Acne Guidelines

Use of hormonal therapy in acne

Julie C Harper MD
Conflict of Interest Disclosure

• Speaker/Advisor
  • Allergan
  • Bayer
  • Galderma
  • Valeant

• Investigator
  • Bayer
Our task:

What is the effectiveness and what are the potential side effects of hormonal agents in the treatment of adult acne and acne vulgaris in adolescents to adults including:

a) contraceptive agents
b) Spironolactone
c) Antiandrogens
d) oral corticosteroids
## SORT grading

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Recommendation based on consistent and good-quality patient-oriented evidence</td>
</tr>
<tr>
<td>B</td>
<td>Recommendation based on limited-quality patient-oriented evidence</td>
</tr>
<tr>
<td>C</td>
<td>Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening</td>
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<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of recommendation</th>
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<tbody>
<tr>
<td>Contraceptive Agents</td>
<td>A</td>
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<tr>
<td>Spironolactone</td>
<td>B</td>
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<tr>
<td>Antiandrogens</td>
<td>B</td>
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<tr>
<td>Oral corticosteroids</td>
<td>B</td>
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</tbody>
</table>
Oral Contraceptives
Oral contraceptives

Which COC’s work in acne??
Risks:

- Venous thromboembolism
- Stroke
- MI
- Breast cancer

Venous thrombosis

Cochrane meta-analysis

- 26 studies

Conclusions:

All COC use increases the risk of VTE compared to non-use

The relative risk of venous thrombosis for COCs with 30-35μg of ethinyl estradiol and gestodene, desogestrel, cyproterone acetate, or drospirenone was similar and about 50-80% higher than for COCs with levonorgestrel

deBastos et al. Cochrane Database. Online pub March 2014.
DOI:10.1002/14651858.CD010813.pub2.
<table>
<thead>
<tr>
<th>Risks of VTE in perspective</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive age non-COC user</td>
<td>4 to 5</td>
</tr>
<tr>
<td>Reproductive age COC users</td>
<td>8 to 9</td>
</tr>
<tr>
<td>Pregnancy (third trimester)</td>
<td>12</td>
</tr>
<tr>
<td>Puerperium</td>
<td>30</td>
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</tbody>
</table>

Risks according to age alone:

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Risks per 10 000 women per year</th>
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</thead>
<tbody>
<tr>
<td>45 to 49</td>
<td>6</td>
</tr>
<tr>
<td>55 to 59</td>
<td>13</td>
</tr>
<tr>
<td>65 to 69</td>
<td>22</td>
</tr>
<tr>
<td>75 to 79</td>
<td>43</td>
</tr>
</tbody>
</table>

Numbers represent the incidence of VTE per 10 000 women per year.\(^5,21,40,41\)

The FDA has funded its own study to evaluate the risk of VTE in DRSP compared to other hormonal contraceptives.

Findings suggest that there is a 1.5 fold increase in the risk of blood clots for women who use OCs containing DRSP compared to other OCs.

“To put this into perspective, if the risk of developing a blood clot among women using other oral contraceptives is about 6 women in 10 thousand, then the risk of developing a blood clot among women using drsp-containing oral contraceptives would be about 10 women in 10 thousand.”

www.fda.gov
Treating acne with COCs

- Frequently takes at least 3 cycles of COC to see meaningful changes in acne reduction
- Papinocolauo smear and bimanual pelvic exam are no longer deemed mandatory prior to initiating the use of a COC
- Obtaining a thorough medical history and a blood pressure measurement are important prior to prescribing a COC

Oral contraceptives and antibiotics

- Of all alleged antibiotic-oral contraceptive interactions, 76% involve rifampin
- Rifampin and griseofulvin are the only anti-infectives that interact with COCs, lessening their effectiveness

Take a history!

**Contraindications:**

- Pregnancy
- Breast cancer (current)
- Breast feeding <6 weeks postpartum
- Age >35 and heavy smoker (>15 cigarettes/day)
- HTN
- DM with nephropathy, retinopathy, neuropathy, vascular disease
- DVT-hx or current
- Hx of heart disease
- Hx of stroke
- Migraine headaches (with focal neurological symptoms at any age or without focal neurological symptoms but >35 years of age)
- Cirrhosis or liver tumor (benign or malignant)
Spironolactone
139 Japanese patients with acne (116 females, 23 males) started on 200mg daily of spironolactone for 20 weeks of treatment. The dose was lowered by 50mg every 4 weeks after the initial 8 weeks. 64 females completed the 20 week study. Gynecomastia developed in 3 males within 4-8 weeks and subsequently treatment was discontinued in all males. 

Spironolactone-efficacy

- 52 of 116 females dropped out of study for various reasons including menstrual irregularities although most patients who completed the regimen also experienced menstrual irregularities (80% of 116)

- All 64 females who completed the 20 week regimen exhibited clinical improvement
  - 53% excellent
  - 47% good

Fig. 2. A 27-year-old female with acne vulgaris from the jawline to the neck who did not improve with repeated alpha hydroxy acid (AHA) peeling and oral antibiotics. (A) Before treatment. (B) After 20 weeks of oral spironolactone (excellent results, fewer inflammatory spots).

Fig. 3. A 31-year-old female with acne vulgaris and seborrheic dermatitis on the whole face. (A) Before treatment. (B) After 4 months of oral spironolactone (excellent results). Sebum discharge was markedly reduced, and seborrheic dermatitis and acne both improved.
Spironolactone- side effects

- Side effects are dose-related:
  
  diuresis (29%)
  menstrual irregularities (22%)
  breast tenderness (17%)
  breast enlargement
  fatigue
  headache
  dizziness

- **Pregnancy category C:** Concomitant use of COC is recommended to both regulate menses and to prevent pregnancy in many patients

Spironolactone is not FDA-approved for the treatment of acne

Spironolactone and K+

- Retrospective study of 974 healthy young women taking spironolactone for acne vs 1165 healthy young women taking and not taking spironolactone

- 18-45 years of age with no cardiovascular disease, renal failure, or use of medications that affect the renin-angiotensin-aldosterone system

Plovanich M et al. JAMA Dermatology online March 22, 2015.
Spironolactone and K+

RESULTS:
- There were 13 abnormal serum potassium measurements in 1,802 measurements obtained among young women receiving spironolactone therapy for acne (hyperkalemia rate = 0.72%). Baseline rate of hyperkalemia in this population is 0.76%.

CONCLUSION:
Routine potassium monitoring is unnecessary for healthy women taking spironolactone for acne.

Plovanich M et al. JAMA Dermatology online March 22, 2015.
Spironolactone and K+

Check K+ if:

✓ Older age
✓ Hx of renal or cardiac disease
✓ Hx of impaired hepatic function (minor alterations of fluid and electrolyte balance may precipitate hepatic coma)
✓ Higher doses of spironolactone (200mg/day)

Spironolactone is not FDA-approved for the treatment of acne
Spironolactone and K+

- Check K+ if on certain medications:
  - ACE inhibitors
  - Angiotensin II antagonists
  - Aldosterone blockers
  - NSAIDS (i.e. indomethacin)
  - Salt substitutes
  - K+ supplementation
  - Trimethoprim/sulfamethoxazole
Spironolactone and breast cancer

• FDA Black Box Warning:

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Spironolactone should be used only in those conditions described under Indications and Usage. Unnecessary use of this drug should be avoided.

(Dosages used in these rat studies were 25-100 times higher than those administered to humans; benign adenomas of the thyroid and testes, malignant mammary tumors, proliferative changes in the liver)


Spironolactone is not FDA-approved for the treatment of acne
Spironolactone use and the risk of breast and gynecologic cancers

• 2.3 million women ≥20 years of age followed for 28.8 million person-years using a Danish nationwide prescription drug registry

• 1.3 million spironolactone prescriptions between 1995-2010

• No evidence of increased risk of breast, uterus or ovarian cancer with spironolactone use.

Spironolactone and risk of incident breast cancer in women older than 55 years: retrospective, matched cohort study.

- 1,290,625 women older than 55 (8.4 million patient years)
- Exposed cohort included women who received at least 2 prescriptions of spironolactone after 55 years of age
- 2 unexposed matched controls per case
- 29,491 new cases of breast cancer were recorded in the study population
- No difference in breast cancer rates between exposed and nonexposed cohorts (hazard ratio 0.99, 95%CI 0.87-1.12)

Spironolactone and pregnancy/nursing

- Spironolactone is pregnancy category C
  - Spironolactone should NOT be used during pregnancy
  - Increased risk of hypospadias and feminization of the male fetus

- Spironolactone’s active metabolite canrenone has been found in breast milk but at 0.2% of the maternal dose. Both the AAP and the WHO classify spironolactone as compatible with lactation.

Murase et al. JAAD 2014;70:401.e1-14.
Butler et al. JAAD 2014;70:417.e1-10.
Spironolactone

- Dosages 25mg-200mg (I prefer a max dose of 100mg)
- **Higher doses = higher rate of side effects**
- Food increases bioavailability by almost 100% (package insert)
- May take 3 months to “kick in”
- Long term unless side effects, pregnancy, no longer needed
  - Surveys of 91 women followed for 8 years (200 person years exposure to spironolactone; mean treatment length=28.5 months) found no serious illness thought to be attributed to spironolactone
  - Concomitant use of oral contraceptive lessens menstrual irregularities and prevents pregnancy (risk of feminization of male fetus in late first trimester)


*Spironolactone is not FDA-approved for the treatment of acne*
American Acne & Rosacea Society

Founded by dermatologists dedicated to professional education, patient care, and research

www.acneandrosacea.org