Acne and Rosacea Update
Maui Derm NP+PA FALL 2017

Heather Roebuck DNP, FNP-BC
James Treat MD
George Martin MD

Case Study

- 32 yr. old female w/ chronic mild – moderate papulopustular acne on the central and lower face
- On BPO wash only – normal menses; no hormonal therapy
- She admits to picking
- She has “sensitive” skin

What Do We Really Understand About the Nature of Acne in the Adult Female?

374 FEMALE PATIENTS WITH ACNE

Distribution of Comedones, Inflammatory and Nodular Lesions

Study Conclusions

- Two distinct presentations:
  - ~90% similar to adolescent acne
  - ~10% mild, inflammatory/nodular acne localized to mandibular region
- Most women do not have hormonal abnormalities
- Acne is typically found in active, working women in their 20’s to 40’s
What Does the Study Results Suggest Us in Terms of Treatment??

- Treat their underlying disease as though they are a teenage acne patient
- Maintenance program (long term):
  - Topical retinoid
  - Retinoid/BPO
  - Retinoid/topical antibiotic combo
  - BPO-combo

What About Hormonal Manipulation?

- Oral Contraceptives
- Spironolactone

Acne Combination Therapy
Establishes Synergy Among Agents

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<tr>
<th>Decreases Sebum Production</th>
<th>Normalizes Keratinization or is Keratolytic</th>
<th>Decreases P. acnes</th>
<th>Decreases Inflammation</th>
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<td>Topical Therapy:</td>
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<td>Antibiotics</td>
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<td>Spironolactone</td>
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Excess Androgens in Women

- Excess production of androgens from the ovary may also cause acne
- Should be excluded in females with:
  - acne that is persistent
  - of late onset
  - associated with hirsutism [1]
- Serological investigation in these women has revealed high circulating levels of free testosterone and DHEAS and a low concentration of sex hormone-binding globulin.[2,3]

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<td>MOA: Is a K+ sparing diuretic that inhibits actions on both the androgen receptor and 5α-reductase (T -&gt; 5-DHT)</td>
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<tr>
<td>Reduces sebum production by 30-75% depending on the dose [1-4]</td>
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<td>Used &quot;OFF LABEL&quot; for acne...not FDA approved</td>
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<td>Dosing: 50-100 mg daily (bid dosing with meals)....Most often started at 100 mg/d</td>
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<td>Women with sporadic outbreaks can be successfully managed with as little as 25 mg daily[4]</td>
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<th>SPIRONALACTONE</th>
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<td>Little data despite widespread use</td>
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<td>Cochrane analysis: &quot;effectiveness indeterminate&quot;</td>
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<td>Study of 85 women with acne, 93% demonstrated at least partial improvement in their acne, with 66% showing a marked improvement or complete clearance [1]</td>
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<td>Similar to other hormonal therapies: response is slow and it may take up to 3 months of continuous treatment before any benefit is observed [2]</td>
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SPIRONOLACTONE: SIDE EFFECTS
- Usually dose dependent (>100 mg/d)
- Menstrual irregularities, potential hyperkalemia, breast tenderness, fatigue, headache, fluid retention and, rarely, melasma
- Potential for feminization effects:
  - Males: spironolactone should NOT be prescribed
  - Females: should be advised to avoid pregnancy owing to potential abnormalities to the male fetus.
- Hyperkalemia: baseline laboratory for kidney function; avoid K+ containing sports drinks

You recommend starting spironolactone but the patient reads on the internet and asks:

What about:
Hyperkalemia? Cancer?

Is serum K+ monitoring in young healthy women on Spiroanolactone necessary?

- Study Population:
  - 974 healthy young women taking spironolactone for acne
  - 1165 healthy young women not taking spironolactone
- Exclusion criteria:
  - cardiovascular disease, renal failure, and the use of medications that affect the renin-angiotensin-aldosterone system.
- There were 13 abnormal serum potassium measurements (6 erroneous/7 no action taken) in 1802 measurements obtained among young women receiving spironolactone therapy.
- Yielding a hyperkalemia rate of 0.72%, equivalent to the 0.76% baseline rate of hyperkalemia in this population.

TAKE HOME POINT
- Get a baseline K+ level/renal function
- K+ monitoring in healthy females NOT necessary
- Avoid sports drinks containing K+
- “Healthy” = no disease in exclusion criteria

SPIRONOLACTONE: WARNING
- Aldactone® spironolactone tablets, USP 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 avoid

Aldactone: PDR Safety Data in Rats
- 18-month study using doses of about 50, 159 and 500 mg/kg/day, there were statistically significant increases in benign adenomas of the thyroid and testes and, in male rats, a dose-related increase in proliferative changes in the liver (including hepatocytomegaly and hyperplastic nodules).
- 24-month study in which the same strain of rat was administered doses of about 10, 30, 100 and 150 mg Aldactone/kg/day, the range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes.
2013 Danish study: Spironolactone and Uterine/Breast/Ovarian Cancer

- Danish database was used to study the association of breast, uterine and ovarian cancer with use of spironolactone and furosemide (comparator drug)
  - Women > 20 years old (2.3 million women)
- Increased use of both drugs in the year before cancer diagnosis: Rx was linked to cancer symptoms or hypertension
- Overall conclusion is that use of spironolactone does not increase the risk of these cancers


Start Her On

- **Spironolactone 100 mg/d**
- PLUS
- 1. A **topical retinoid** 2x/week and increase gradually (over months) as tolerated OR **BPO/Abx combo**
- 2. Gentle skin care
- 3. Cotton gloves for pickers

Optimal use of oral antibiotic therapy for the treatment of adult acne

- United States guidelines recommend oral antibiotic duration be limited to 3 to 6 months for acne.
- **Topical retinoids** are recommended in combination with and as maintenance therapy after antibiotics.


STUDIES: Combination Oral Antibiotic and Topical Retinoid

- Minocycline + Tazarotene
- Doxycycline + Adapalene
- Doxycycline + Adapalene/BPO


Moderate-Severe Acne: Take Home Point:

- Start patient on an oral antibiotic + topical retinoid for 1 – 3 months
  - Preferably use a “cycline” i.e. tetracycline, doxycycline or minocycline
- Discontinue the oral antibiotic in 1-3 months and continue the use topical retinoid
ACNE AND PREGNANCY

CLINICAL REVIEW

Treatment of Acne in Pregnancy

Anna L. Chien, MD, J. Qi, BA, Barbara Rainer, MD, Dana L. Sachs, MD, and Yolanda R. Helfrich, MD

CLINICAL REVIEW: Treatment of Acne in Pregnancy: Anna L. Chien, MD, J. Qi, BA, Barbara Rainer, MD, Dana L. Sachs, MD, and Yolanda R. Helfrich, MD
JABFM March–April 2016 Vol. 29 No. 2 254–262 http://www.jabfm.org

Severe Acne During Pregnancy

30 yo WF primigravid – 14 week pregnant
Presents w/ painful acne 6-7 x weeks
Treatment at time of initial visit: she was on oral erythromycin after failing oral amoxicillin and cephalexin
Hx of acne as teen controlled w/adapalene, PO minocycline and oral contraceptives ALL of which were D/C’s 6 weeks before conception

Differential Dx:

- Acne conglobata:
  - Long hx of acne
  - Truncal involvement
  - Lack of trigger-induced flares

- Pyoderma faciale:
  - Facial distribution c/w PF
  - Trigger-induced flushing: “Rosacea fulminans”
  - No preceding hr x acne
  - Lack truncal involvement
  - Lack of comedones
  - Demographics

Severe Acne During Pregnancy

A Different Case of: Pyoderma Faciale
Therapeutic Options: TOPICALS

- **TOPICALS**: First Line Agents for Mild-Moderate Acne in Pregnancy
  - **Topical clindamycin** (Category B) - rare reports of C. Difficile (? Clinically significant)
  - **Topical erythromycin** (Category B)

- **Benzoyl peroxide (BPO)** (Category C)
  - Strong keratolytic, comedolytic, and antibacterial properties
  - Issue of Category C: risk of congenital malformations is theoretically small
  - Most experts agree on its safety during pregnancy

- **BPO/Clindamycin Combination**: superior to each case individually and may decrease the risk of antibiotic resistance

- **Azelaic acid**: Category B
  - Bacteriostatic broad antimicrobial effects (mechanism unknown)
  - Used in acne, rosacea, perioral dermatitis "good for "overlap cases"
  - Well documented safety profile during pregnancy

Therapeutic Options: SYSTEMIC

- **Beta-lactams**: first-line agents
  - Penicillins and cephalosporins: compatible with pregnancy and show efficacy in the treatment of acne
  - **Amoxicillin** (Category B) - aminopenicillin and has shown good efficacy
  - Increased risk for cleft lip and palate after third trimester
  - Often been used during pregnancy for a variety of conditions
  - Most studies support its safety

- **Macrolides**: recommended the next indicated class of antibiotics when macrolides fail
  - Erythromycin base or ethylsuccinate is recommended over erythromycin estolate due to the non-negligible risk of maternal hepatotoxicity
  - **Azithromycin**: effective; compatible with pregnancy

Therapeutic Options: TOPICALS...Cont’d

- **Topical retinoids**: adapalene, tretinoin, tazarotene
  - Systemic retinoids absolutely contraindicated
  - Animal studies: equivocal teratogenicity with "supra-therapeutic" doses of topical tretinoin BUT none with adapalene; tazarotene (Category X) has 6% absorption

- **Sodium sulfacetamide**: (Category C)
  - Inhibits bacterial dihydropteroate synthetase → decreases folic acid formation.
  - No reports of congenital anomalies have been linked to sulfacetamide OR the combination of sulfacetamide/sulfur
  - **Not contraindicated during pregnancy**

**SUMMARY**: The PLLR is designed, when consulting with an individual regarding risk/benefit of a drug, to facilitate the communication regarding a “patient based” decision.

**PLLR**: each newly approved medication.
Therapeutic Options: SYSTEMIC

**Tetracyclines:**
- Contraindicated after 15 weeks of gestation due to deposition fetal tooth and bones with subsequent malformations
- Avoid during pregnancy unless the benefits clearly outweigh the risks.

**Trimethoprim:**
- Use associated with an increased risk of spontaneous abortion
- Avoid during pregnancy unless the benefits clearly outweigh the risks.

**Fluoroquinolones:**
- Associated with tendinopathy and chondrotoxicity in animals, teninopathy in adverse event self-reporting databases
- No clear fetal risk has been established, amounts of fluoroquinolones cross the placenta
- Avoid during pregnancy: theoretical risk of fetal cartilage damage and the relative benignity of acne.

**Therapeutic Options:**
- In refractory cases, alternative methods of treatment may be considered.
- Narrowband ultraviolet B (NB-UVB) phototherapy:
  - Anti-inflammatory properties that have been shown to be effective in the treatment of acne during pregnancy
  - Excellent safety record during pregnancy
  - Risk: decrease in serum folate levels with as few as 18 sessions of NB-UVB – check serum levels and supplement
  - Short-term treatment during pregnancy is likely safe and the highest risk with folate deficiency occurs in the early stages of pregnancy. Still, experts recommend caution
- Oral prednisone:
  - May be linked to cases of cleft palate
  - High-doses should generally be coordinated with an obstetrician. Our patient presented with a rare case of severe acne
  - Acne that is refractory to multiple modalities, prednisone may be used in low-to-moderate doses in controlled courses.
  - Safety alternatives exist and we do not advocate the routine use of corticosteroids during pregnancy unless the benefits clearly outweigh the risks.
- Intramuscular steroids:
  - Effective in treating individual acne nodules
  - Generally 2.5 mg/cc Triamcinolone suspension used
  - Risk of depressed scar with too high a concentration or amount
  - Monitor cumulative amount injected

**Therapeutic Options:**
- Photodynamic Therapy (PDT): Category C
  - Animal reproductive studies are not available.
  - Efficacious in controlled studies.
  - Painful and requires multiple session in a dermatology office
  - Lack of insurance coverage
- Pulsed dye, KTP (potassium-titanyl phosphate), NdYAG (neodymium-doped yttrium aluminum garnet):
  - Demonstrable efficacy for the treatment of acne with excellent overall safety in general population
  - Depth of penetration generally poses little risk to the fetus
  - Effects of a painful stimulus in the late stages of pregnancy are unclear
  - Actual reports of use during pregnancy are limited and make it difficult to establish clear safety guidelines

**INITIAL Therapeutic Course**
- Prednisone 40 mg/d initiated due to patient’s pain following OB-GYN consult
- Erythromycin continued at 250 bid PO
- 14 WEEKS PREGNANT

**20 - 28 Weeks Gestation**
- Week 20: slight acne flare on trunk likely due to PO steroids
  - Prednisone lowered to 20 mg/d and PO erythromycin doubled to 500 mg bid PO
- Week 28: no worsening BUT no improvement
  - Erythromycin PO D/C’d
- Metronidazole PO started at 250 bid
  - Sodium sulfacetamide (1%) and sulfur (5%) topical solution started
- 20 WEEKS PREGNANT
34 Weeks Gestation

Several weeks of: oral metronidazole, low dose prednisone and topical sulfacetamide and sulfur lotion
Prednisone tapered off

One Month of Isotretinoin Therapy Post Delivery and Breastfeeding

Successful delivery and no complications
Remained on therapy
After finishing 3 months breastfeeding she was begun on isotretinoin therapy

Changing the Paradigm on Isotretinoin Dosing

Retinoids

How Does Isotretinoin Work?

- **Inhibition of sebum secretion**
  - Apoptosis of sebocytes (90% by 1 week on 1 mg/kg/day)

- "Normalizing" anti-*P. acnes* response
  - Down-regulates TLR2 receptor on mononuclear cells

**ISOTRETINOIN DOSING**

- Recommended duration and dose: determined by clinical response
- NOT cumulative dose


High Dose Isotretinoin

- Traditional: 120-150 mg/kg (i.e. 1mg/kg/day for 4 – 5 months) has a ~20% relapse rate
  - youth/severity/diet/hormones
- High dose: 290 mg/kg (≥ 1.3 mg/kg/day) had 12% relapse over 3 years (retrospective study; n=80)

Isotretinoin Adverse Events

Common AEs
- dry skin
- dry lips
- high TGs
- acne flare

Uncommon AEs
- elevated CK
- elevated AST & ALT
- dry eyes
- decreased night vision
- depression
- acne fulminans

Setting Expectation: What Happens AFTER Stopping Isotretinoin

- F/U 1 – 10 years (> 1,100 pts) post clearance using Isotretinoin
  - Topicals alone: 16-21%
  - 3.3 – 39% topicals + oral antibiotics
  - 16 – 23% retreated w/ at least 1 course of Iso

Patients (%) Receiving 2 or More Txs Based on Age

Isotretinoin Efficacy

- Dose ranging studies in the 1970s showed 0.1 mg/kg/day is as effective as 1 mg/kg/day
- Relapse rate was dose dependent
  - 10-20% at 1 yr. following 1mg/kg/day
  - 40% at 1 yr. following 0.1 mg/kg/day
- Isotretinoin has a profound stimulus to granulation tissue
Can We Give Isotretinoin Once Daily?
- No significant changes in PK profile after 5 days (steady state)
- After 25 days of Iso 40 BID serum levels were stable (n=20)
- Switch to Iso 80 QD after Day 30 caused a marked rise in peak (Cmax) Iso blood levels compared to Iso 40 BID
  - BID dosing may minimize side effects (unstudied)
  - BID dosing of Iso may minimize reduced GI absorption if there is an absorption ceiling with a single high dose (endogenous or exogenous)

Treatment Duration….How Long Should We Treat?
- **Males**: maintain on low dose (10-20 mg/day)….2-3 months after clearance; restart if necessary
- **Females**: Consider maintenance on low dose for 2-3 months after clearing then change to spironolactone to minimize isotretinoin exposure

Isotretinoin “Failures”
- 80% treated with 120-150 mg/kg (cumulative dose) never have acne again
- **Causes of failure**
  - Under dosing (compliance/failure to take w/ meals)
  - Virilization
  - Young pt. with bad disease
In a fed state, the maximum drug concentration of generic isotretinoin was approximately 2.9 times more than in the fasting state.


Sotret prescribing information. Jacksonville, FL: Ranbaxy Laboratories, Inc; February 2010.

Isotretinoin Flares: What to Do?

Approx. 6% of pts. will experience a moderate-to-severe flare in their acne during the first few weeks of treatment.

**ISOTRETINOIN: Initial Severe Flare**

- Approaches to decreasing the risk of acne flares with isotretinoin

**Regimen A**

- **FIRST**: Treat with p.o. prednisone 1 mg/kg/day for 3-4 weeks to calm the inflammation and taper off
- **THEN**: add low-dose isotretinoin 10 mg/day and gradually increase the isotretinoin as you taper off the prednisone

**Regimen B**

- **FIRST**: low-dose isotretinoin 10 mg/day at the same time as beginning prednisone at 1 mg/kg/day
- Treat with prednisone and low-dose isotretinoin for at least a month
- Then begin to taper the prednisone and increase the isotretinoin dose as in Regimen A
Isotretinoin Laboratory Monitoring

...What Should We Be Doing?

CBC, LFT, TG/Chol Levels: B/A Isotretinoin

- **Leukopenia or thrombocytopenia** (clinically insignificant) occurred in 1.4% and 0.9% of pts.
- **Elevated LFTs**: infrequent and not significantly increased compared with baseline (1.9% vs 1.6% at baseline).
- **Significant elevations occurred with triglyceride (19.3%) and cholesterol (22.8%) levels.**
  - The most severe abnormalities were grade 2 (moderate).
  - Mean duration of treatment before abnormalities were detected was: 56.3 days (increased TG), 61.9 days for (increased liver ALA), and 80.1 days (increased cholesterol).

**STUDY: Lab Testing Recommendations**

- **Conclusion:** In healthy patients with normal baseline lipid panel and liver function test results, repeated studies should be performed after 2 months of isotretinoin therapy.
  - If findings are normal, no further testing may be required.
- **Routine complete CBC monitoring is not recommended.**

Can I give Isotretinoin to young children?.....Frozen Isotretinoin inside a Milky Way Bar

**Study Design**

- Reviewed lab data from 515 patients with acne undergoing 574 courses of isotretinoin from March 2003 to July 2011.
- Frequency, timing, and severity of abnormalities were determined.