPs Are Most Effective for Treating 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>
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Hormonal Contraceptives: Patient Assessment of Acne

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 30mcg


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 CYPA had RR 50-80% higher than for OCP containing levonorgestrel

de Bastos M 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>

The American College of Obstetricians and Gynecologists Committee opinion 540. [http://www.acog.org](http://www.acog.org)

Spironolactone

• Aldosterone antagonist $\rightarrow$ diuresis

• Competitive inhibition at the androgen receptor

• High doses $\rightarrow$ ↓ androgen synthesis via P450 inhibition

• Inhibits 5α-reductase

• $\uparrow$ hepatic SHBG synthesis

• Some affinity for progesterone receptor
Spironolactone

- Not approved by the FDA for dermatologic indications
- Acne vulgaris
  - Reduces sebum (dose-dependent)
- Hirsutism
- Female androgenetic alopecia
- Dose: 50-200mg
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 with hypertension and acne (2 birds with 1 stone)
- Patients unable to take/access/afford other acne medications
Cost of Medications

- Spironolactone 50mg $0.58 per pill
- Doxycycline hyclate 100mg $1.51 per pill
- Doxycycline monohydrate 100mg $1.04 per pill
- Minocycline 100mg $3.27 per pill
- Isotretinoin 30mg $8.48 per pill

Data obtained from Pharmacychecker.com for zipcode 60091 on July 28, 2016.
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.**
Spironolactone for Acne

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

Sato K et al. *Aesth Plast Surg* 2006; 30: 689.
Spironolactone for Acne

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

Spironolactone: In My Clinical Practice

- Starting dose: 50mg to 100mg
  - Drospirenone 3mg = 25mg spironolactone
- Once daily dosing until 100mg po BID
- 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 ($\uparrow/\downarrow$)</td>
<td>6% /4%</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>15%</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>

Serum K: To Monitor or Not?

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

- Contraception, pregnancy testing

- ROS: thirst, weakness, lethargy, muscle cramps, dizziness, ↑ HR, ↓ urination
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$^3$

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

- Danish national prescription drug registry
- 1995-2010, 2.3 million women, ≥ 20yo
- 28.8 million person-years

The Dermatology Foundation has supported & advanced my career.