Polycystic Ovary Syndrome

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CHUV

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

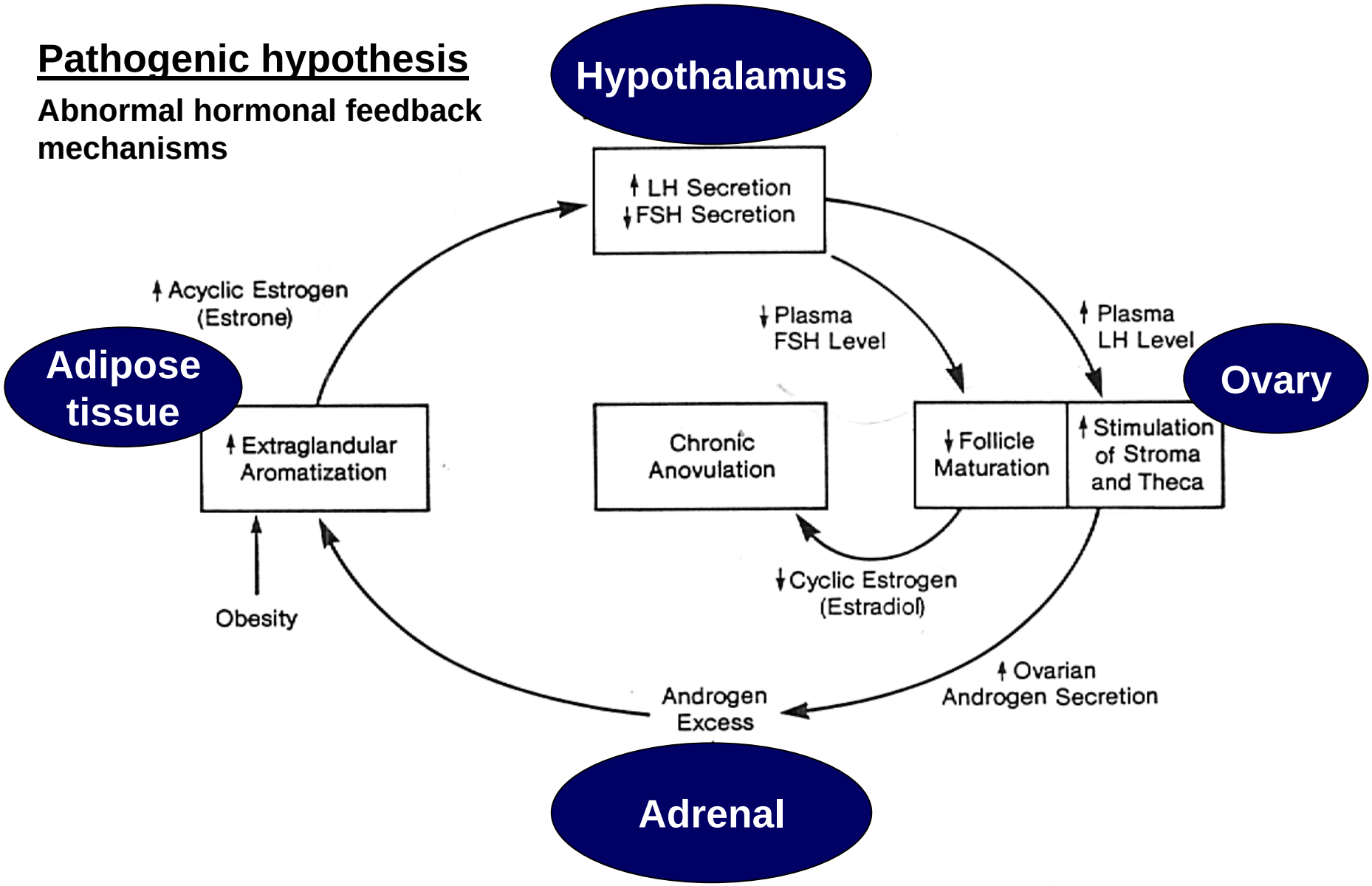
Clinical presentation

- 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

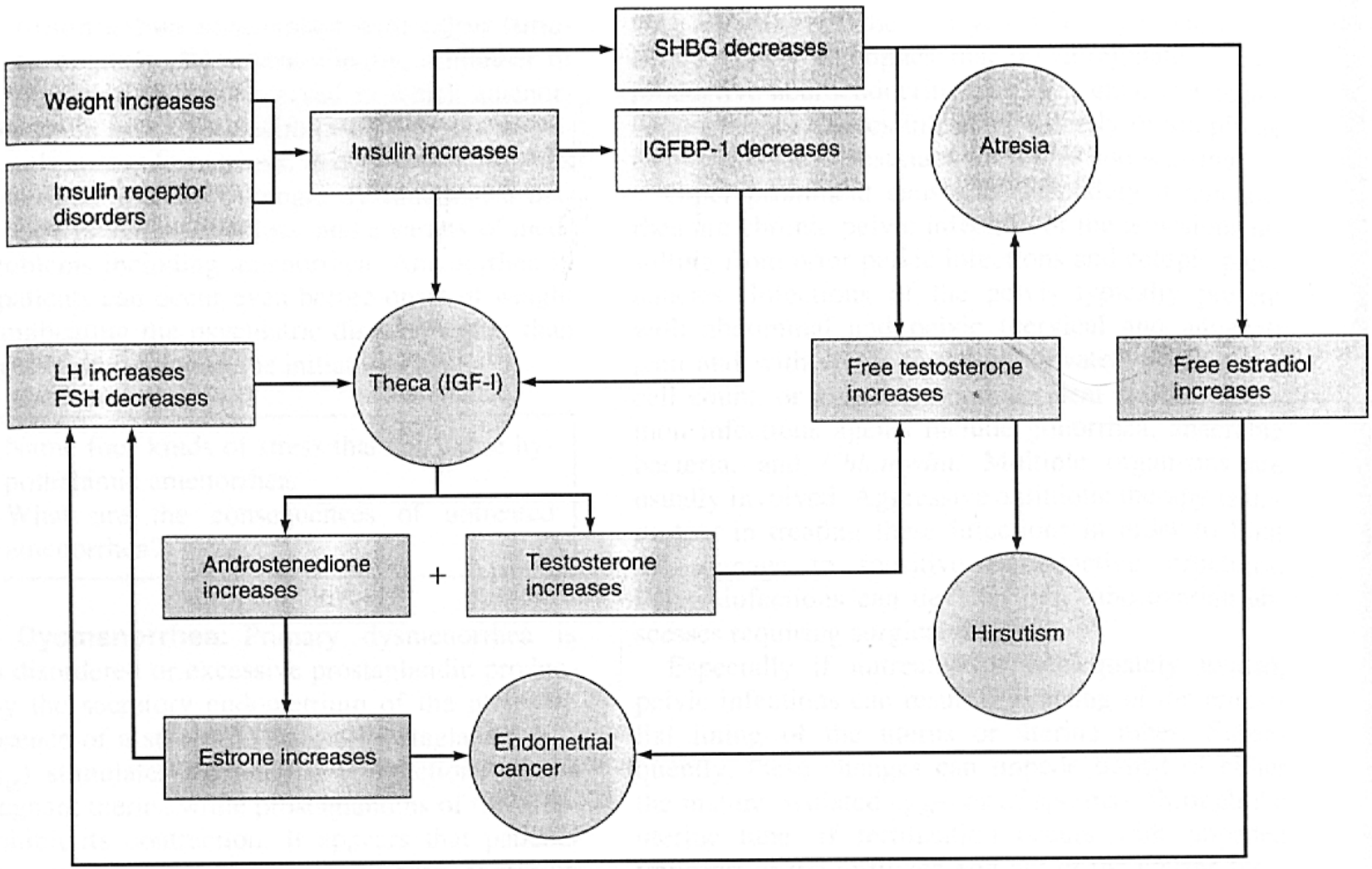
Abnormal hormonal feedback mechanisms



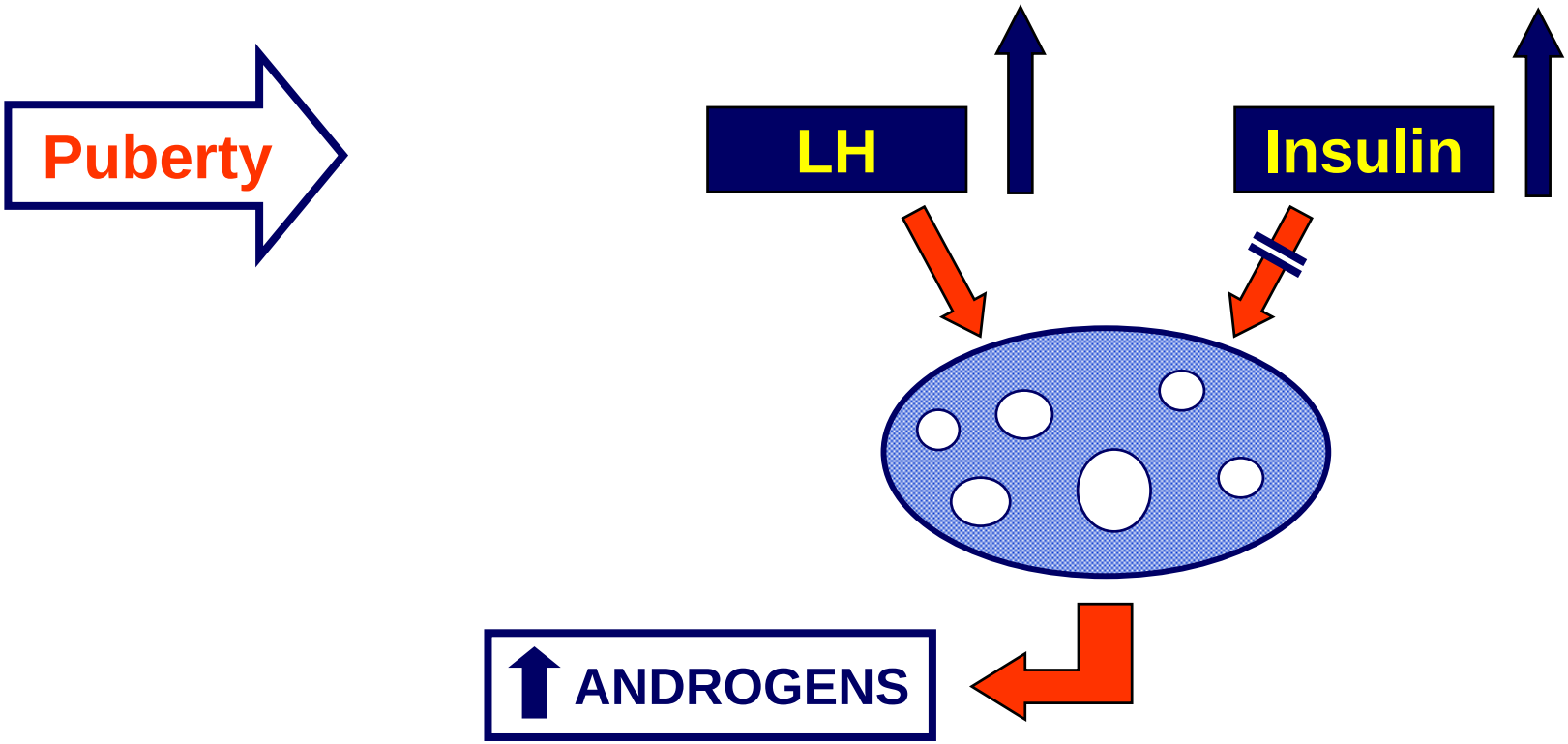
PCOS: THE TEXTBOOK VIEW II

Pathogenic hypothesis

Obesity and insulin resistance



PCOS: A DEVELOPMENTAL VIEW



- Hirsutism
- Acne
- Alopecia

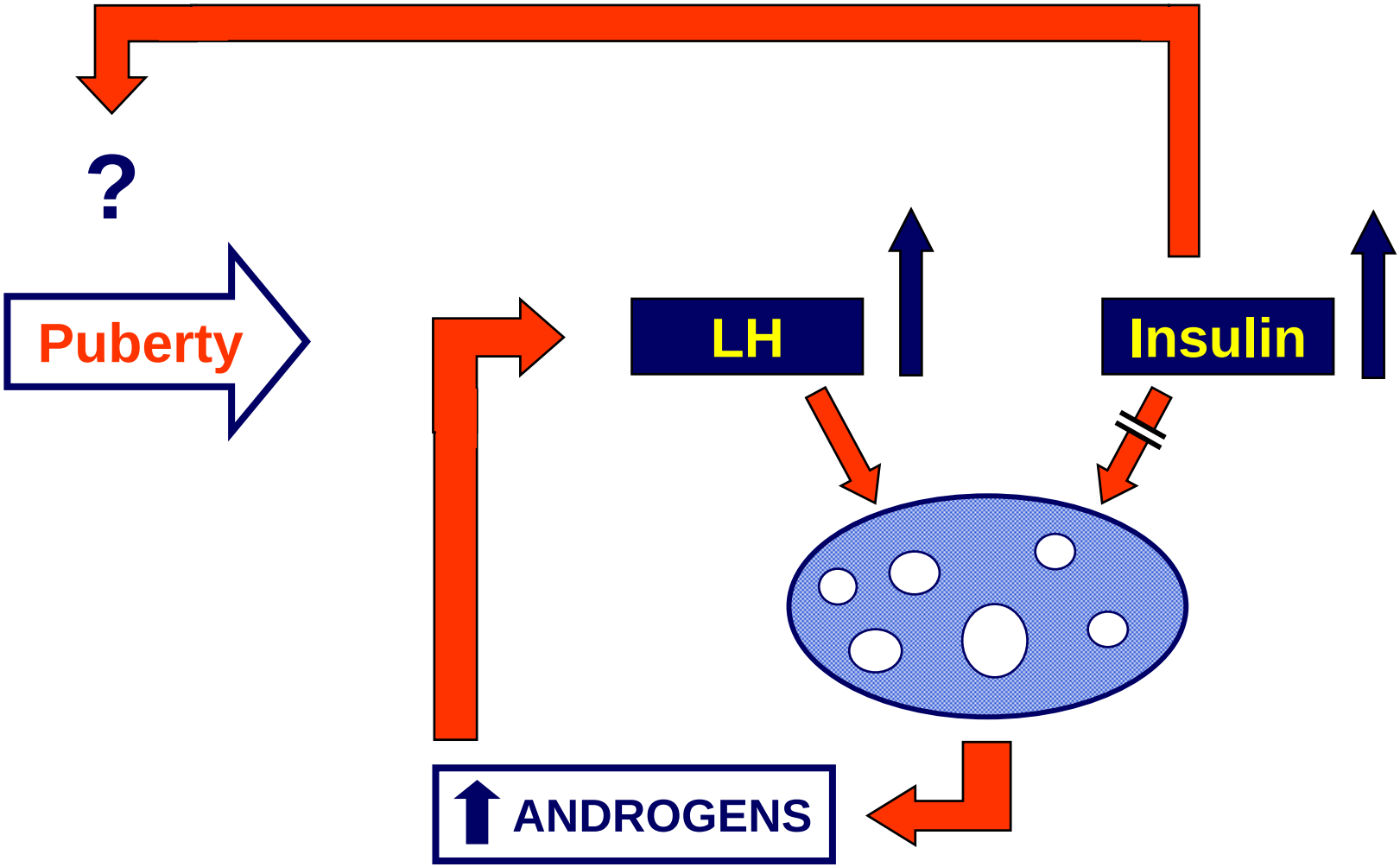
Adapted from S Franks, 2002

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



- Hirsutism
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- Alopecia

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 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.

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**

NEJM 309, 1983

A CHRONOBIOLOGIC ABNORMALITY IN LUTEINIZING HORMONE SECRETION IN TEENAGE GIRLS WITH THE POLYCYSTIC-OVARY SYNDROME

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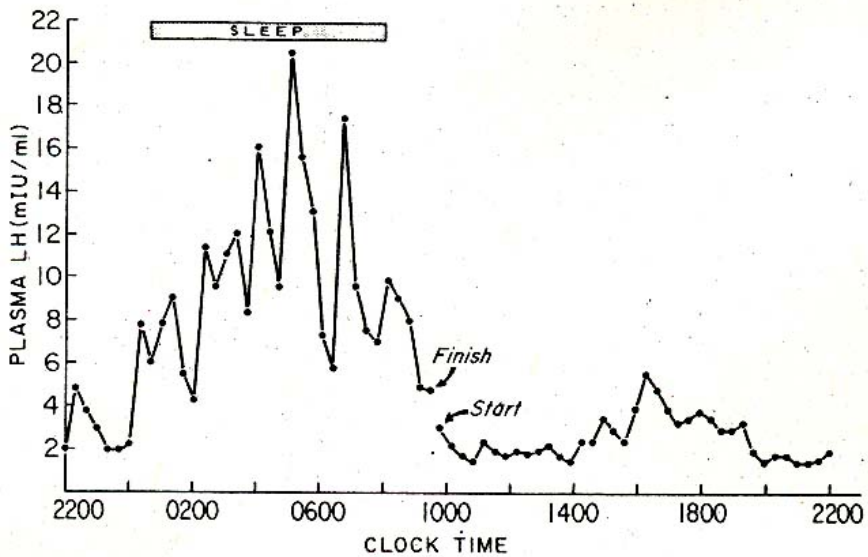
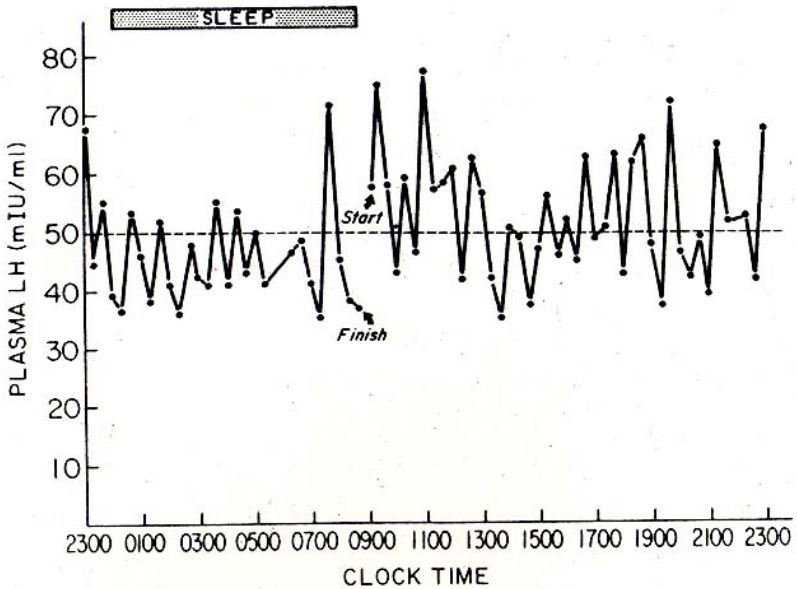




Abnormality present in 4 of 5 patients

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

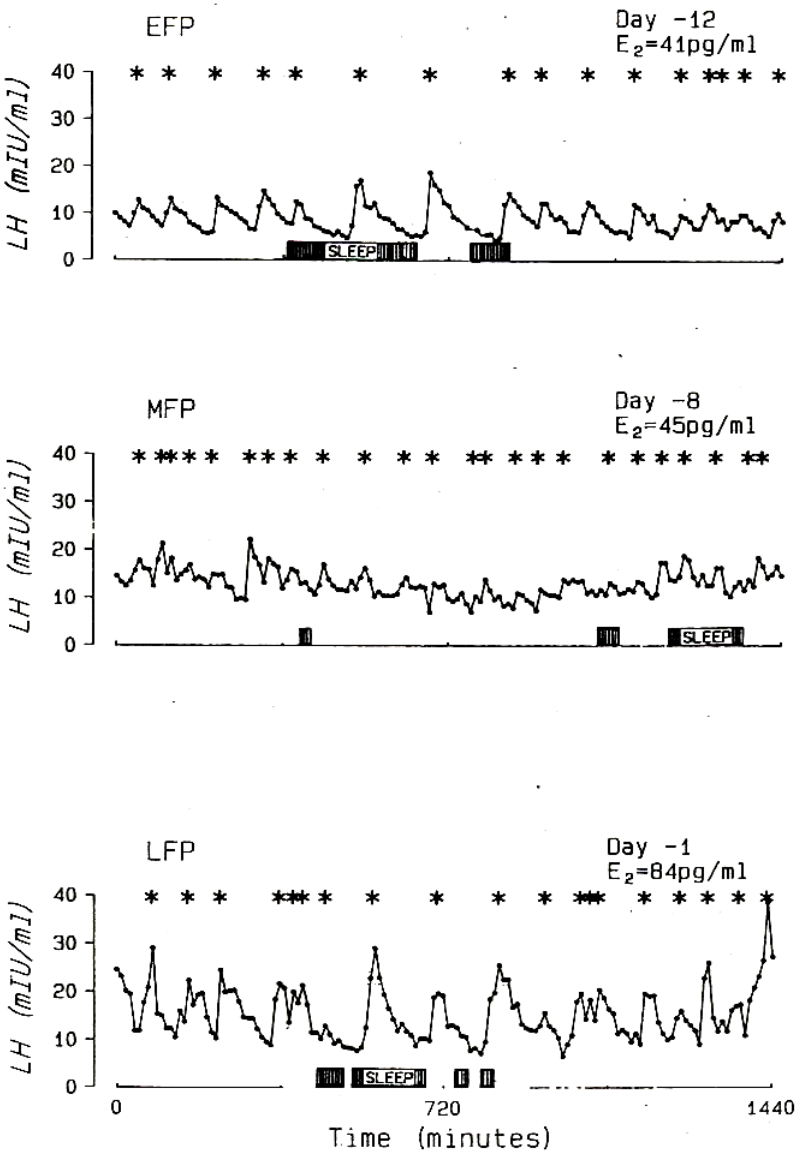
Diagnostic criteria:

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

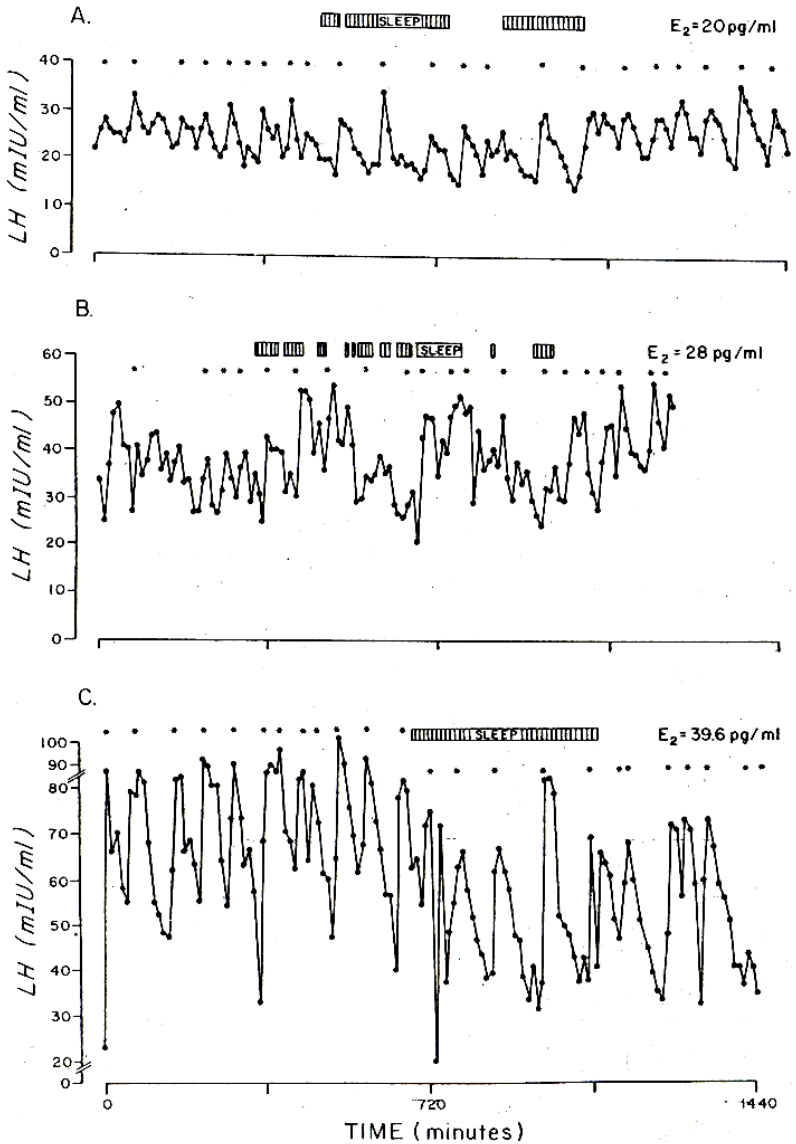
- **E2 lower than controls in MFP and LFP**
- **Estrone higher than controls in EFP and MFP, lower in LFP**

J Clin Endocrinol Metab 66, 1988

Normal



PCOS



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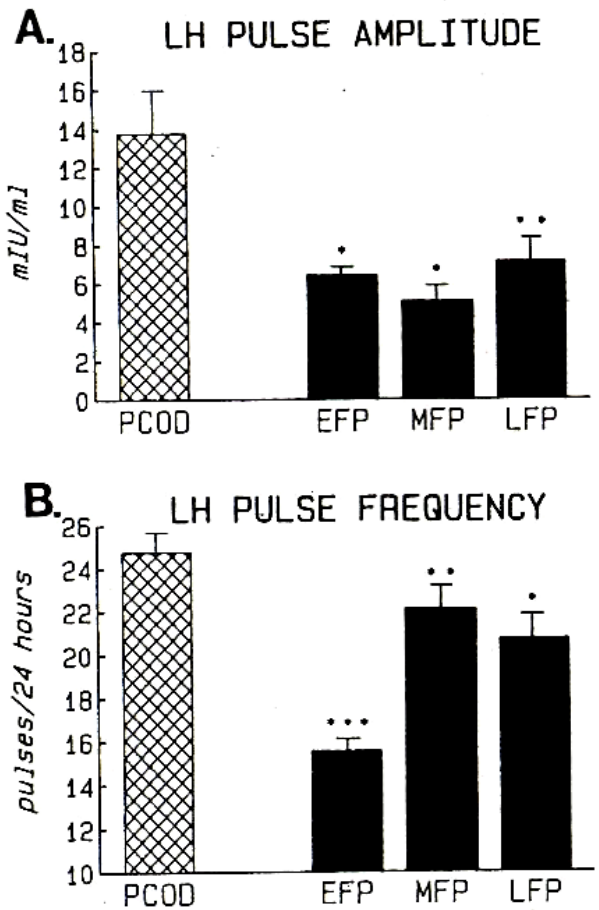

J Clin Endocrinol Metab 66, 1988

Accelerated 24-Hour Luteinizing Hormone Pulsatile Activity in Adolescent Girls with Ovarian Hyperandrogenism: Relevance to the Developmental Phase of Polycystic Ovarian Syndrome*

D. APTER†, T. BÜTZOW, G. A. LAUGHLIN, AND S. S. C. YEN‡

Department of Reproductive Medicine, University of California-San Diego School of Medicine, La Jolla, California 92093–0802

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**

J Clin Endocrinol Metab 79, 1994

Accelerated 24-Hour Luteinizing Hormone Pulsatile Activity in Adolescent Girls with Ovarian Hyperandrogenism: Relevance to the Developmental Phase of Polycystic Ovarian Syndrome*

TABLE 1. Clinical characteristics of the hyperandrogenic subjects

Subject no.	Age (yr)	Age at menarche (yr)	BMI	Menstrual pattern	Hirsutism score[a]	Acne	Acanthosis nigricans
1	11.6		21.8	Premenarche	10	–	No
2	11.9	11.9	34.6	Oligomenarche	7	+	Yes
3	12.8	11.5	39.5	Oligomenarche	15	+	No
4	13.5	11.6	21	Oligomenarche	10	–	No
5	14.7	12.0	33	Oligomenarche	16	++	Yes
6	14.7	12.7	33.2	Regular	10	+	No
7	15.4	12.8	34.2	Oligomenarche	12	+	No
8	16.2		43.5	Amenorrhea	20	++	Yes
9	16.4	12.2	23.1	Oligomenarche	16	+	No
10	17.1	12.5	20.4	Regular	8	–	No
11	17.1	12.1	21.9	Oligomenarche	8	–	No
12	17.7	12.6	21.7	Oligomenarche	17	–	No
13	18.1	12.5	26.4	Amenorrhea	21	++	No
HA[b]	15.1 ± 0.6	12.3 ± 0.2	28.0 ± 1.6[c]		13.1 ± 1.3		
Normal[b]	14.8 ± 0.3	12.4 ± 0.3	22.1 ± 1.2		<7.0		

[a] According to Ferriman and Gallwey (12).
[b] Mean ± SE for group.
[c] $P = 0.005$ *vs.* normal.

J Clin Endocrinol Metab 79, 1994

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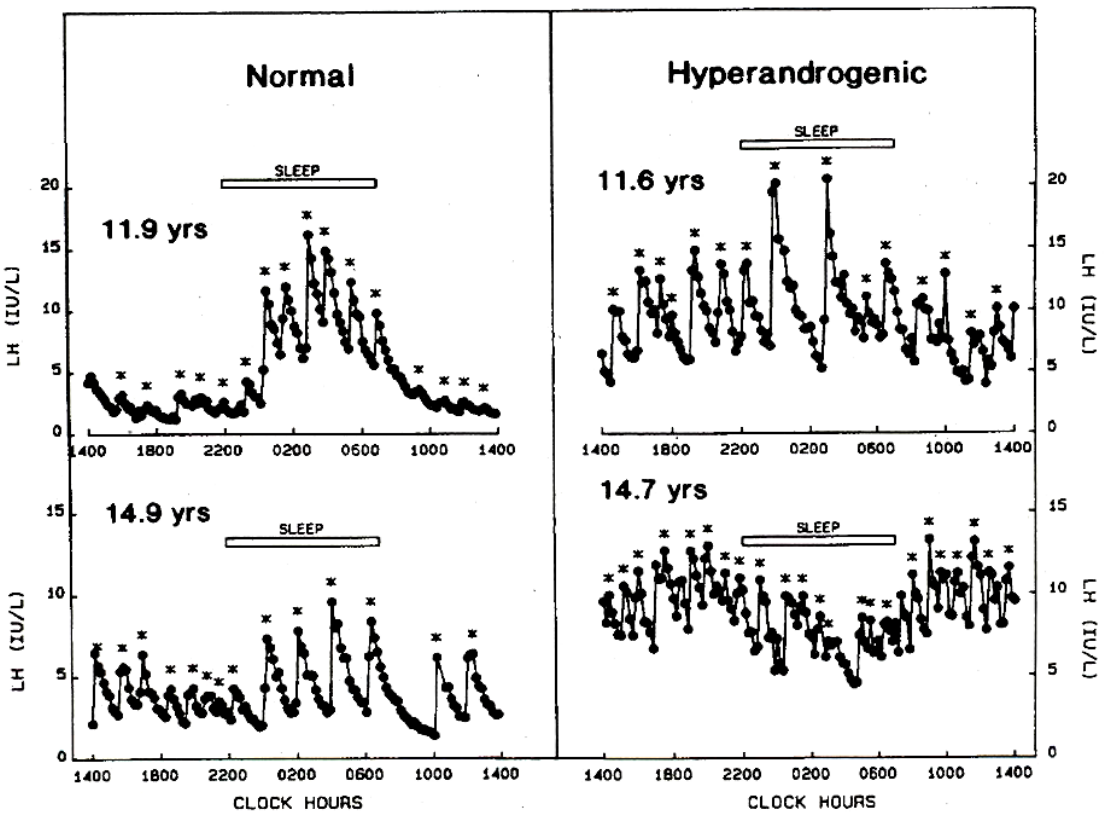

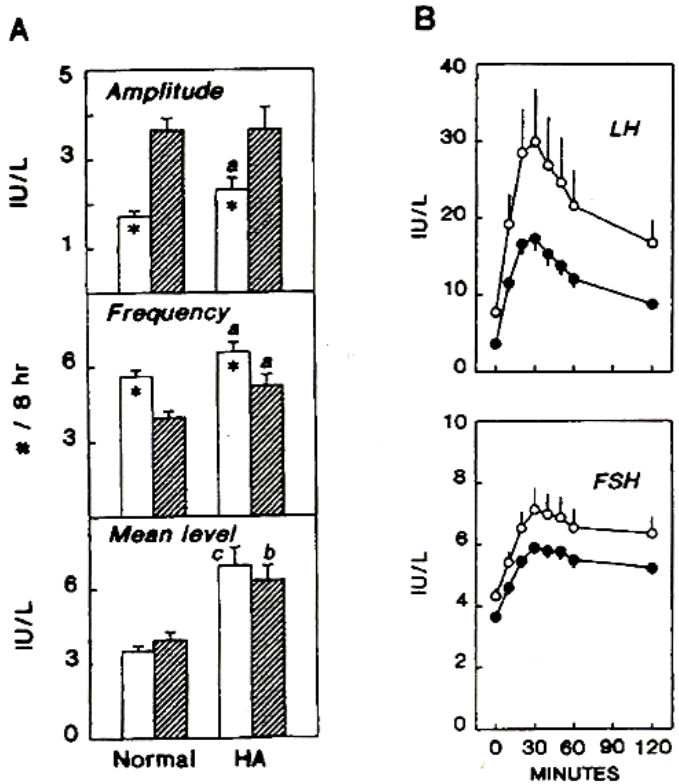

J Clin Endocrinol Metab 79, 1994

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**

J Clin Endocrinol Metab 82, 1997

Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

	Anovulatory PCOS patients (n = 52)		Post-ovulatory PCOS patients (n = 9)		Normal women (n = 24)		*P* for ANOVA
	Median	Range	Median	Range	Median	Range	
Age (yr)	29	16–42	28	19–37	26	18–42	0.335
Cycle day	40[a]	4–862	2[b]	−5–6	3	1–7	**<0.001**
BMI (kg/m^2)	33.8[c]	17.0–60.2	26.2	21.5–40.1	25.4	19.6–50.9	0.022
Hirsutism score	11[a]	0–29	13.5[a]	8–18	5	0–9	**<0.001**
Ovarian volume (cm^3)	14.4[a]	5.7–44.8	14.6[c]	9.7–21.5	9.8	2.7–16.7	**<0.001**
LH pool (IU/L)	15.4[a]	5.3–112.9	8.0[b]	2.1–10.8	5.8	2.0–12.4	**<0.001**
FSH pool (IU/L)	9.5	4.0–29.1	9.4	2.0–16.4	10.8	6.7–16.4	.110
LH/FSH ratio	1.58[a]	0.70–15.68	1.05[a,b]	0.40–1.82	0.51	0.21–1.05	**<0.001**
LH pulse amplitude (IU/L)	7.1[c]	2.6–50.7	8[a]	5.3–66.5	4.5	2.0–14.9	**0.004**
LH pulse frequency (#/24 h)	18[a]	4–28	8[b]	2–13	15	6–21	**<0.001**
Testosterone (ng/mL)	1.3[a]	0.4–4.2	0.8[a,b]	0.7–1.0	0.6	0.4–1.4	**<0.001**
Androstenedione (ng/mL)	3.7[a]	1.5–12.6	2.4	1.0–5.0	2.6	0.9–5.0	**0.004**
17-OH progesterone (ng/mL)	1	0.3–3.6	0.8	0.5–2.7	0.7	0.3–2.3	0.052
DHEA-S (μg/dL)	148	20–455	150	50–592	158	20–395	0.866
Estradiol (pg/mL)	83	16–235	80	34–178	84	40–142	0.845
Estrone (pg/mL)	82	14–606	65	28–298	64	23–119	0.075

[a] $P < 0.004$ *vs.* normal.
[b] $P < 0.004$ *vs.* anovulatory PCOS.
[c] $P < 0.05$ *vs.* normal.

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J Clin Endocrinol Metab 82, 1997

Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

High prevalence of gonadotropin secretion abnormalities in PCOS patients

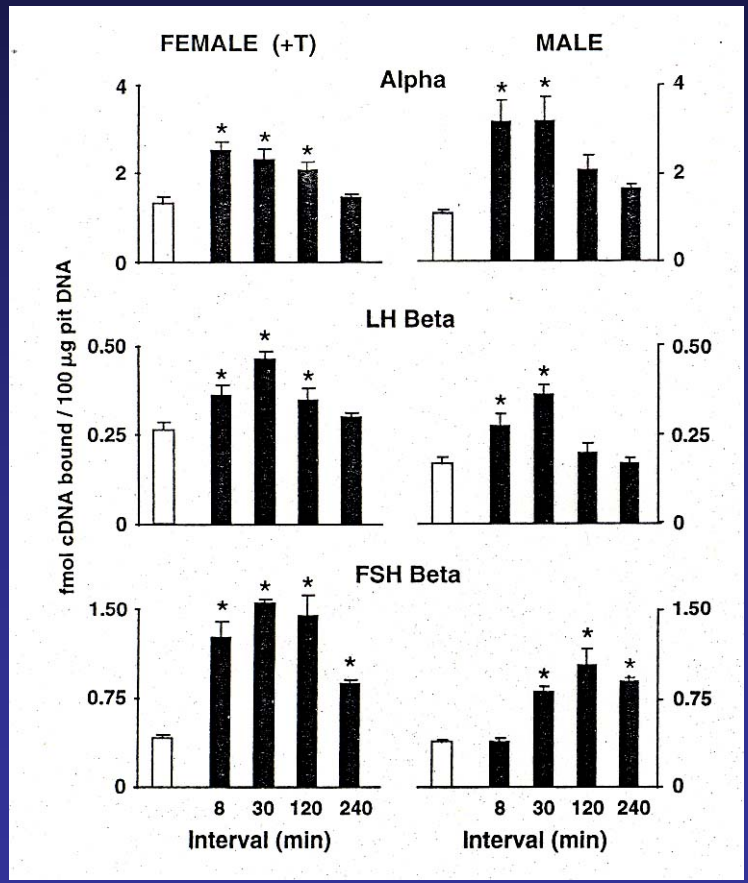
Important associations between the elevated LH secretion and recent ovulation or LH pulse frequency, *but NOT sex steroids*

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



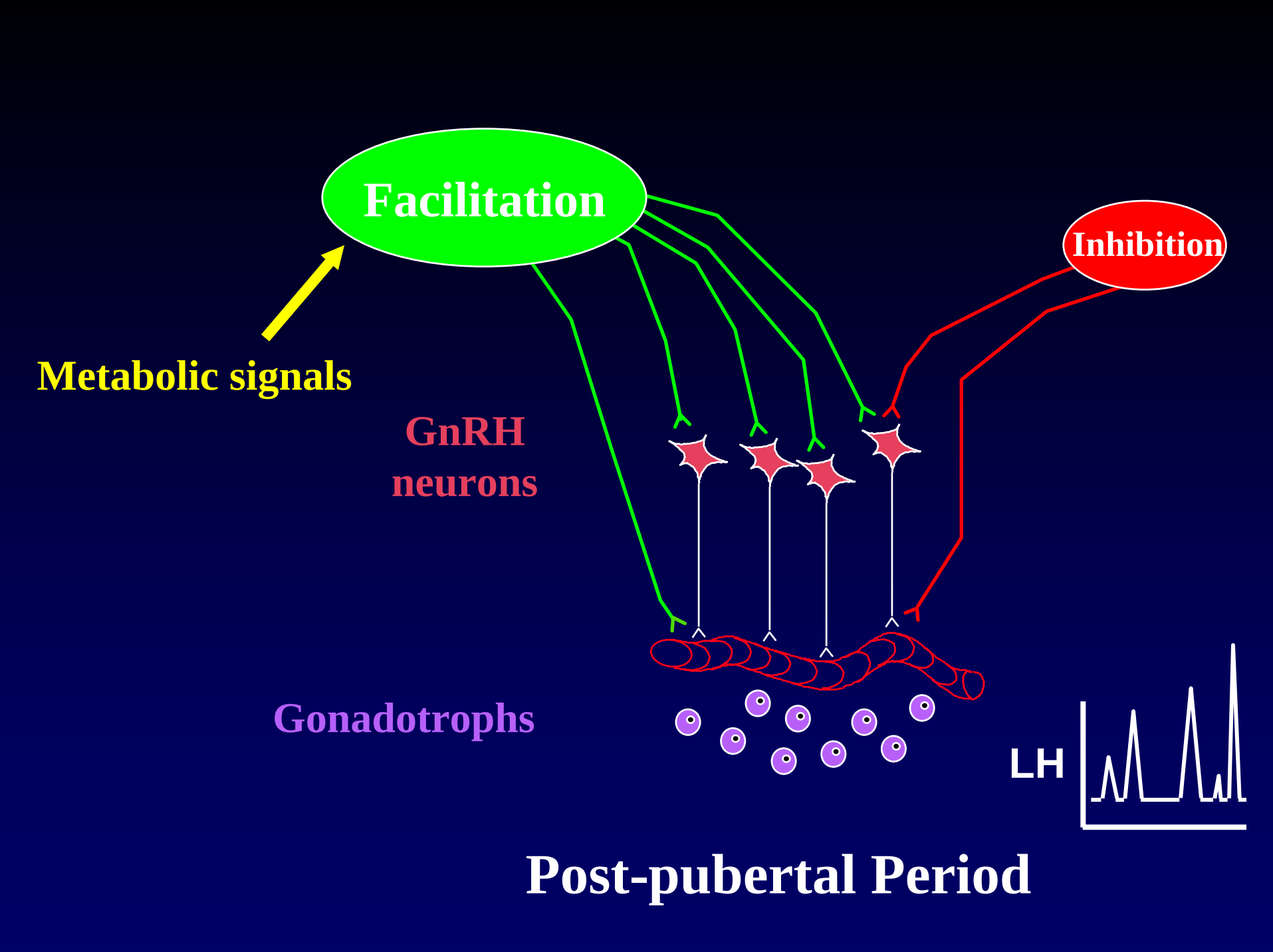
Marshall and Eagleson, 1999

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?



Post-pubertal Period

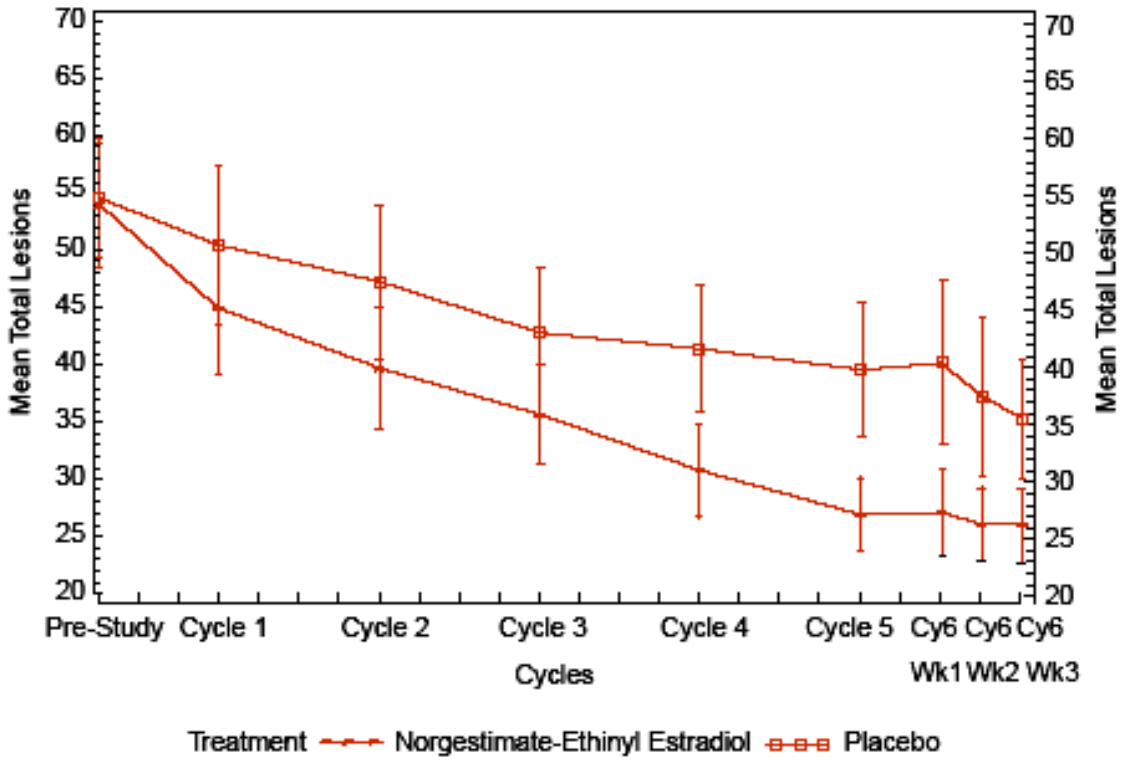
Treatment of hyperandrogenism

“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

	Diane	Yasmine
acne	**-62%**	**-58%**
SHBG	**x3**	**x3**
hirsutism	Moderate reduction	Moderate reduction

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

Cyproterone acetate for hirsutism.

Van der Spuy and Le Roux, Cochrane Database Syst Rev. 2003;(4):CD001125

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.

Van der Spuy and Le Roux, Cochrane Database Syst Rev. 2003;(4):CD001125

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.

Van der Spuy and Le Roux, Cochrane Database Syst Rev. 2003;(4):CD001125

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

European Journal of Endocrinology (2002) 147 217–221

CLINICAL STUDY

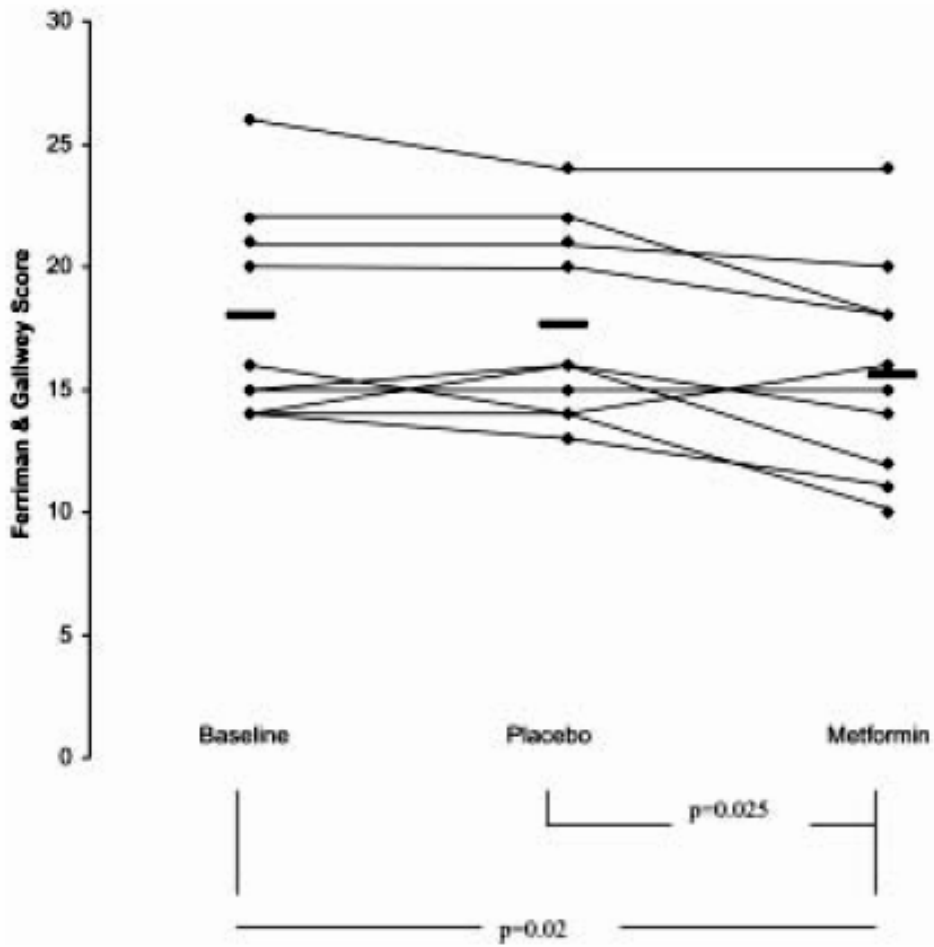
The effect of metformin on hirsutism in polycystic ovary syndrome

Christopher J G Kelly and Derek Gordon

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

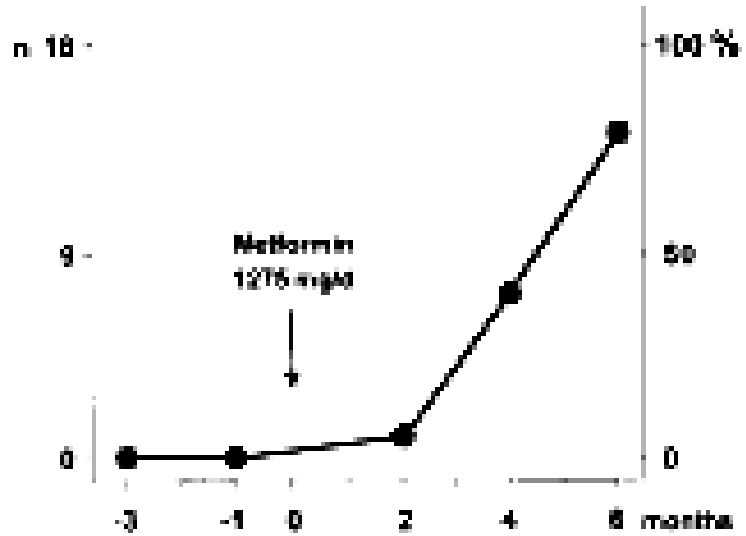
LOURDES IBÁÑEZ, CARME VALLS, ANGELA FERRER, MARIA VICTORIA MARCOS, FRANCISCO RODRIGUEZ-HIERRO, AND FRANCIS DE ZEGHER

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

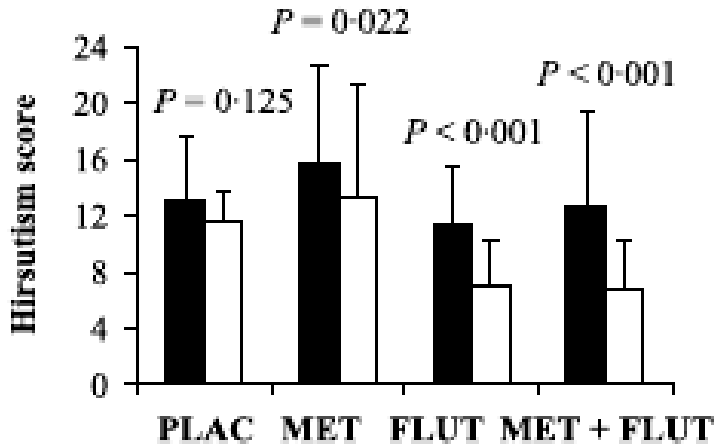
Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome

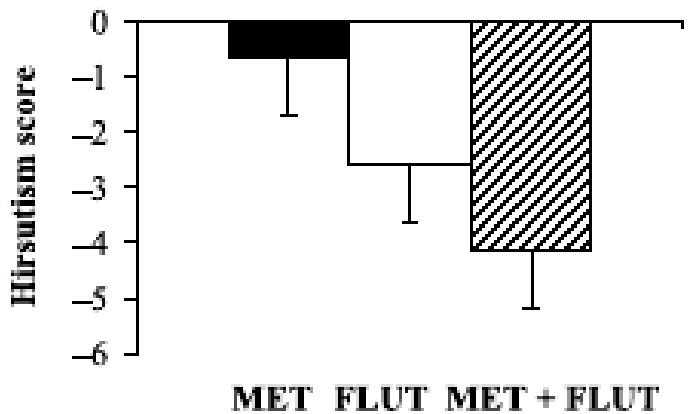
40 obese women with PCOD, under hypocaloric regimen

6 months of treatment simple blind, after on month off Rx

<u>Groupes</u>:

- 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

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Prevalence of metabolic syndrome

PCOD	46%
Controls	23%

Glueck *et al,* Metabolism 52, 2003

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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