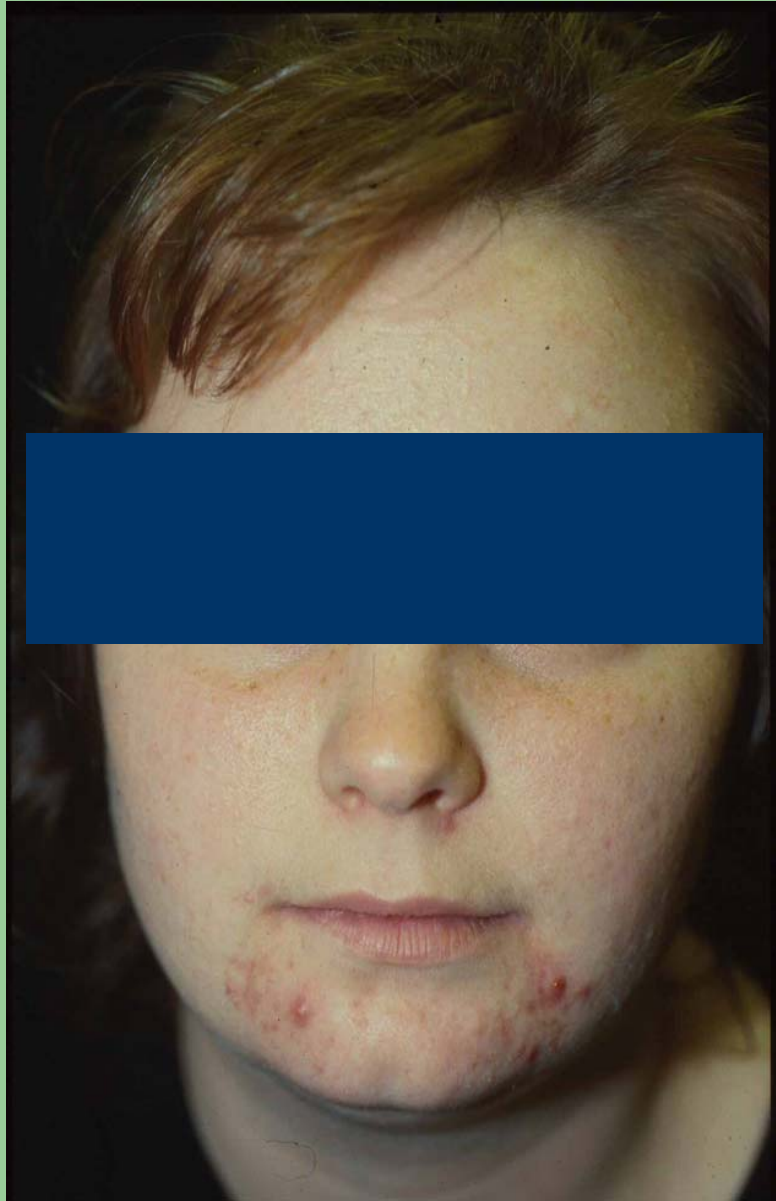


Hormonal Approaches to Acne Therapy

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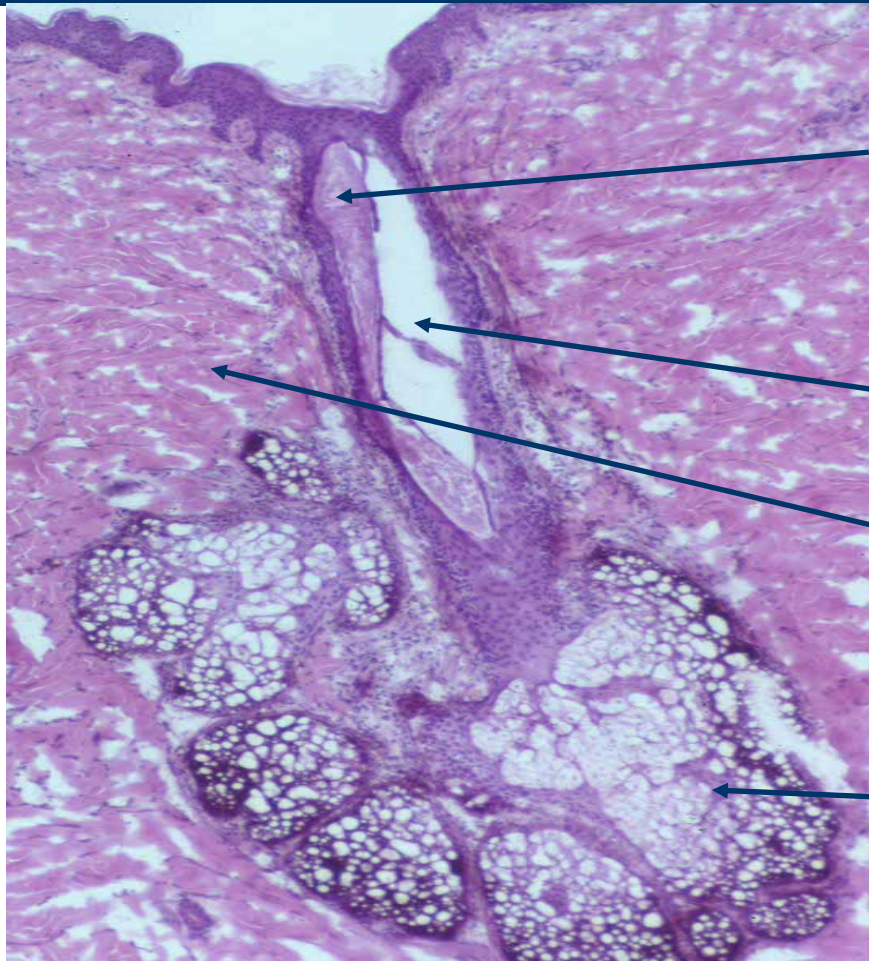




Approach to acne in adult females

- Conventional therapy
 - Topical retinoid/Benzoyl peroxide/Antibiotic
- Endocrine Evaluation
- Hormonal therapy

4 Main Pathogenic Features of Acne



Follicular
hyperkeratinization

P. acnes

Inflammation

Sebum production

Therapeutic acnes target acne pathophysiology

Sebum production

- Oral retinoids
- Hormonal therapy

Hormonal Therapy: Indications

- Ovarian or adrenal hyperandrogenism
- Normal serum androgens
- Alternative to repeat courses of isotretinoin or antibiotics

When to suspect an endocrine abnormality

- sudden onset of severe acne
- acne associated with:
 - hirsutism
 - irregular menstrual periods
 - signs of hyperandrogenism

Suggested work-up for an endocrine disorder

- Serum dehydroepiandrosterone sulfate (DHEAS)
- Total and free testosterone
- LH/FSH ratio
- 17-hydroxyprogesterone
- Must be OFF oral contraceptives

When to test

- Not near ovulation
- During period or week prior to period
- Patient must NOT be on OCP
- Wait 6 weeks after stopping of OCP

Interpretation

DHEAS (adrenal source)

> 8000 ng/ml adrenal tumor

4000-8000 ng/ml congenital adrenal
hyperplasia

Total Testosterone (ovarian/adrenal source)

> 150 - 200 ng/dl ovarian tumor

mild elevations PCO

LH/FSH ratio >3 PCO

Hormonal Therapy

- Oral contraceptives
 - Blocks ovarian production
- Glucocorticoids
 - Blocks adrenal production
- Antiandrogens
 - Blocks effects on skin

Androgen receptor blockers

- Spironolactone
- Cyproterone acetate
- Flutamide

Spirolactone

- Dose: 25-100 mg. Twice daily
- Frequent side effects:
 - Breast tenderness
 - Menstrual irregularity
- Avoid pregnancy

Spironolactone

Route of
Administration

Reduction of Sebum
Excretion Rate

Systemic

35% to 50%

Topical

0%

Flutamide

- used to treat prostate cancer
- 250 mg b.i.d. in combination with an OCP improved acne
- cases of fatal hepatitis reported (rare)
- monitor liver function tests
- avoid pregnancy



Congenital Adrenal Hyperplasia

- 21-hydroxylase or 11-hydroxylase deficiency
- Block in cortisol biosynthetic pathway
- Shunting of steroid precursors into adrenal androgen production

Congenital Adrenal Hyperplasia- Lab findings

Elevated :

- Serum DHEAS,
- 17-hydroxyprogesterone or
- testosterone

Agents that block adrenal androgen production

- oral contraceptives
- low-dose glucocorticosteroids

Low-dose glucocorticoids

- Prednisone 2.5 -5 mg daily at bedtime
- Dexamethasone 0.25-0.75 mg at bedtime
- Increased risk of adrenal suppression with dexamethasone

Laboratory monitoring for low-dose steroids

- Serum DHEAS
- Fasting AM cortisol
- ACTH (cosyntropin) stimulation test

Oral Contraceptives in Acne



OCs: Mechanism of Action in Acne

- Reduce serum androgens : T, DHT and DHEAS
- Reduces free T by increasing SHBG
- Decreases sebum production
 - ? estrogen effect
 - ? reduction in androgens
- Clinical benefit

Components of Oral Contraceptives

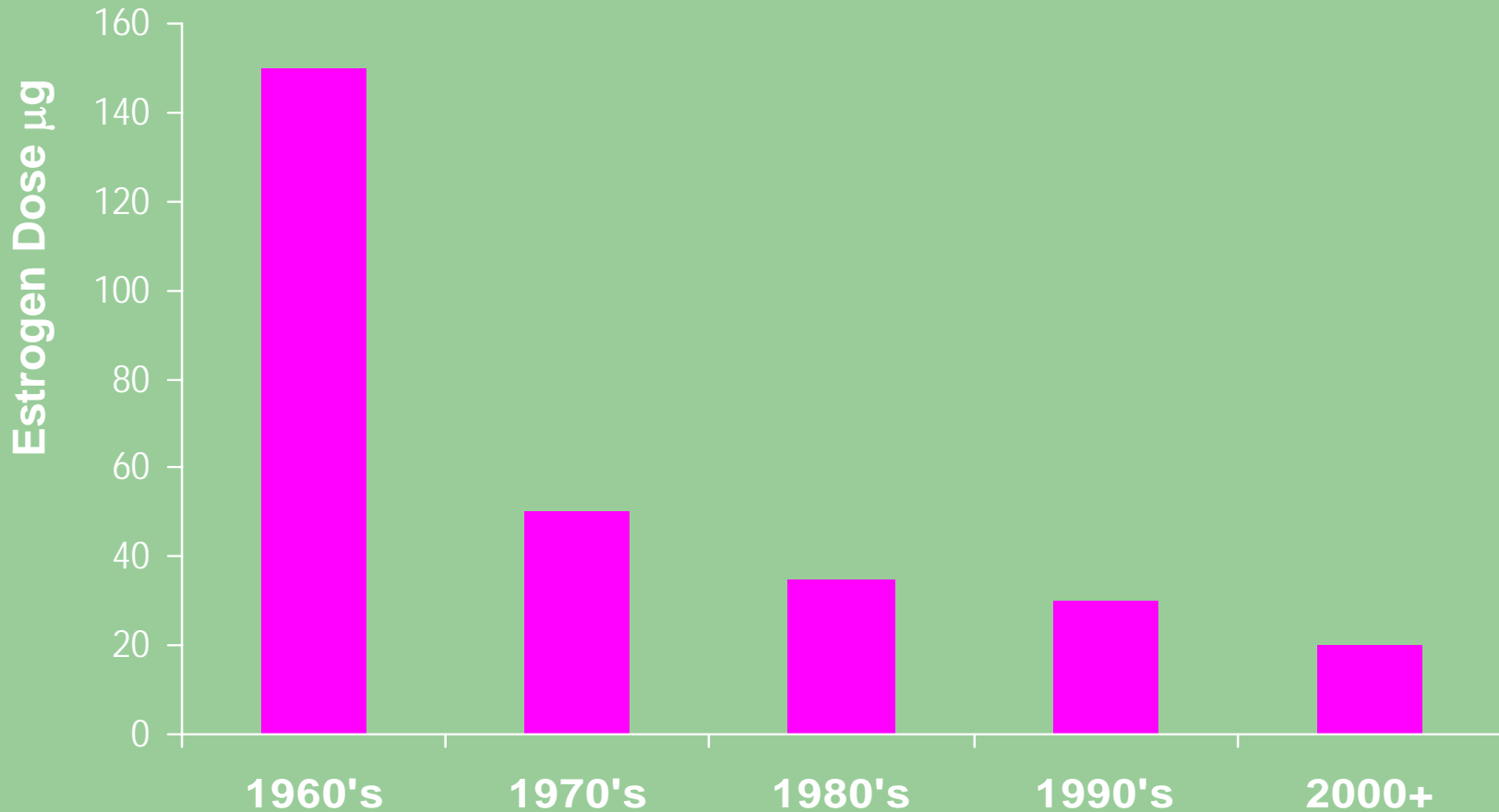
ESTROGEN

Ethinyl estradiol (50 μg , 35 μg , 20 μg)

PROGESTIN

Can cross-react with the androgen receptor

Declining Estrogen Levels in OCs



OCs: Low Dose Estrogen (20 μg)

- Alesse
 - 100 μg levonorgestrel
- Mircette
 - desogestrel
- Loestrin
 - Norethindrone acetate
- Estrostep
 - Norethindrone acetate
- Ortho Tricyclen Lo
 - Norgestimate
- Yaz
 - drospirenone

Third Generation Progestins

- Less cross-reactivity with the androgen receptor
- More “estrogenic”
 - higher levels of HDL and SHBG

OCs with third generation progestins

DESOGESTREL

Desogen

Ortho-Cept

Mircette

NORGESTIMATE

Ortho-Cyclen

Ortho Tri-cyclen

Ortho Tri-Cyclen Lo

Novel Progestin: Drospirenone

- Derivative of 17α -spironolactone
- Antiandrogenic and antimineralocorticoid activity
- OCP with $30\mu\text{g}$ ethinyl estradiol (Yasmin)
- Potential benefit in androgen-mediated skin diseases
- Studies in acne in progress

Biologic Relevance

- Effects of progestins may be offset by estrogen in vivo
- Serum androgens decrease
- SHBG increases
- Acne improves

Oral Contraceptives Studied in Acne



Ethinyl estradiol / norgestimate (Ortho Tri-cyclen TM)

- two 6-month trials, 500 women with moderate acne
- Significant improvement in:
 - inflammatory lesions (50-60%), total lesions and global assessment
- no significant adverse effects
- FDA approved

Safety and Efficacy of Alesse^R vs. placebo in acne

- Two trials (350 & 371 women) with moderate acne
- 6 month treatment vs. placebo
- Lesion counts, global assessment, patient self assessment
- Approximate 47% reduction in inflammatory lesions

Thiboutot et al. Fertil Steril 2001;76:461-468.

Leyden et al. J Am Acad Dermatol 2002;47:399-409.

Ethinyl estradiol/norethindrone acetate (Estrostep^R)

- Two 6-month, placebo-controlled trials
- 593 women
- Lesion counts, global assessment, acne quality of life
- Approximate 47% reduction in inflammatory lesions

Maloney et al. Clin J of Women's Health 1:123-131, 2001

Ethinyl estradiol/drospirenone (Yasmin^R)

- Comparative trial vs. EE/cyproterone acetate (Diane-35)
- 128 women, mild-to-moderate acne
- 9 month trial
- Approximate 60% reduction in inflammatory lesions
- Decreased sebum production
- Increased sex hormone binding globulin

van Vloten et al. *Cutis* 2002;69(4 Suppl):2-15.

Yaz (20 μ g ethinyl estradiol/drospirenone 3 mg)

- 24 days active pills
- 4 days placebo
- Shorter periods
- Approved as a contraceptive in April 2006
- Studied in acne

Yaz #8: Protecting the Green Monster



QUIZ: Which OCPs are FDA-approved for acne?

- A. Orthotricyclen and Alesse
- B. Orthotricyclen and Yasmin
- C. Orthotricyclen and OrthoTricyclen Lo
- D. Orthotricyclen and Estrostep
- E. Demulen and DepoProvera

FDA approved OCs for acne

- Ortho Tricyclen^R
 - 35 μg EE/ norgestimate
- Estrostep^R
 - 20-35 μg EE/norethindrone acetate

Antibiotic/Oral Contraceptive Interaction

- Gut flora are needed to cleave estrogen conjugates
- Risk is greatest with tetracyclines and OCPs with low estrogen content
 - 1.2-1.4 pregnancies/100 women years

Newer forms of contraceptives



Contraceptive Patch (Ortho Evra^R)

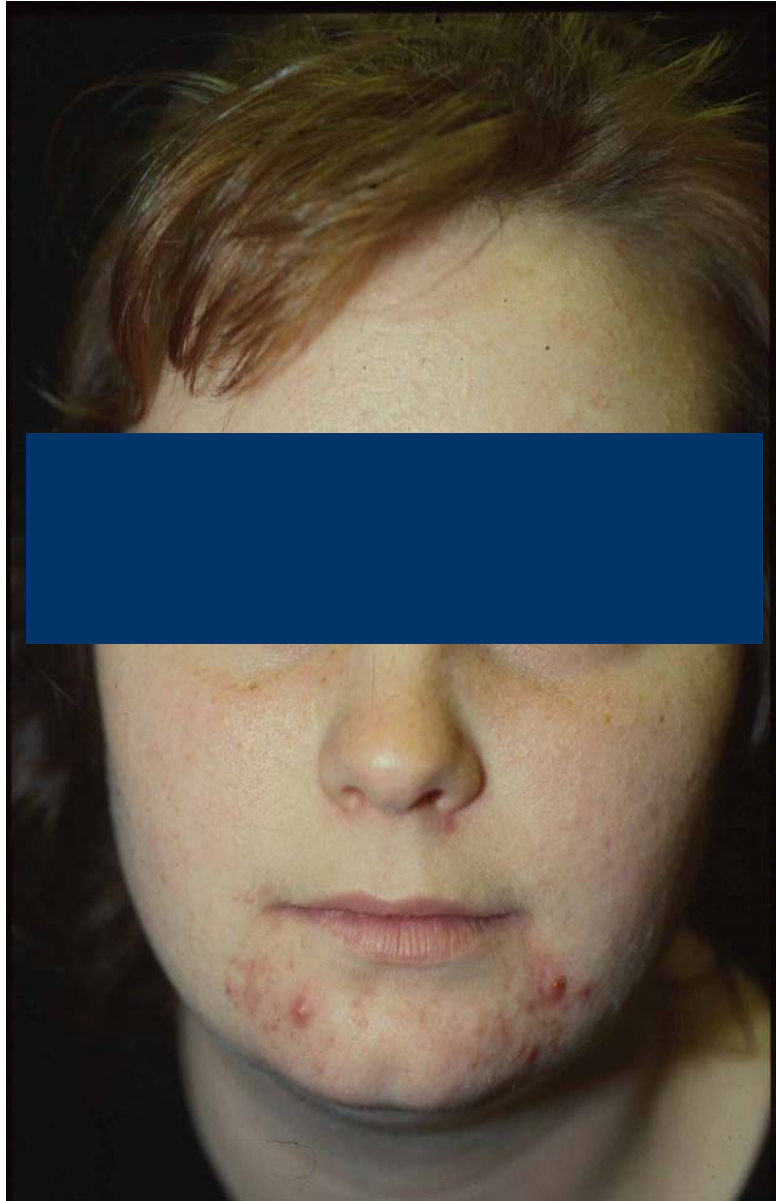
- Ethinyl estradiol 20 µg/norelgestromin
- Changed weekly for 3 weeks, off 1 week
- Patient compliance
- Less influence from GI disturbances
- More consistent serum estrogen levels

Contraceptive Vaginal Ring (NuvaRing^R)

- Ethinyl estradiol 15 µg/ etonogestrel
- Inserted into vagina for 3 weeks out of the month
- Study suggests decreased irregular bleeding

**Should the dermatologist
prescribe OCPs?**





Approach to Acne in Women

- Conventional therapy
 - Topical retinoid/Benzoyl peroxide/Antibiotic
- Endocrine Evaluation
 - DHEAS, total and free testosterone, LH/FSH ratio, 17-OH progesterone
- Hormonal therapy
 - Oral contraceptives
 - Antiandrogens

Combination Therapy

- Addresses a number of pathogenic factors
- Provides the greatest efficacy
- Mainstay is a topical retinoid with:
 - antibiotic
 - benzoyl peroxide
 - or hormonal therapy

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