Hormonal Therapies for Acne

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Conflict of Interest Disclosure

- Speaker/Advisor
  - Allergan
  - Bayer
  - Galderma
  - Valeant

- Investigator
  - Bayer
Contraceptives Agents
Oral contraceptives

- ethinyl estradiol 10-50μg

- Progestin:
  - First generation (estranes): norethindrone
  - Second generation: levonorgestrel, norgestimate
  - Third generation (gonanes): desogestrel, gestodene
  - Fourth generation: drospirenone
Oral contraceptives FDA approved to treat acne

- Ortho-Tri-Cyclen (norgestimate 0.18mg-0.215mg-0.250mg/ee 35μg)

Indicated for the treatment of moderate acne vulgaris in females ≥15 years of age who have no known contraindication to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications.
Oral contraceptives FDA approved to treat acne

- Estrostep FE (Norethindrone acetate 1mg/ee 20-30-35μg and Ferrous Fumarate in the hormone-free interval)

Indicated for the treatment of moderate acne vulgaris in females ≥15 years of age who have no known contraindication to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications.

Estrostep FE should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control and plans to stay on it for at least 6 months
Oral contraceptives FDA approved to treat acne

- YAZ (3mg drospirenone/20μg ee)

  Indicated to treat moderate acne for women at least 14 years old, who have no known contraindications to oral contraceptive therapy and who have achieved menarche. Yaz should only be used to treat acne if the patient desires an oral contraceptive for birth control.

- BEYAZ
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></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.\(^{5,21,40,41}\)

What does the FDA have to say?

- 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
Oral contraceptive

- Stroke risks
  - 2.5x increase in ischemic stroke in women age 20-24 who use OCP’s.
  - Risk is directly proportional with estrogen dose
  - Risk increases with age
  - HTN, cigarette smoking and migraine headaches substantially increase this risk

Oral contraceptive

- MI risks
  - 80% of heart attacks among OCP users are attributable to cigarette smoking, with the remainder occurring in OCP users with other risk factors such as HTN or DM

Oral contraceptives

- **Benefits**
  - Protection against ovarian cancer
  - Protection against endometrial cancer
  - Protection against PID, uterine leiomyomas and ovarian cysts
  - Regulation of menstrual cycle

Treating Acne with COCs

- COCs may be used alone or in combination with other acne treatments.
- COCs may be useful in women with or without a history of “hormonally-induced” worsening of acne (i.e. premenstrual flares).
- COCs may be useful in women with clinical and/or laboratory findings of hyperandrogenism and in women without these findings.
Treating acne with COCs

- Frequently takes at least 3 cycles of COC to see meaningful changes in acne reduction
- Papinocolaou smear and bimanual pelvic exam are no longer deemed mandatory prior to initiating the use of a COC
- Obtain 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
Spironolactone-efficacy

- 139 Japanese patients with acne (116 females, 23 males) started on 200mg daily of spironolactone
- 20 weeks of treatment
  - 200mg daily for first 8 weeks
  - After initial 8 weeks, dose lowered by 50mg every 4 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.
Side effects
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

Risks
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.
Practical approach
Spironolactone

- Dosages 25mg-200mg (I prefer a max dose of 100mg)
- Side effects:
  - menstrual irregularities
  - breast tenderness/swelling
  - fatigue
  - headaches
- Higher doses = higher rate of side effects
- 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
Spironolactone

- Food increases bioavailability by almost 100% (Package insert)
How quickly does it work?

- No good objective answer
  - Studies are small and frequently spironolactone is used as an adjunct to other topical or oral medications
- I counsel patients that it may take 3 months to see a meaningful response, similar to other hormonal based therapies
How long?

- 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

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Portland, OR
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Thank you