ACNE CONTROVERSES

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THE ROLE OF HORMONAL THERAPY IN WOMEN WITH ACNE
I will discuss off-label use of medication
Adult female acne
BACKGROUND
Epidemiology

- 650 million people → 9.4% of global population
- Most common condition seen by dermatologists in the United States
- Dermatology visits for acne
  - 2/3 women
  - Mean age of patients seeking treatment is 24 years
  - 1/3 > 25 years of age.

Tan JK, Br J Dermatol, 2015
Adult female acne persistence and late onset.
... INITIAL CONTROVERSIES ...
In adult patients...

Is the disease severity proportional to the impact on quality of life?
Adult acne is usually mild-to-moderate in severity and may be refractory to treatment.

The lesions are less inflammatory than in adolescents.

Large-scale international study (2015):

82.1% * Mild-to-moderate

Dreno B. J Eur Acad Dermatol Venereol 2013
Dreno B J Eur Acad Dermatol Venereol 2015*
Ramos e Silva M et al.. Br J Dermatol 2015
Quality of life (QoL)

- **Dreno, 2015, International study** – 48.3% of patients with marked impact on QoL.

- **Tan, 2008**:
  - Clinical severity was associated with younger age, male gender, and shorter acne duration (1-5 years).
  - Greater impact was associated with older age, female gender, and longer acne duration (> 5 years).

- **Kokandi, 2010 → Adults**
  - Acne severity is not always related to impact on QoL.
  - Impact was important even with a mild clinical presentation.
Adult acne patients have an important psychological impact
U type or not?
• Not all patients exhibit lesions distribution in lower face: jawline, chin, and neck.

• When androgen abnormalities are significant driver of late onset acne, females may display this pathognomonic presentation.

• Dreno et al (2015): international study (374 patients)
  → 11.2% of patients → acne lesions only at mandibular area.
  → Majority: lesions distribution similar to adolescents

Dreno, B et al., 2015
Del rosso JQ et al., Cutis 2015
• U-SHAPED PATTERN IS BELIEVED TO BE MORE COMMON IN THE LATE-ONSET ACNE

PERKINS AC ET AL., J WOMENS HEALTH 2012
CHOI CW ET AL., J EUR ACAD DERMATOL VENEREOL 2011
KANE A ET AL., INT J DERMATOL 2007

• BUT ..... WE NEED ADDITIONAL STUDIES, ESPECIALLY CORRELATIONS BETWEEN ONSET, AGE AND CLINICAL PATTERNS

DEL ROSSO JQ ET AL., CUTIS 2015
Are lab changes common in adult female Acne?
WOMEN WITH ONLY ACNE ➔ 80% DO NOT PRESENT HORMONAL ALTERATIONS

Carmina 1993, Waltom et al., 1995
Williams C. Am J Clin Dermatol 2006

CONTROVERSY ➔ DHEA-S HAVE BEEN REPORTED IN SOME STUDIES AS ELEVATED

Seirafi H Int J Dermatol. 2007
When acne is associated with:

- HIRSUTISM,
- ALOPECIA,
- Irregular menses/premenstrual acne
- INFERTILITY
- Adult onset/flare

⇒ Hyperandrogenism

Lucky et al., 1983
Lockingbill et al. 1985
Derman, 1996
Yarak et al., 2005
THE FOLLOWING SCREENING SHOULD BE CARRIED OUT:

HORMONES:

Total testosterone
Free testosterone *
S-DHEA,
LH / FSH ???
17-oh Progesterone (17-OH P)

ULTRASONOGRAPHY (OVARIES)

FOLLICULAR PHASE (START WITH MENSES)

Lucky et al., 1983
Lockingbill et al 1985
Derman, 1996
Yarak et al., 2005
Testosterone

++++

Ovaries - Tumor

++++

+ or “LH/FSH”

PCOS

++++

Adrenal Tumor

++++

S-DHEA

+ or “LH/FSH”

Adrenal Hyperplasia

17-OH P
Most common

- POLYCYSTIC OVARY SYNDROME (PCOS) → 80%
The dermatologic manifestation of hyperandrogenism: A retrospective chart review

**Conclusion**

- **Acanthosis nigricans** and **hirsutism** were found to be useful clinical markers for hyperandrogenism, whereas androgenic alopecia was not
Hirsutism

- The most common clinical sign of hyperandrogenism

- The intensity of hirsutism does not always correlate directly with plasma levels of androgens

Rosenfield RL. N Engl J Med, 2005
“Doctor, my hormones are “normal” !!!
Remember...

Role Of Peripheral Hyperandrogenism

DHEA
1 Testosterona = 100 DHEA
1 DHT = 500 DHEA

Gilliver SC. Clin Dermatol. 2007
Peripheral conversion

OVARIES

ADRENAL

DHEA-S

Testosterone

DHT

Sebocyte

Testosterone

Metabolites (>70% ADT-G)

Giltay, E. J Clin Endocrinol Metab, 2000
STUDY:
40 adult women with acne X
10 controls

Hormonal evaluation

Total Testosterone (TT) and Free (FT), DHEA-S

New “in house” method for ADT-G (LC-MS/MS)
RESULTS

ADT-G (p=0.013)
10.4±4.0 ng/ml (95%IC – [2.3; 18.5])

No difference in the mean values of TT, FT and DHEA-S
USE OF HORMONAL AGENTS FOR ACNE TREATMENT
HORMONAL TREATMENT - WHEN?

- Hyperandrogenemism ... and

- Late-onset or persistent (>25yo)
- Acne at lower face, neck
- Perimenstrual flare
- Comedonal acne with seborrhea
- Resistant to “conventional” therapies
- Alternative to repeat isotretinoin
Combined Oral Contraceptives

• Ethinyl estradiol

• Progestins

Old:
  Levonorgestrel **2

New:
  Desogestrel ***3
  Norgestimate ***3
  Ciproterone
  Drospirenone
Family Tree of Contraceptive Progestins

Classification of Progestins

Progestins

C-21 progestins
- Medroxyprogesterone acetate
- Megestrol acetate
- Cyproterone acetate

19-nor testosterones
- Norethindrone
- Norethindrone acetate
- Ethynodiol diacetate
- Lynestrenol
- Norethynodrel

Gonanes
- Norgestrel
- Levonorgestrel
- Norgestimate
- Desogestrel
- Gestodene

Spironolactone
- Drospirenone

Raudrant D Drugs. 2003
Lakshmi C. Indian J Dermatol Venereol Leprol. 2013
**ESTROGEN**

1. SHBG

2. LH/FSH

3. Free Testosterone

**PROGESTIN**

3. Androgenic receptor

**ANDROGENIC RECEPTOR**
**Absolute Contraindications:**
- Heart attack, stroke, coronary artery disease or blood clots history
- Liver Tumors or impaired liver function
- Known or suspected cancer of the breast or reproductive system
- Known or suspected pregnancy

**Strong Contraindications:**
- Severe headache
- Hypertension
- Diabetes or familial history of diabetes
- Undiagnosed abnormal vaginal bleeding
Efficacy

- After 6 to 9 months: 30 to 60% reduction of inflammatory lesions.
- There is also a reduction of non-inflammatory lesions.

Which is the best oral contraceptive?
### Activity of Progestin Agents

<table>
<thead>
<tr>
<th>Generation</th>
<th>Progestin</th>
<th>Androgenic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST</strong></td>
<td>Norethindrone</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Norgestrel</td>
<td>+++</td>
</tr>
<tr>
<td><strong>SECOND</strong></td>
<td>Levonorgestrel</td>
<td>++++</td>
</tr>
<tr>
<td><strong>THIRD</strong></td>
<td>Norgestimate</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Desogestrel</td>
<td>++</td>
</tr>
<tr>
<td><strong>FOURTH</strong></td>
<td>Drospirenone</td>
<td>-</td>
</tr>
</tbody>
</table>

Dickerson LM, Bucci KK. Contraception 2002;5:1445-1461
Meta-Analysis: Combination OCPs and Acne
The Cochrane Database of Systematic Reviews

23 trials → 7162 Patients

Conclusions:

• Combined oral contraceptives were more effective than placebo.

• No significant differences were found between the analyzed OCPs.

AO Arowojolu et al. The Cochrane Database of Systematic Reviews 2007; CD004425.
... SOMETHING MORE ...
SPIRONOLACTONE
• Used since 1957

• Antagonist of aldosterone (diuretic)
  • Acts as anti-androgen

• Monotherapy or combined with COC
  • Dose: 50-200 mg / day (with feed)

King K J. Clin Aesthetic Dermatol 2012; 5:35-50
Spironolactone

Androgenic Receptor

Test

DHT

Kim, Del Rosso Clinl Aesthetic Dermatol 2012
Results

116 Asian women
- 64 completed 20 weeks
- 53% excellent response
- 47% good response

80% of patients presented menstrual irregularity.

No change in serum K.

Risk of teratogenicity.

SIDE EFFECTS

DOSE-DEPENDENT

INCREASED DIURESIS
HEADACHE
DIZZINESS, MENSTRUAL CHANGES
BREAST PAIN
FATIGUE
INCREASED POTASSIUM

SHAW JC JAAD 2000;43:498-502
Low Usefulness of Potassium Monitoring Among Healthy Young Women Taking Spironolactone for Acne

Retrospective study, 2000-2014
974 healthy women
Mean age = 27.5
Baseline x treatment = 0.72% x 0.76%

No need for control

Plovanich M et al. JAMA Dermatol 2015
**REMEMBER**

**You should check Potassium**

- **Older age**
- **History of renal or cardiac disease**
- **Co-administration with other medications** (ACE inhibitors, Sulfa, etc)
- **If you use higher dosages**

GOOD CANDIDATE

WOMEN WITH INTRAUTERINE DEVICE WITH LEVONORGESTREL

ANDROGENIC ACTION
**Combination therapy: OCs + Spironolactone**

- **Increased efficacy in androgenic blockade**
- **Use of lower doses of Spironolactone**
- **Reduction of common side effects (spironolactone):**
  - Breast pain and menstrual irregularity
- **Reduction risk of pregnancy**
  
  Spironolactone associated hypospadias and feminization of male fetus

Kim, Del Rosso CliniL Aesthetic Dermatol 2012
Krunic et al., JAAD 2008;58:60-62
Efficacy and tolerance of acne treatment using both spironolactone and a combined contraceptive containing drospirenone

- N = 27, 18-43 years, severe papulonodular acne
- 30mcg EE / 3mg DSP + 100mg spironolactone x 6 months
- No weight gain or menstrual irregularities
- Serial K = 3.8-4.8mmol/L (mean 4.35)
- Improvement: complete (11%); > 75% (74%); > 25% and no improvement (7.5%)

STUDIES IN MICE RECEIVING 15 TO 150 TIMES THE RECOMMENDED DOSE FOR HUMANS HAVE DEVELOPED:

- BENIGN ADENOMAS
- THYROID CARCINOMA, TESTICULAR TUMORS AND ADENOMAS
- ENDOMETRIAL POLYPS
- BREAST CANCER
8 YEARS OF FOLLOW-UP
NO CASES OF BREAST CANCER

Shaw and White, J Cut Med Surg 2002:541-545

1475 WOMEN X 3-7 YEARS
NO INCREASE IN BREAST CANCER INCIDENCE

Friedman et al., J Nat Cancer Inst 1980;65:723
Contraceptives with drospirenone did not present a higher risk of VTE than other third generation COCs.

DeBastos et al., Cochrane Database Syst Rev 2014 Mar 3;3
Non-Pregnant Non-COC user

COC-User

Pregnancy *

Postpartum (12 weeks only)

Ranges from 1 to 5

Ranges from 3 to 9

Ranges from 5 to 20

Ranges from 40 to 65

Number of Women with a Blood Clot out of 10,000 Women Years (WY)

Buzney et al., Am Acad Dermatol 2014
Heit et al., Ann Intern Med 2005
Should PCOS patients always be treated with COCs?
Patients with hyperandrogenism

- PCOS: 80%
- Other causes: 20%

PCOS

- Metabolic syndrome: 35%
- Without metabolic syndrome: 65%

EHRMANN DA J clin Endocrinol Metabo, 2006
Metabolic syndrome (MS)
ASSOCIATED WITH RISK OF DEVELOPING CARDIOVASCULAR DISEASE AND TYPE 2 DIABETES.

STUDIES HAVE SHOWN THE ESTIMATED PREVALENCE OF 34% IN AMERICAN ADULT POPULATION, INCREASING WITH AGE.

- ABDOMINAL (CENTRAL) OBESITY
- ELEVATED BLOOD PRESSURE
- ELEVATED FASTING PLASMA GLUCOSE
- HIGH SERUM TRIGLYCERIDES
- LOW HIGH-DEMANDITY LIPOPROTEIN (HDL)

Ford ES JAMA. 2002
PCOS/SM RELATIONSHIP

35% without metabolic syndrome

35% metabolic syndrome

INSULIN RESISTANCE

Hyperinsulinemia

Excess levels of insulin

Increased production of androgens

IGF inhibits aromatase and decreases the production of SHBG

Increased production of IGF I and II

Goodarzi M J Clin Endocrinol. Metab. 2005
Rosenfield RL. Endocrinol Metab Clin North Am. 1999
PCOS and MS

Most frequent manifestations: central obesity and reduced HDL

Bentley-Lewis Nat Clin Pract Endocrinol Metab. 2007
In patients with PCOS: MS occurs earlier (mean age: 35 years) than those without (50 to 60 years)

Young women with PCOS and MS: 7 x increased risk for developing cardiovascular disease

Apridonidze T J clin Endocrinol Metabol 2005
• OCC are good treatment option for women with PCOS who do not want to be pregnant

  Cycle regulation
  Improvement of dermatological manifestations
  Reduction of endometrial cancer risk

• OCC x metabolic adverse effects

  Attention to patients with Insulin resistance
  Diabetes and cardiovascular disease

• Some studies suggest that OCCs may reduce insulin sensitivity.

  Diamanti-Kandarakis J Clin Endocrinol Metab. 2003
Metformin
- **Metformin** -> There are studies showing androgenic decrease and increase of SHBG even in patients without PCOS

- **Systematic reviews still inconclusive**

- **Use of metformin in patients with PCOS and acne complaint reduced the number of lesions by only 14%**.


Thank You

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