Polycystic Ovary Syndrome

François Pralong
Division of Endocrinology
Definition

- Evidence of oligo-anovulation
- Clinical and/or biochemical signs of excess androgens
- Polykystic morphology on ovarian ultrasound

Exclusion of other causes of hyperandrogenism (Cushing, late onset congenital adrenal hyperplasia...)

ESHRE consensus, Rotterdam 2004

Heterogeneous condition with a spectrum of clinical/biochemical features

Estimated prevalence: 25% of all women, full blown syndrome in ~5% of women of reproductive age
Clinical presentation

- Hirsutism (95%), acne, alopecia
- Enlarged ovaries (95%)
- Sterility (75%)
- Amenorrhea (55%)
- Obesity (40%)
- Dysmenorrhea (28%)
- Chronic anovulation (20%)
PCOS: THE TEXTBOOK VIEW I

Pathogenic hypothesis
Abnormal hormonal feedback mechanisms

Hypothalamus

- LH Secretion
- FSH Secretion

Adipose tissue

- Extraglandular Aromatization
- Acyclic Estrogen (Estrone)

Ovary

- Follicle Maturation
- Stimulation of Stroma and Theca

- Cyclic Estrogen (Estradiol)
- Ovarian Androgen Secretion

Adrenal

- Androgen Excess

- Obesity
Pathogenic hypothesis
Obesity and insulin resistance

- Weight increases
- Insulin receptor disorders

- Insulin increases
- IGFBP-1 decreases

- SHBG decreases

- LH increases
- FSH decreases

- Theca (IGF-I)

- Free testosterone increases
- Hirsutism
- Free estradiol increases

- Androstenedione increases
- Testosterone increases

- Estrone increases
- Endometrial cancer
PCOS: A DEVELOPMENTAL VIEW

Puberty

LH

Insulin

ANDROGENS

• Hirsutism
• Acne
• Alopecia

Adapted from S Franks, 2002
Gonadotropin Secretion in PCOS

*Increased LH secretion:*

- Ratio of LH/FSH: 2-3/1
- Prevalence: 30 to 90%!

*Importance of assessing LH secretion in relation to recent menses*
Adapted from S Franks, 2002

Insulin

ANDROGENS

• Hirsutism
• Acne
• Alopecia

Puberty

LH

Adapted from S Franks, 2002
Possible Mechanisms of Abnormal LH Secretion in PCOS

**Altered sex steroid feedback:**

- Increased spontaneous LH pulse amplitude
- Increased LH response to GnRH
- Normal FSH response to GnRH

**Inherent neuroendocrine abnormality**
A CHRONOBIOLLOGIC ABNORMALITY IN LUTEINIZING HORMONE SECRETION IN
TEENAGE GIRLS WITH THE POLYCYSTIC-OVARY SYNDROME

Barnett Zumoff, M.D., Ruth Freeman, M.D., Susan Coupey, M.D., Paul Saenger, M.D.,
Morri Markowitz, M.D., and Jacob Kream, Ph.D.

Study of 5 teenage, post-pubertal girls with PCOS, compared to
age-matched controls

Diagnostic criteria:
• Chronic anovulatory syndrome
• Exclusion of other virilizing syndromes (Cushing, CAH...)
• Normal TFTs and PRL
A CHRONOBIOLOGIC ABNORMALITY IN LUTEINIZING HORMONE SECRETION IN TEENAGE GIRLS WITH THE POLYCYSTIC-OVARY SYNDROME

Barnett Zumoff, M.D., Ruth Freeman, M.D., Susan Coupey, M.D., Paul Saenger, M.D., Morri Markowitz, M.D., and Jacob Kream, Ph.D.

Abnormality present in 4 of 5 patients

NEJM 309, 1983
Hyperfunction of the Hypothalamic-Pituitary Axis in Women with Polycystic Ovarian Disease: Indirect Evidence for Partial Gonadotroph Desensitization*

JOANNE WALDSTREICHER, NANETTE F. SANTORO, JANET E. HALL†, MARCO FILICORI‡, AND WILLIAM F. CROWLEY, JR.

Study of 12 women with PCOS, compared to 21 normal controls

Diagnostic criteria:

- Perimenarchal onset of oligo/amenorrhea
- Hirsutism and/or acne
- Raised LH/FSH ratio
- Raised T/androstenedione levels

- E2 lower than controls in MFP and LFP
- Estrone higher than controls in EFP and MFP, lower in LFP

J Clin Endocrinol Metab 66, 1988
Normal

EFP

Day -12
E₂ = 41 pg/ml

LH (mIU/ml)

0 10 20 30 40

TIME (minutes)

MFP

Day -8
E₂ = 45 pg/ml

LH (mIU/ml)

0 10 20 30 40

LFP

Day -1
E₂ = 84 pg/ml

LH (mIU/ml)

0 10 20 30 40

PCOS

A.

LH (mIU/ml)

0 10 20 30 40

TIME (minutes)

E₂ = 20 pg/ml

B.

LH (mIU/ml)

0 10 20 30 40

TIME (minutes)

E₂ = 28 pg/ml

C.

LH (mIU/ml)

0 10 20 30 40

TIME (minutes)

E₂ = 39.6 pg/ml

J Clin Endocrinol Metab 66, 1988
Hyperfunction of the Hypothalamic-Pituitary Axis in Women with Polycystic Ovarian Disease: Indirect Evidence for Partial Gonadotroph Desensitization*

A. LH PULSE AMPLITUDE

B. LH PULSE FREQUENCY

J Clin Endocrinol Metab 66, 1988
Study of 13 women (aged 11-18) with hyperandrogenism, compared to 28 aged-matched normal controls

Patients from Adolescent Medicine/Repro Endo clinics, UCSD

Diagnostic criteria:

• Chief complaint: hirsutism
• No hormonal medication for 3 months
Accelerated 24-Hour Luteinizing Hormone Pulsatile Activity in Adolescent Girls with Ovarian Hyperandrogenism: Relevance to the Developmental Phase of Polycystic Ovarian Syndrome*

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Age (yr)</th>
<th>Age at menarche (yr)</th>
<th>BMI</th>
<th>Menstrual pattern</th>
<th>Hirsutism score&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Acne</th>
<th>Acanthosis nigricans</th>
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<td>11.6</td>
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<td>7</td>
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<td>12.8</td>
<td>34.2</td>
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<td>43.5</td>
<td>Amenorrhea</td>
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<td>++</td>
<td>Yes</td>
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<td>9</td>
<td>16.4</td>
<td>12.2</td>
<td>23.1</td>
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<td>16</td>
<td>+</td>
<td>No</td>
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<tr>
<td>10</td>
<td>17.1</td>
<td>12.5</td>
<td>20.4</td>
<td>Regular</td>
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<td>12</td>
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<td>Oligomenarche</td>
<td>17</td>
<td>-</td>
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<td>13</td>
<td>18.1</td>
<td>12.6</td>
<td>26.1</td>
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<td>21</td>
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<td>No</td>
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<td>HA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15.1 ± 0.6</td>
<td>12.3 ± 0.2</td>
<td>28.0 ± 1.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>13.1 ± 1.3&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Normal&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14.8 ± 0.3</td>
<td>12.4 ± 0.3</td>
<td>22.1 ± 1.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>&lt;7.0</td>
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<sup>a</sup> According to Ferriman and Gallwey (12).

<sup>b</sup> Mean ± s.e. for group.

<sup>c</sup> P = 0.005 vs. normal.
Accelerated 24-Hour Luteinizing Hormone Pulsatile Activity in Adolescent Girls with Ovarian Hyperandrogenism: Relevance to the Developmental Phase of Polycystic Ovarian Syndrome*
Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

ANN E. TAYLOR*, BRIAN MCCOURT, KATHRYN A. MARTIN, ELLEN J. ANDERSON, JUDITH M. ADAMS, DAVID SCHOENFELD, AND JANET E. HALL

Reproductive Endocrine Unit and National Center for Infertility Research, Massachusetts General Hospital, Boston, Massachusetts 02114

Study of 61 women with PCOS, compared to 24 normal controls (EFP)

Diagnostic criteria:
- Chronic oligoamenorrhea (<9 cycles/yr) or amenorrhea
- Hyperandrogenism (clinical or biochemical)
- Exclusion of late-onset CAH
- Normal TFT and PRL
- Off all medication for at least 2 months
Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

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<th>Anovulatory PCOS patients (n = 52)</th>
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<td>16–42</td>
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<tr>
<td>Cycle day</td>
<td>40a</td>
<td>4–862</td>
<td>2b</td>
<td>−5–6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.8c</td>
<td>17.0–60.2</td>
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<tr>
<td>Hirsutism score</td>
<td>11a</td>
<td>0–29</td>
<td>13.5a</td>
<td>8–18</td>
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<tr>
<td>Ovarian volume (cm³)</td>
<td>14.4a</td>
<td>5.7–44.8</td>
<td>14.6c</td>
<td>9.7–21.5</td>
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<tr>
<td>LH pool (IU/L)</td>
<td>15.4a</td>
<td>5.3–112.9</td>
<td>8.0b</td>
<td>2.1–10.8</td>
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<tr>
<td>FSH pool (IU/L)</td>
<td>9.5</td>
<td>4.0–29.1</td>
<td>9.4</td>
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<td>LH/FSH ratio</td>
<td>1.58a</td>
<td>0.70–15.68</td>
<td>1.05a.b</td>
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<td>LH pulse amplitude (IU/L)</td>
<td>7.1c</td>
<td>2.6–50.7</td>
<td>8a</td>
<td>5.3–66.5</td>
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<td>LH pulse frequency (#/24 h)</td>
<td>18a</td>
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<td>8b</td>
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<td>Testosterone (ng/mL)</td>
<td>1.3a</td>
<td>0.4–4.2</td>
<td>0.8a,b</td>
<td>0.7–1.0</td>
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<tr>
<td>Androstenedione (ng/mL)</td>
<td>3.7a</td>
<td>1.5–12.6</td>
<td>2.4</td>
<td>1.0–5.0</td>
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<tr>
<td>17-OH progesterone (ng/mL)</td>
<td>1</td>
<td>0.3–3.6</td>
<td>0.8</td>
<td>0.5–2.7</td>
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<tr>
<td>DHEA-S (µg/dL)</td>
<td>148</td>
<td>20–455</td>
<td>150</td>
<td>50–592</td>
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<td>Estradiol (pg/mL)</td>
<td>83</td>
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<td>Estrone (pg/mL)</td>
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*a P < 0.004 vs. normal.

b P < 0.004 vs. anovulatory PCOS.

c P < 0.05 vs. normal.
**Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome**

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<td>Cycle day</td>
<td>49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4–862</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>33.8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17.9–60.2</td>
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<td>Ovarian volume (cm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>14.4&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>LH/FSH ratio</td>
<td>1.58&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>LH pulse amplitude (IU/L)</td>
<td>6.1</td>
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<td>LH pulse frequency (#/24 h)</td>
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<tr>
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<td>0.8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.7–1.0</td>
</tr>
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<td>Androstenedione (ng/mL)</td>
<td>3.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5–12.6</td>
<td>2.4</td>
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<td>17-OH progesterone (ng/mL)</td>
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<td>DHEAS (μg/dL)</td>
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<sup>a</sup> P < 0.001 cs. normal.

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<tr>
<td>Age (yr)</td>
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<td>Cycles/day</td>
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<td>BMI (kg/m²)</td>
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<td>Ovarian volume (cm³)</td>
<td>Median 14.4, Range 5.7–41.8</td>
<td>Median 14.8, Range 9.7–21.5</td>
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<td>LH peak (IU/L)</td>
<td>Median 15.4, Range 5.3–112.9</td>
<td>Median 8.0, Range 2.1–10.8</td>
<td>Median 5.8, Range 2.0–12.4</td>
<td>&lt;0.001</td>
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<tr>
<td>FSH peak (IU/L)</td>
<td>Median 5.8, Range 4.0–29.1</td>
<td>Median 8.5, Range 2.0–16.4</td>
<td>Median 6.7–16.4</td>
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<td>LH/FSH ratio</td>
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<td>Median 1.05, Range 0.40–1.82</td>
<td>Median 0.51, Range 0.21–1.05</td>
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<td>LH pulse amplitude (IU/L)</td>
<td>Median 5.1, Range 2.6–50.7</td>
<td>Median 8.0, Range 5.3–66.5</td>
<td>Median 4.5, Range 2.0–14.9</td>
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<td>LH pulse frequency (#/24 h)</td>
<td>Median 18, Range 4–28</td>
<td>Median 8, Range 2–13</td>
<td>Median 15, Range 6–21</td>
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<td>Testosterone (ng/mL)</td>
<td>Median 0.13, Range 0.4–4.2</td>
<td>Median 0.8, Range 0.7–1.0</td>
<td>Median 0.6, Range 0.4–1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Androstenedione (ng/mL)</td>
<td>Median 3.7, Range 1.5–12.6</td>
<td>Median 2.4, Range 1.0–5.0</td>
<td>Median 2.6, Range 0.9–5.0</td>
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<tr>
<td>17-OH progesterone (ng/mL)</td>
<td>Median 0.3, Range 0.3–3.6</td>
<td>Median 0.8, Range 0.5–2.7</td>
<td>Median 0.7, Range 0.3–2.3</td>
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<td>DHEAS (μg/dL)</td>
<td>Median 148, Range 20–455</td>
<td>Median 150, Range 50–592</td>
<td>Median 158, Range 20–395</td>
<td>0.866</td>
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<td>Estradiol (pg/mL)</td>
<td>Median 83, Range 16–235</td>
<td>Median 80, Range 34–178</td>
<td>Median 84, Range 40–142</td>
<td>0.845</td>
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<td>Estrone (pg/mL)</td>
<td>Median 82, Range 14–606</td>
<td>Median 65, Range 28–298</td>
<td>Median 64, Range 23–119</td>
<td>0.075</td>
</tr>
</tbody>
</table>

*P < 0.004 vs. normal.

b P < 0.004 vs. anovulatory PCOS.

c P < 0.05 vs. normal.
High prevalence of gonadotropin secretion abnormalities in PCOS patients

Important associations between the elevated LH secretion and recent ovulation or LH pulse frequency, but NOT sex steroids

Strong association between LH pulse frequency and pool LH levels or LH/FSH ratio may suggest an etiologic relationship

J Clin Endocrinol Metab 82, 1997
CONCLUSIONS

Rapid GnRH pulse frequency probably has a role in the abnormal LH secretion pattern in PCOS

Marshall and Eagleson, 1999
CONCLUSIONS

Rapid GnRH pulse frequency probably has a role in the abnormal LH secretion pattern in PCOS.

The defect in hypothalamic GnRH secretion seems to be intrinsic to PCOS patients.

Could there be a role of elevated insulin levels/insulin resistance in this abnormal GnRH secretion pattern?
GnRH neurons

Facilitation

Inhibition

Metabolic signals

GnRH neurons

Gonadotrophs

LH

Post-pubertal Period
Treatment of hyperandrogenism

“Classical” approach: oral contraception
Norgestimate and ethinyl estradiol in the treatment of acne vulgaris

Multicentric, randomised, double-blind and placebo controlled study
250 subjects, aged 15-49 ans

Redmond et al, Obst Gynecol 89, 1997
Treatment of hyperandrogenism

“Classical” approach: oral contraception

Addition of a compound with intrinsic anti-androgen activity:

**Diane 35**
ethinyl estradiol 35 µg / acétate de cyprotérone 2 mg

**Yasmine**
ethinyl estradiol 30 µg / drospirénone 3 mg
Compared effects of Diane and Yasmine on hyperandrogenism in PCOD

Population
- 128 patients with hyperandrogenism (acne, hirsutism)
- Double blind, randomised, over 9 consecutive cycles

Résults

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<thead>
<tr>
<th></th>
<th>Diane</th>
<th>Yasmine</th>
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<tbody>
<tr>
<td>acne</td>
<td>-62%</td>
<td>-58%</td>
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<tr>
<td>SHBG</td>
<td>x3</td>
<td>x3</td>
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<tr>
<td>hirsutism</td>
<td>Moderate reduction</td>
<td>Moderate reduction</td>
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</tbody>
</table>

van Vloten et al, Cutis 69, 2002
Treatment of hyperandrogenism

“Classical” approach: oral contraception

Progestogenic compound with intrinsic anti-androgen activity

“Classical” approach: addition of higher dosage anti-androgen
Choice of anti-androgen compound

- Cyproterone acetate
- Spironolactone
- Flutamide
- Finasteride
OBJECTIVES The objective of this review was to investigate the effectiveness of cyproterone acetate alone, or in combination with ethinyl estradiol, in reducing hair growth in women with hirsutism secondary to ovarian hyperandrogenism.

DATA COLLECTION AND ANALYSIS Eleven studies were identified which fulfilled the inclusion criteria. Nine randomised studies were included in the review, and two were excluded because of insufficient information. Only one study had more than 100 women included in the analysis.
Cyproterone acetate for hirsutism.


MAIN RESULTS

… no clinical trials comparing cyproterone acetate alone with placebo.

… one small study comparing cyproterone acetate in combination with ethinyl estradiol to placebo: significant subjective reduction in hair growth with cyproterone acetate therapy, although the confidence limits were large.
Cyproterone acetate for hirsutism.


MAIN RESULTS

... In studies where cyproterone acetate was compared to other drug modalities (ketoconazole, spironolactone, flutamide, finasteride, GnRH analogues) no difference in clinical outcome was noted. There were, however, endocrinological differences in androgen and estrogen levels between different drug therapies.
Treatment of hyperandrogenism

“Modern” approach: insulin sensitizers

Metformin

Thiazolidinediones
Cross over, double blinde, placebo-controlled study
16 women with PCOD and hirsutism
6 months of treatment (metformin vs placebo), separated by 2 months off Rx
Sensitization to Insulin Induces Ovulation in Nonobese Adolescents with Anovulatory Hyperandrogenism

Lourdes Ibáñez, Carme Valls, Angela Ferrer, María Victoria Marcos, Francisco Rodríguez-Hierro, and Francis De Zegher

18 adolescents (16.5±0.4 years, 3-7 years after menarche)
Inclusion criteria:
- anovulation
- précocious pubarche
- hyperandrogenism

6 months treatment with metformin (1275 mg/d single dose)

FG score goes from $15.4±0.8 (12-22)$ before Rx tp $11.2±0.6 (8-16)$ after 6 months on metformin (p<0.001)

JCEM 86, 2001
Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome

40 obese women with PCOD, under hypocaloric regimen
6 months of treatment simple blind, after one month off Rx

**Groupes:**
- Placebo
- Metformin (2x850 mg/j)
- Flutamide (2x250 mg/j)
- Metformin and flutamide

Gambineri *et al*, Clin Endocrinol 60, 2004
Advantage of metformin

Targets metabolic syndrome

Prevalence of obesity in PCOD  30-50%

Cattrall and Healy, Best Pract & Res Clin Obst Gynaecol 18, 2004
Advantage of metformin

*Targets metabolic syndrome*

Prevalence of obesity in PCOD 30-50%

Cattrall and Healy, Best Pract & Res Clin Obst Gynaecol 18, 2004

Prevalence of metabolic syndrome

<table>
<thead>
<tr>
<th></th>
<th>PCOD</th>
<th>Controls</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>46%</td>
<td>23%</td>
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</tbody>
</table>

Glueck *et al*, Metabolism 52, 2003
Advantage of metformin

Targets metabolic syndrome

Prevalence of obesity in PCOD 30-50%
Cattrall and Healy, Best Pract & Res Clin Obst Gynaecol 18, 2004

Prevalence of metabolic syndrome

- PCOD 46%
- Controls 23%
Glueck et al, Metabolism 52, 2003

Risk of diabetes mellitus

5-10x celui des CT
Ovalle and Aziz, Fert Steril 77, 2002
Treatment of metabolic syndrome

Necessity of both early and long term treatment

- Obesity
- Hypertension
- Glucose intolerance / diabète
- Dyslipidemia