

PCOS - ORIGINS IN ADOLESCENCE

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DISCLOSURES

Nothing to declare

SUBJECT - 17yo hirsute, irreg menses, overweight

History - normal childhood, always heavy, menarche at 12y, never established regular cycles, 4-5 menses/year. First noted facial hair at 14y which has become more marked.

Exam - Ht 5'7", Wt 204lb, **BMI 34**. BP 115/85. LMP 60 days ago.
Skin - increased hair chin, mustache, sideburns, mild acne, early acanthosis nigricans neck, axilla. No striae

Obese - mainly central, no proximal wasting, not clinically Cushingoid.

Labs - **Free T - 15pg/ml (< 6), SHBG - 10 (>30), LH - 14, FSH - 3,**
17 OHProg - 170 (<300), 24h UFF - 28 (< 45), DHEAS 188.
LDL - 115, HDL - 30, TG - 145. FBS - 97

Diagnosis - androgen excess, PCOS, Metabolic Syndrome.

POLYCYSTIC OVARIAN SYNDROME

CLINICAL FEATURES (1079 Pts)

REPRODUCTIVE	- Infertility	74%
	- Hirsutism	69%
	- Amenorrhea/ Anovulation	51%
METABOLIC	- Obesity	50%
	- Diabetes	30%
	- Hyperandrogenemia	85%

WIDE SPECTRUM - Regular menses → amenorrhea
- Mild hirsutism → virilized

PREVALENCE - 6 – 8% of reproductive aged women

ONSET IN PUBERTY-ADOLESCENCE



POLYCYSTIC OVARIAN SYNDROME

ONSET: adolescence, early teens

HORMONAL ABNORMALITIES:

PLASMA ANDROGENS -

- ↑ testosterone (T), low SHBG.
- ↑ androstenedione (A)
- ↑ dehydroepiandrosterone (DHEA-S) in 40%

LH -

- ↑ 75-95% (excluding recent ovulation)

INSULIN -

- fasting ↑ and responses to glucose
- insulin resistance (80% of obese, 30% of lean)

PCOS and THE METABOLIC SYNDROME (MBS)

MBS PREVALENCE IN PCOS

ADULTS

- 35 – 60%
- increases with age, 20 – 60% (<19-40y)
- 2-fold increase over comparable BMI
- Risk doubled with higher testosterone

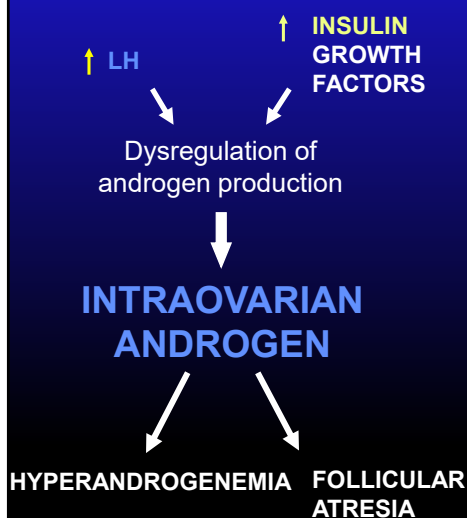
ADOLESCENTS

- 30 – 60%
- 4 to 5-fold increase over age/BMI matched
- 5-fold increase with highest testosterone

ELEVATED FREE TESTOSTERONE - INCREASED RISK OF MBS

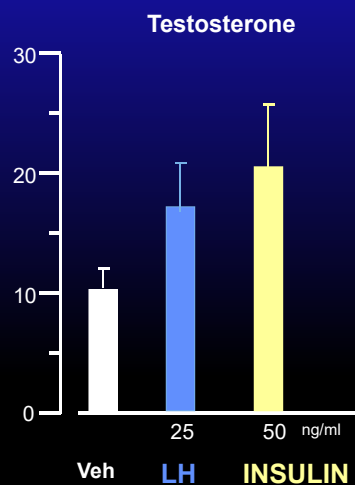
Weiss et al, NEJM 2004; Apridonidze et al, JCEM 2005; Ehrman et al, JCEM 2006; Coviello et al, JCEM 2006.

OVARIAN HYPERANDROGENISM

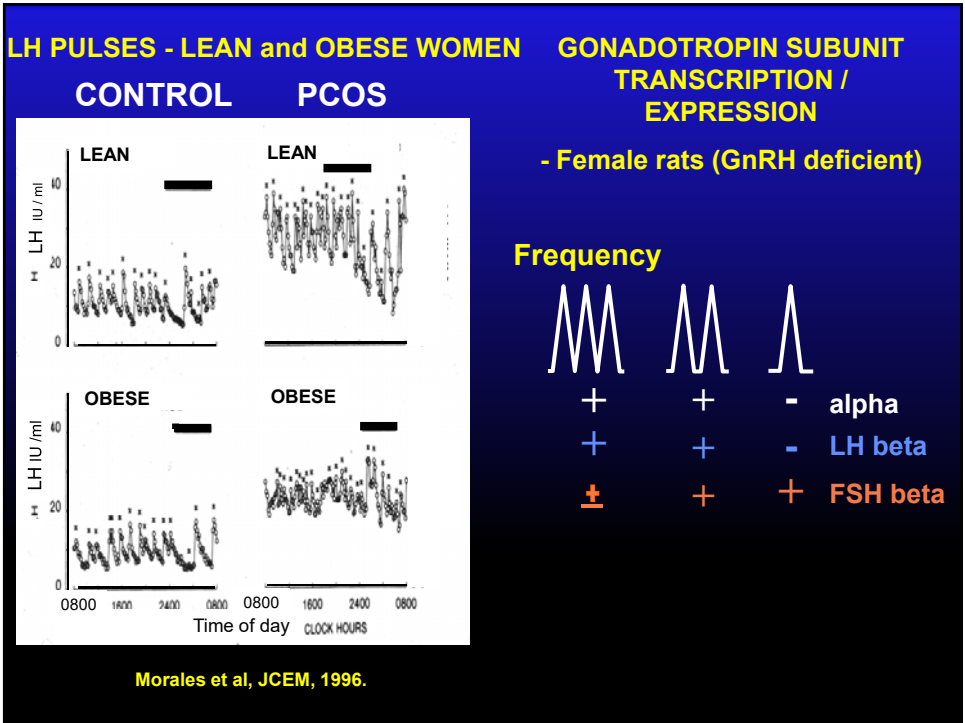
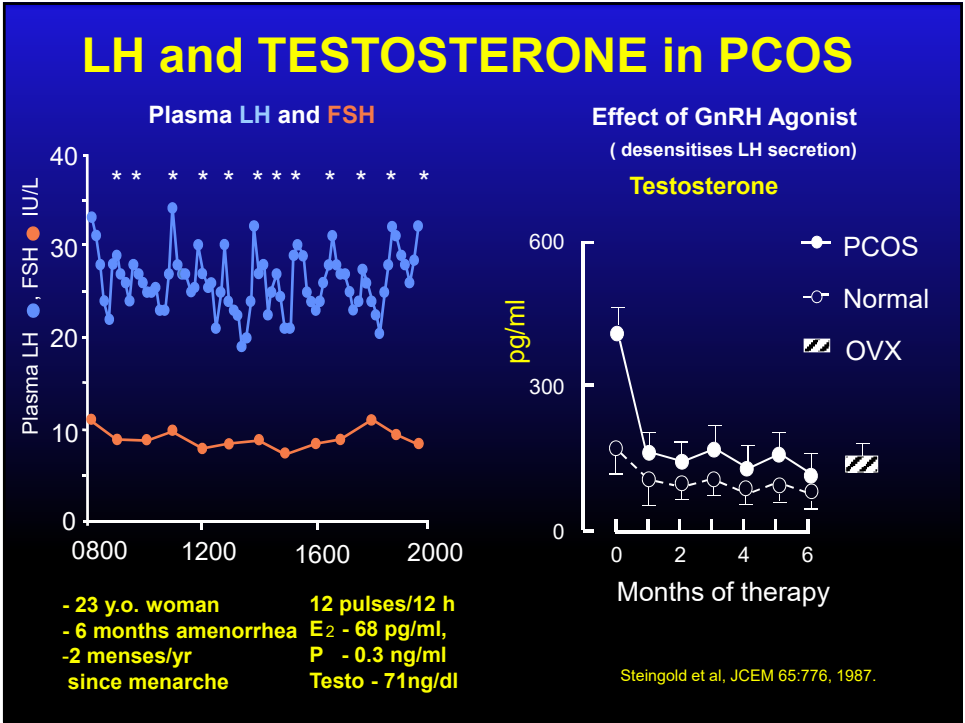


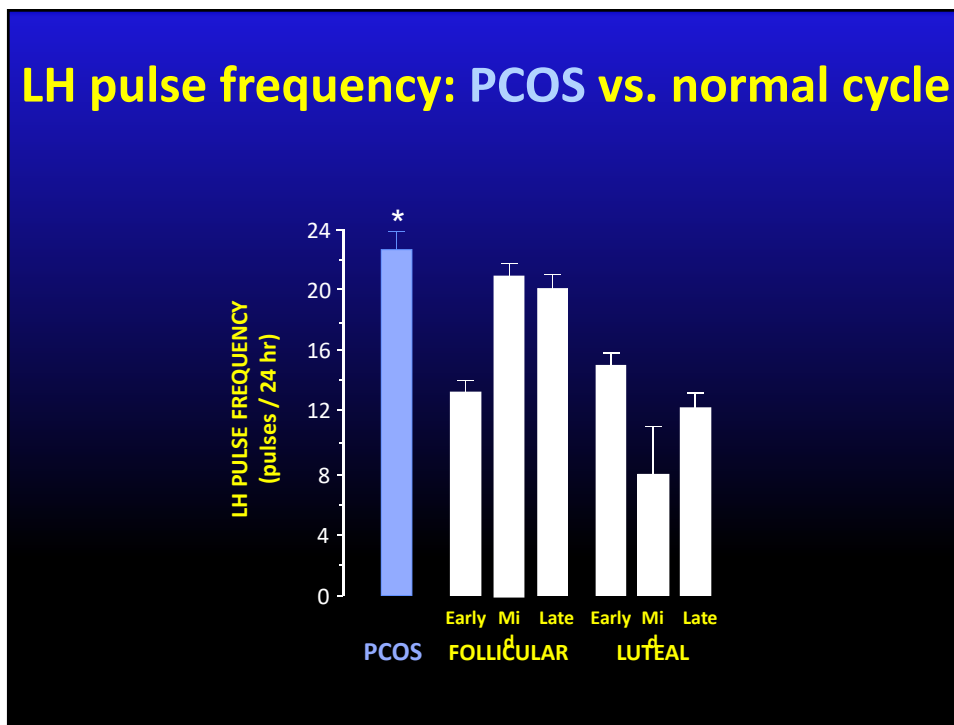
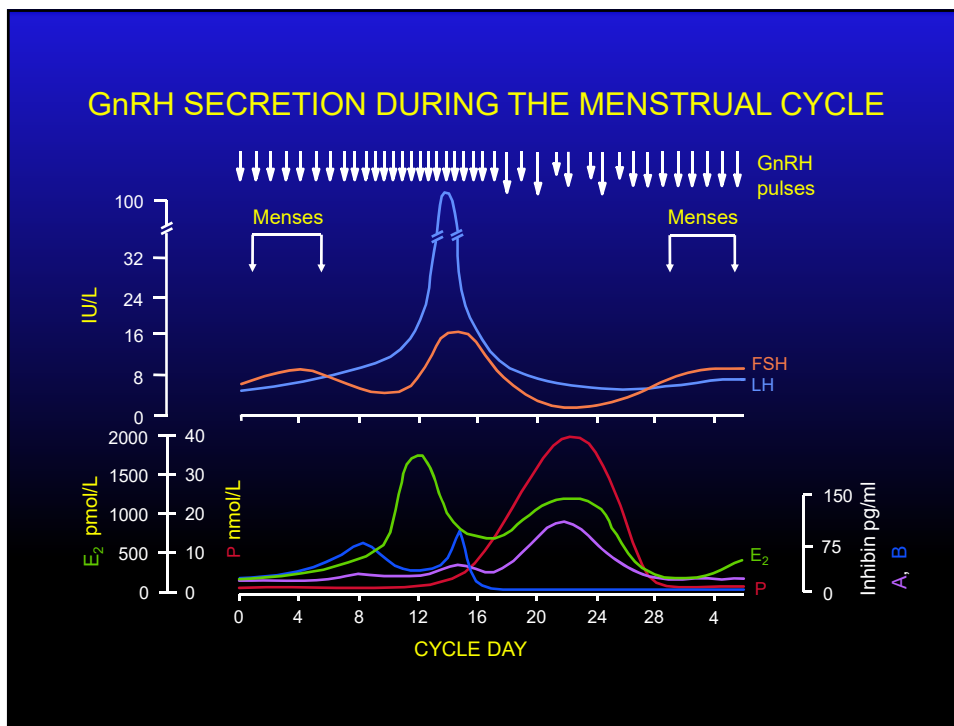
(after Ehrman & Rosenfield)

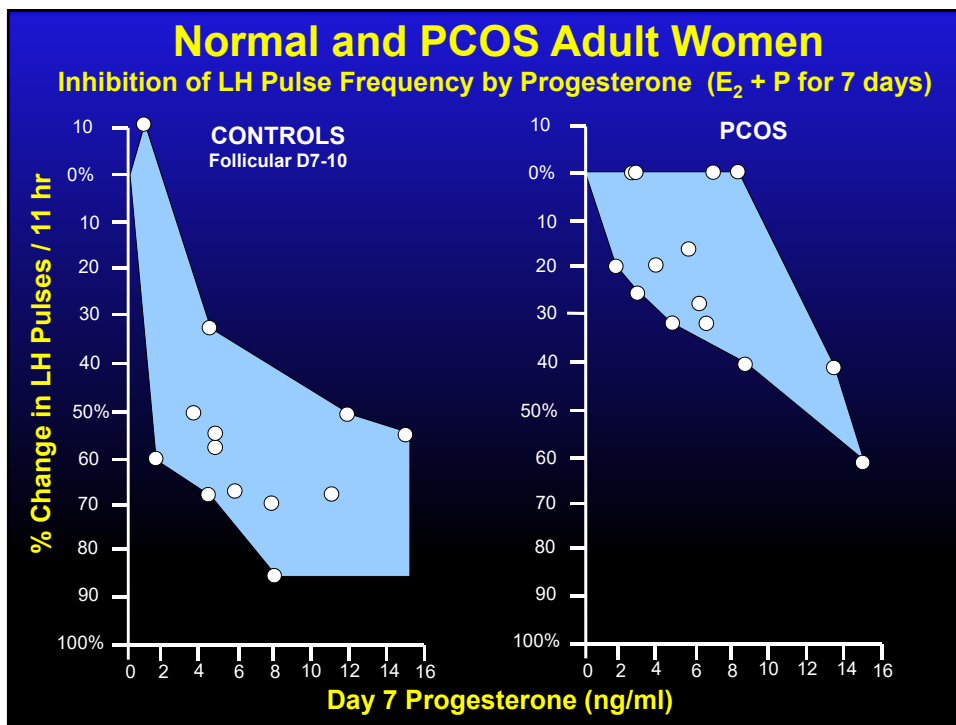
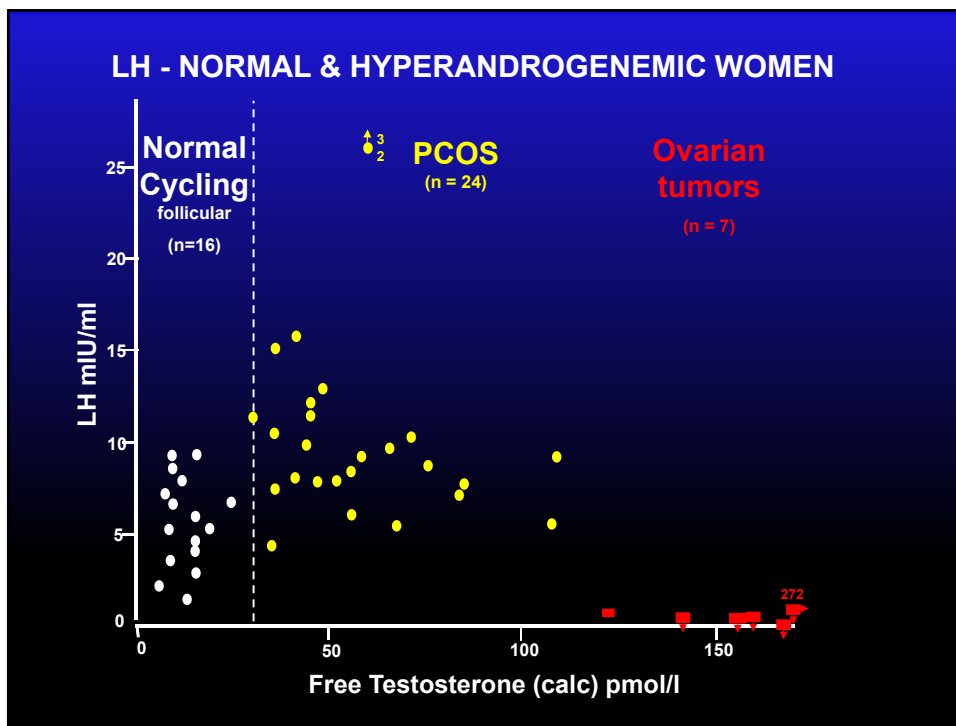
LH, INSULIN on PCOS ovary stroma

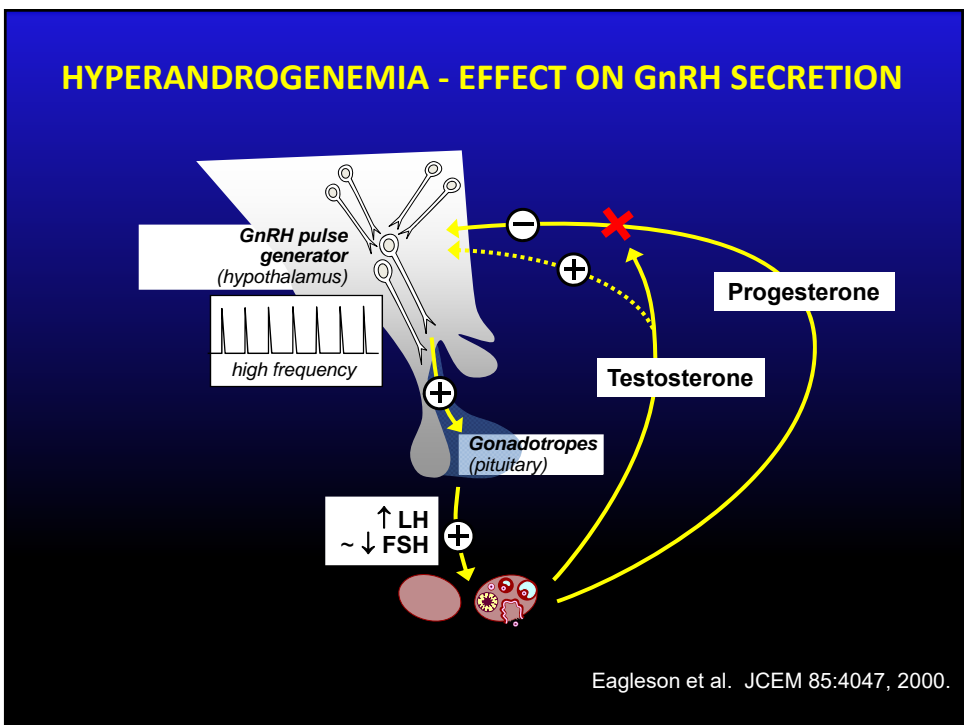
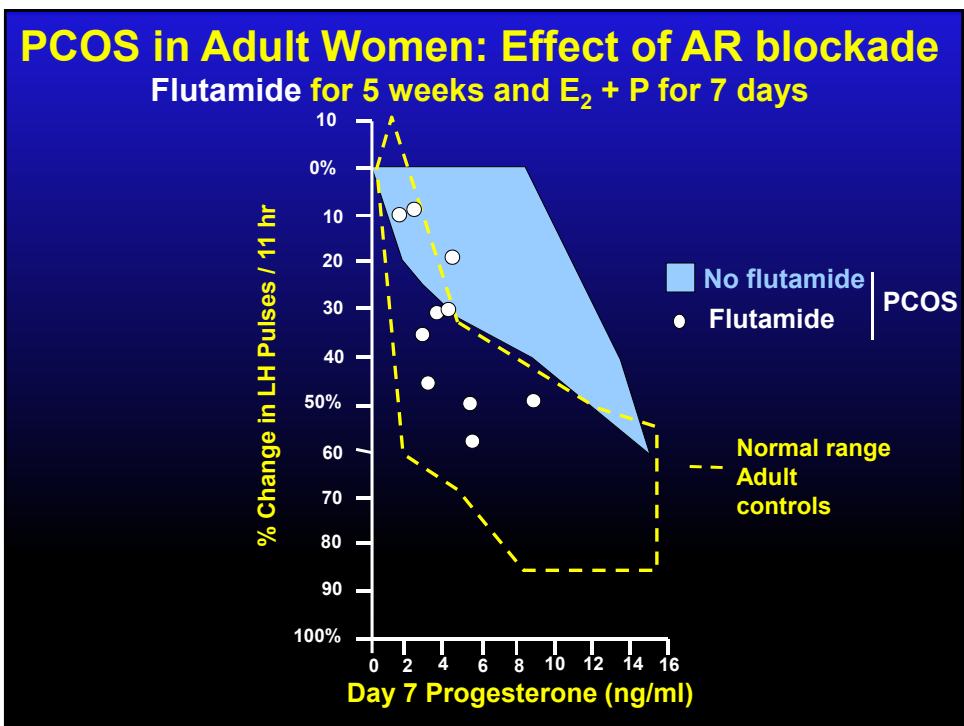


From Barbieri et al, JCEM, 1986.



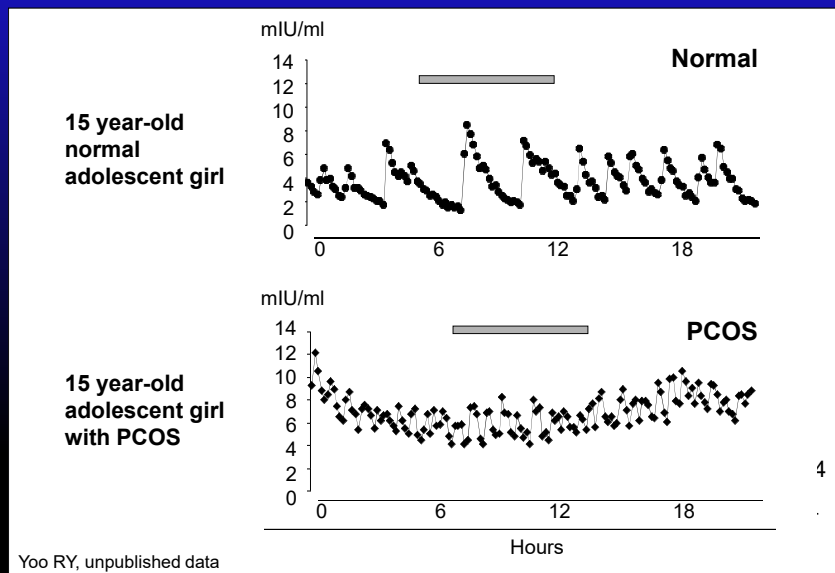




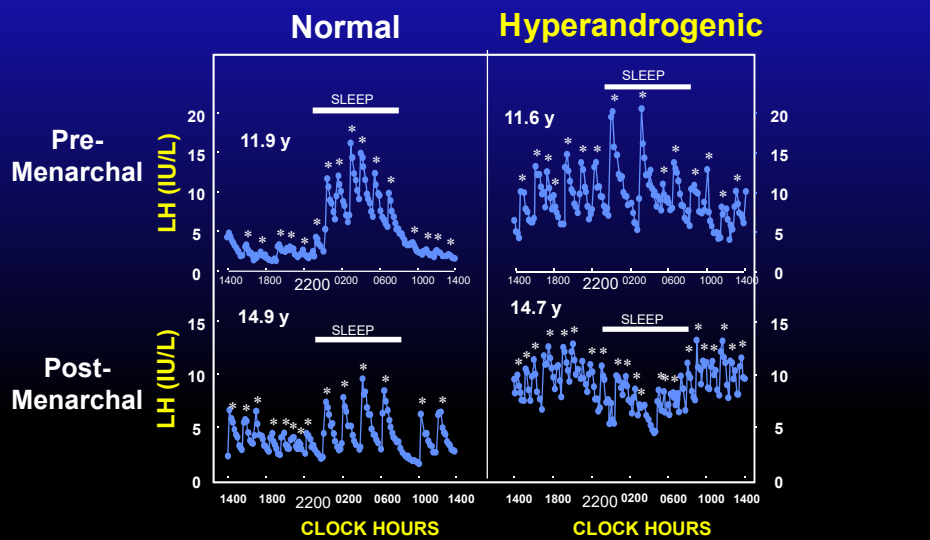


Eagleson et al. JCEM 85:4047, 2000.

Adolescents - 24-hour LH Pulse Secretion Pattern



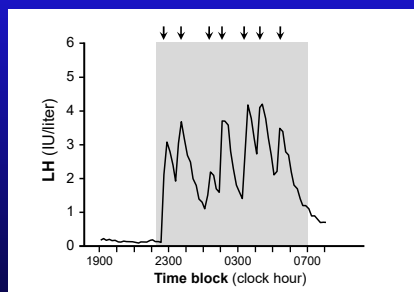
Plasma LH in Pre- and Post-Menarchal Normal and Hyperandrogenic Peripubertal Girls



Apter et al JCEM, 79: 119,1994

Role of progesterone and testosterone in normal Pubertal Maturation

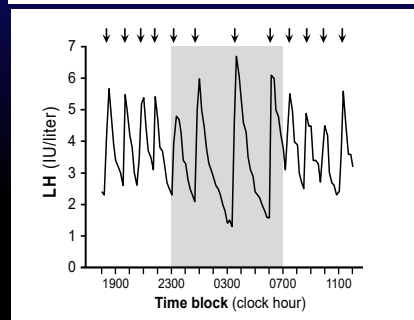
LH PULSE SECRETION DURING PUBERTY



EARLY PUBERTY

Tanner 1-2

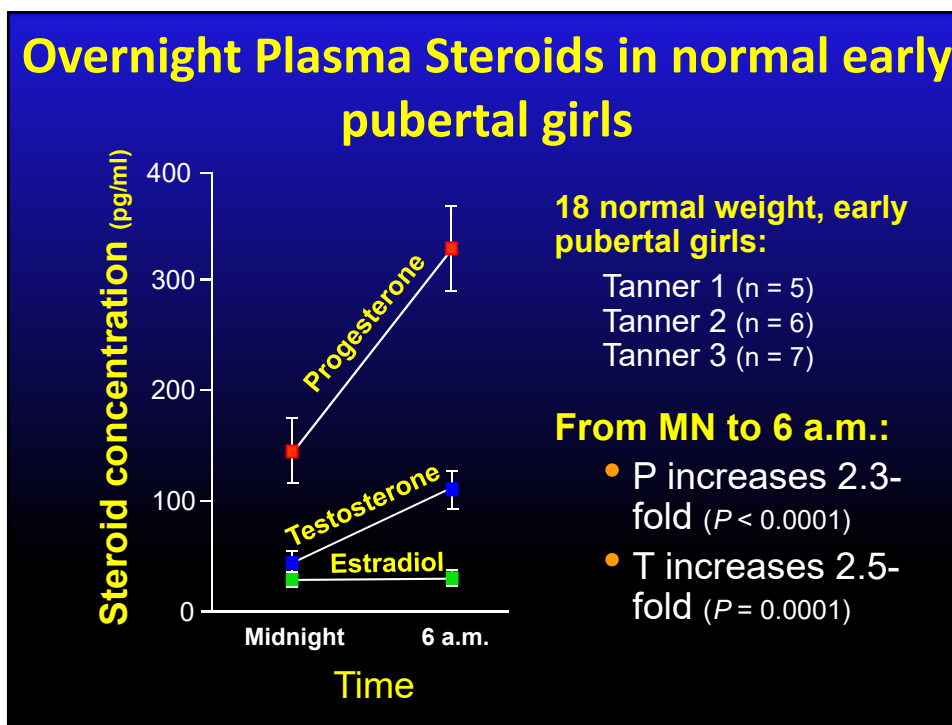
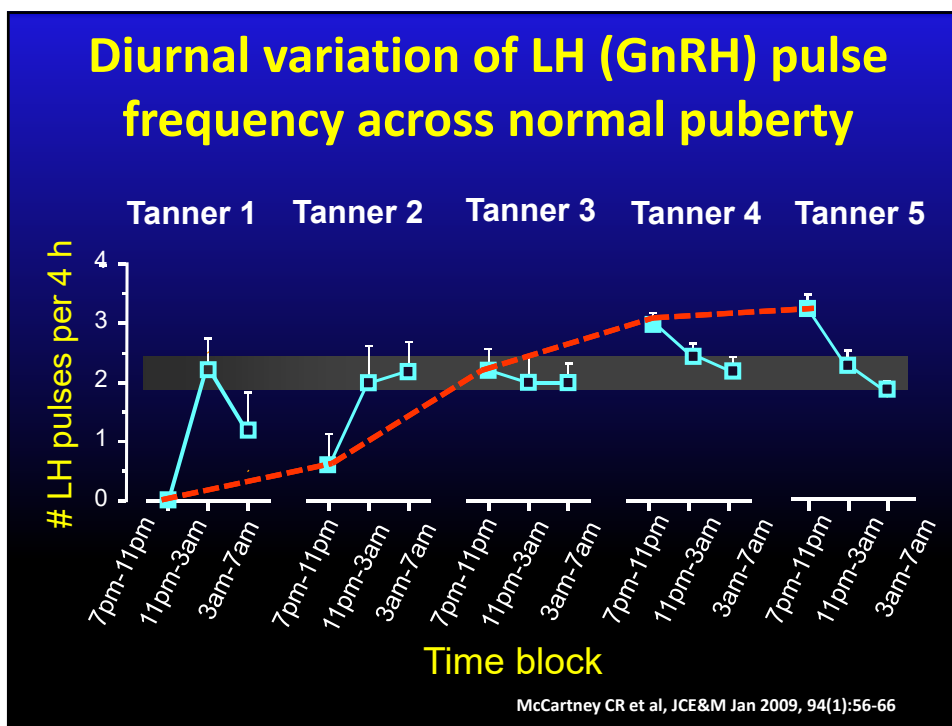
SLEEP RELATED



LATE PUBERTY /ADULT

Tanner 3-5

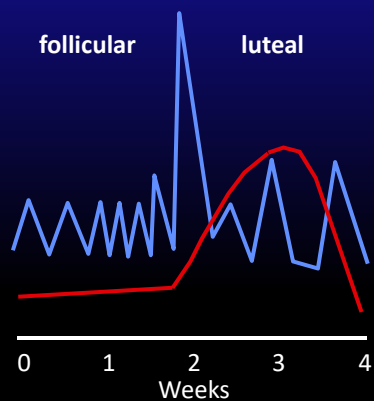
24 HOUR



Regulation of GnRH pulse frequency

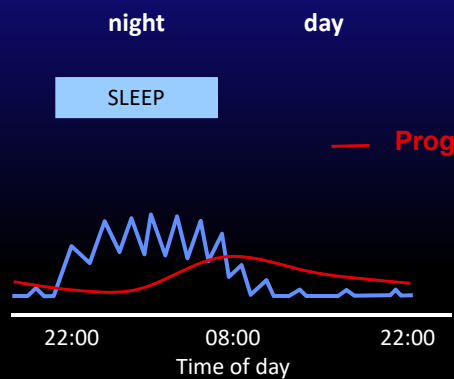
Ovulatory cycle:

P (with E₂) mediates follicular / luteal GnRH frequency.

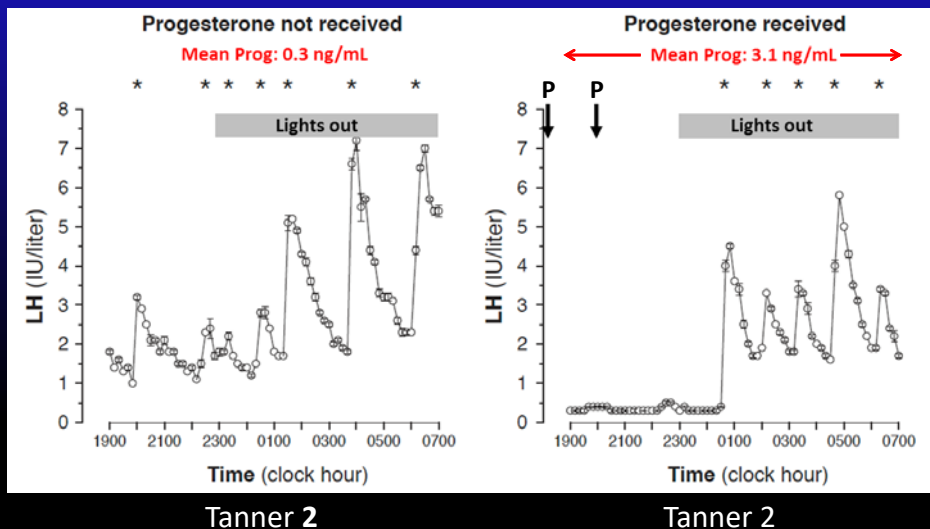


Pubertal maturation:

? P (with E₂) decreases daytime GnRH frequency.

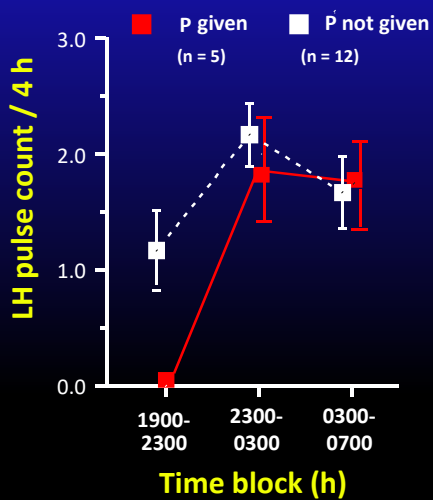


Progesterone suppresses daytime (awake) but not night time GnRH secretion (normal T2-3 girls)



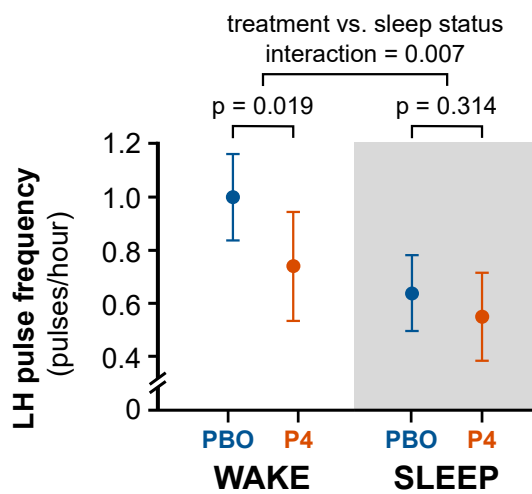
Collins JS et al, Neuroendocrinology, 2012;96(3):222-7

Progesterone suppression of daytime (awake) but not night time GnRH secretion (Tanner 2-3 normal girls)



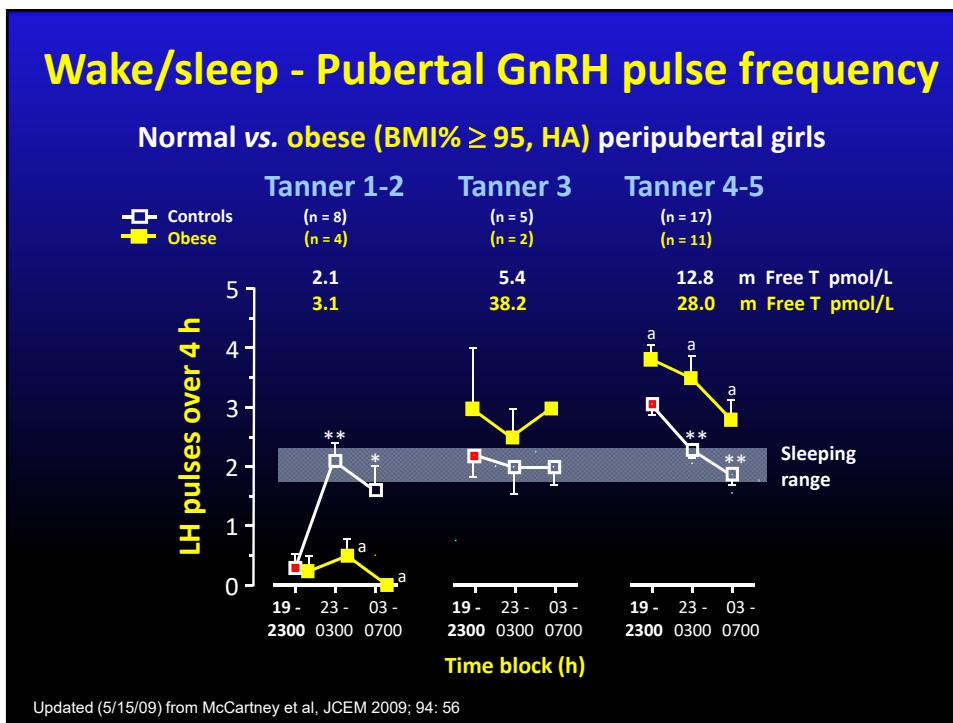
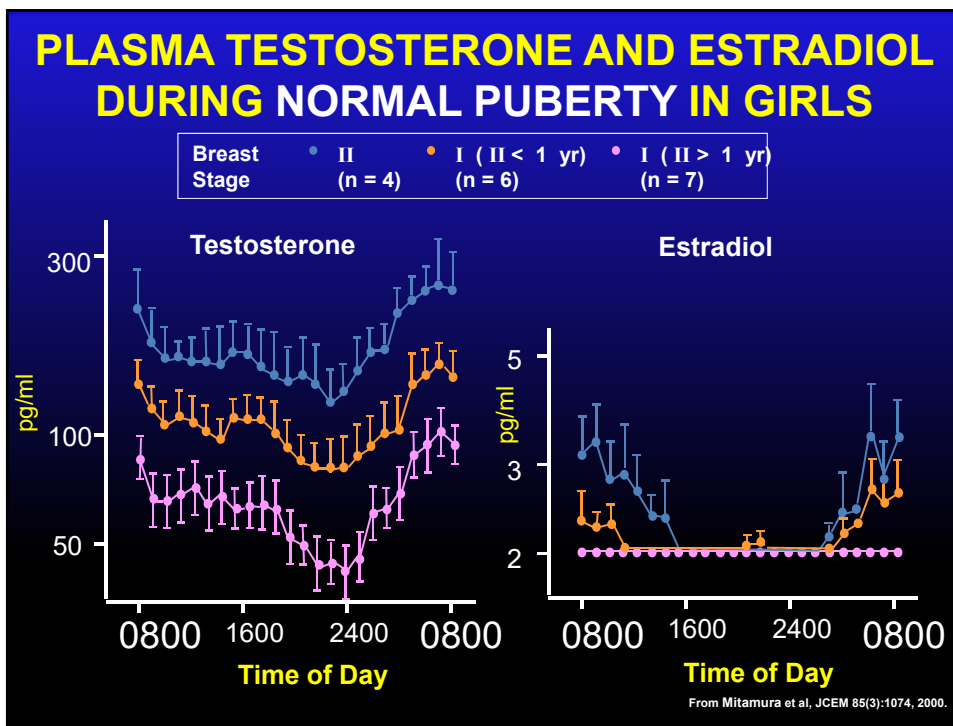
Collins JS et al, Neuroendocrinology, 2012;96(3):222-7

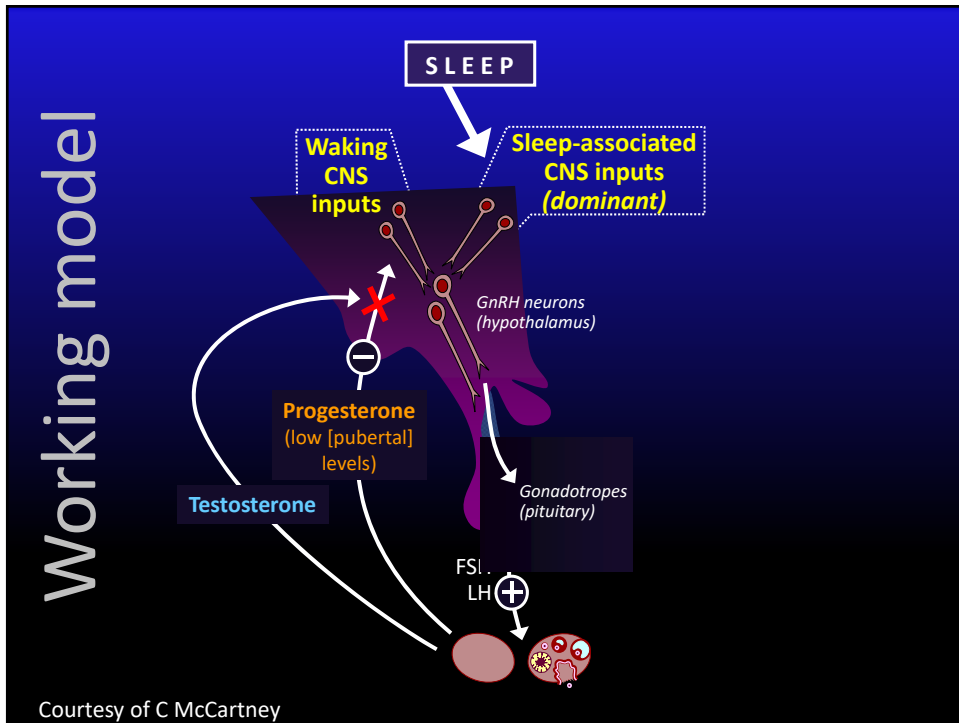
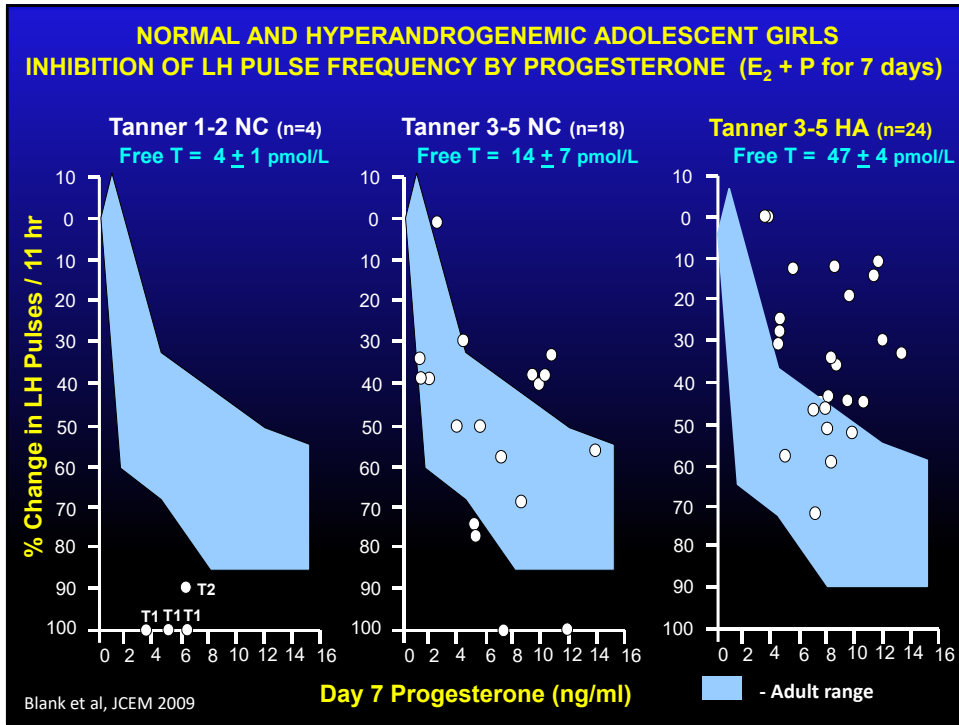
Progesterone suppresses daytime but not sleeping LH pulse secretion in late pubertal girls



Mean \pm 95%CI

Kim SH, JCEM 2018; 103: 1112-21





SOURCES OF EXCESS ANDROGEN IN GIRLS

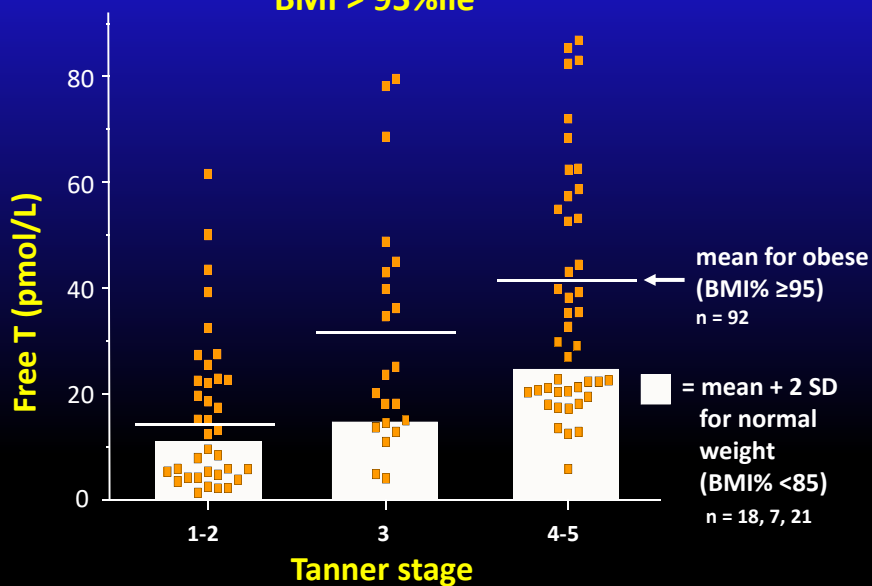
INSULIN - augments ovarian and adrenal androgen secretion

ADIPOSE TISSUE - ? increased 11 oxygenated steroid production
- 11 Ketotestosterone(equipotent testosterone)

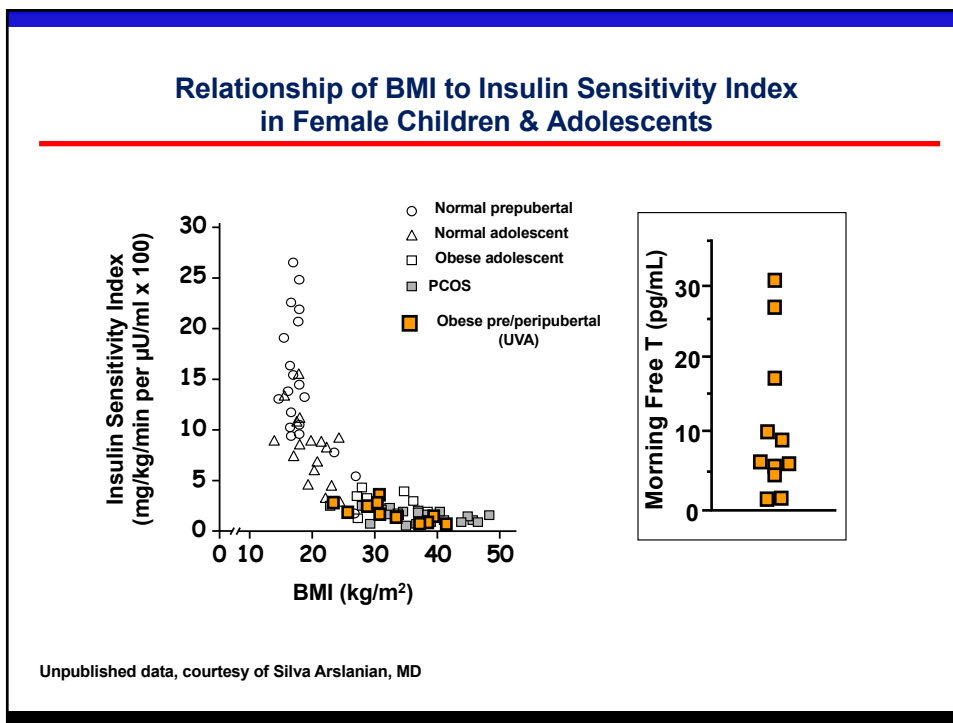
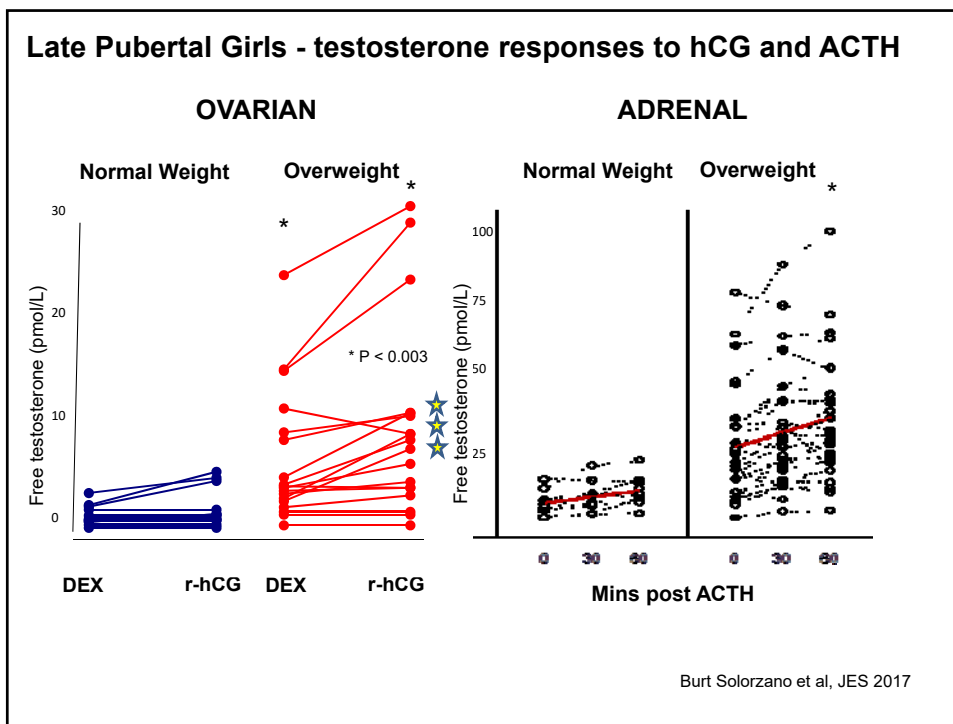
GENETIC PREDISPOSITION - ? DENND1A v2 mutations

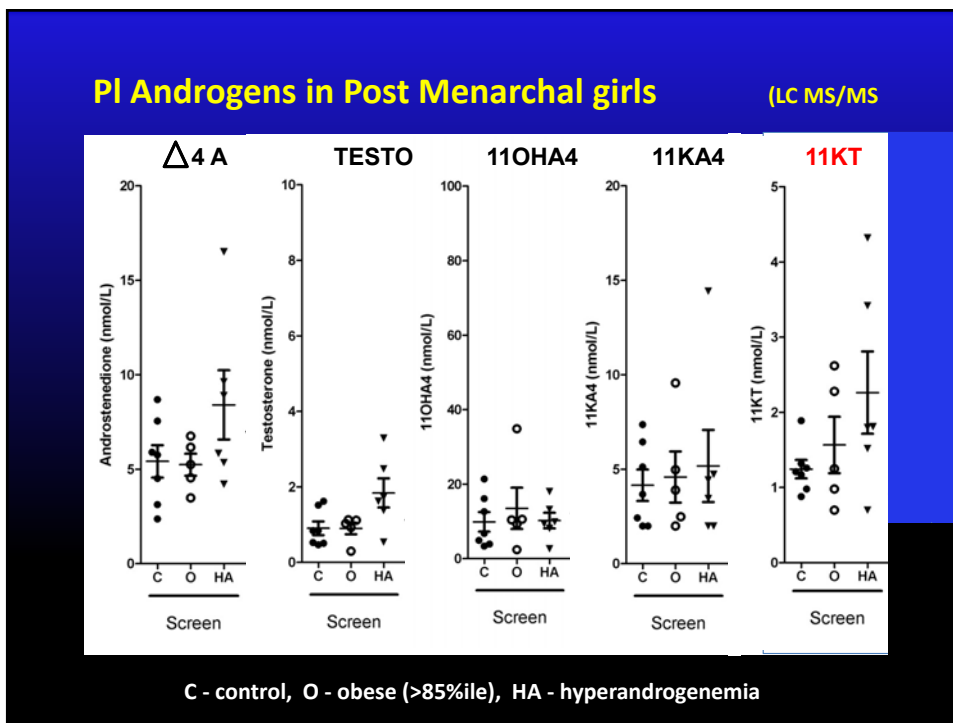
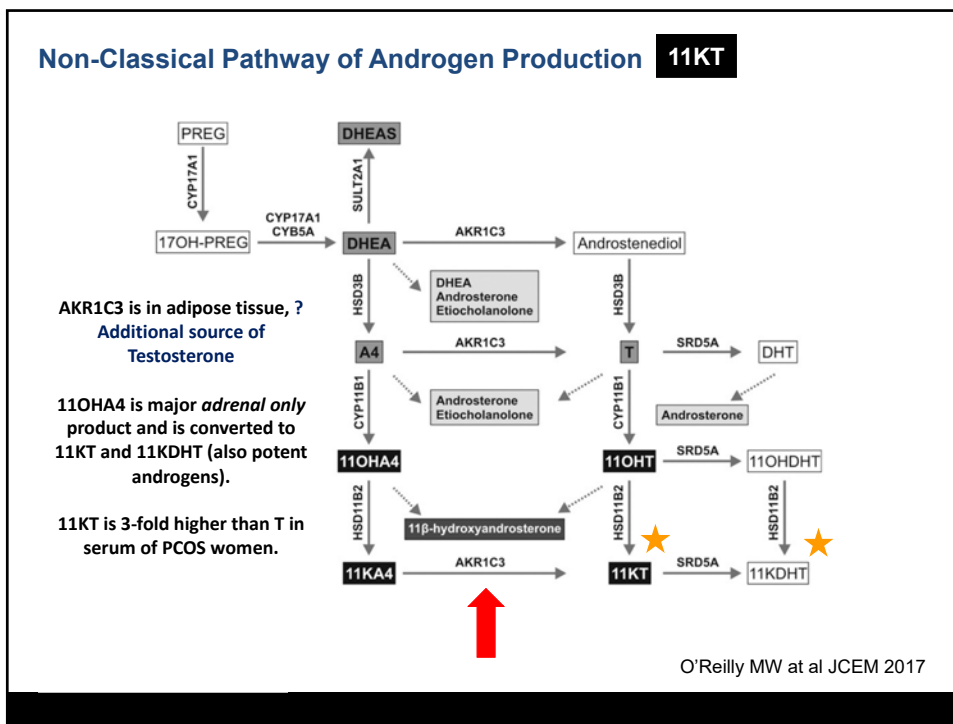
Free T levels are variable in peripubertal obesity

BMI > 95%ile



Knudsen et al. Obesity 2010





DENND1A

(Differentially Expressed in Normal and Neoplastic cell Domains)

GWAS - 1 of 11 PCOS candidate loci in Han Chinese, replicated in Asians and European

DENN domains function as Rab specific guanine nucleotide exchange factors
- involved in membrane trafficking and endocytosis)

DENND1A gene encodes **connecdenn 1** –

two transcripts - 1009 AA DENND1A.V1

- 559 AA DENND1A.V2 (lacks proline rich domain + extra C-terminal 33 AA)

DENND1A expressed in androgen secreting cells - testes

- ovarian theca cells

- H295 adrenal carcinoma cells

DENND1A.V2

(Differentially Expressed in Normal and Neoplastic cell Domains)

DENND1A.V2 - increased mRNA and protein expression in ovarian theca cells from women with PCOS

- overexpression in normal theca cells increases expression of genes encoding steroidogenic enzymes CYP17A1, CYP11A1 and androgen biosynthesis

- knockdown with shRNA in PCOS theca cells or DENND1A.V2 antibody reduces androgen biosynthesis

DENND1A.V2 exosomal mRNA is increased 3 fold in urine from 6 women with PCOS

McCallister JM, Modi B, Miller BA, Beigler J, Bruggeman R, Legro RS, Strauss JF, PNAS (in press) 2014

OBESITY IN YOUNG ADOLESCENT GIRLS

CLINICAL ISSUES:

- **Suspect androgen excess** (not clinically evident for several years)
- **Menarche**
 - establishing regular cycles occurs over 1 year
 - irregular cycles in mid teens are **NOT** 'normal'
- **Investigation**
 - Total T, SHBG, calc free T (m= 16 + 2 pmol/L in stage 4/5)
 - 17 OHP (8am in follicular phase), ? Exclude Cushings
 - DHEA-S
 - LH, FSH, Prolactin
 - Fasting insulin, ? 2 h post-prandial glucose, insulin

OBESITY IN YOUNG ADOLESCENT GIRLS

MANAGEMENT

- **Lifestyle, diet, exercise**
- **Reduce T**
 - LH elevated - combined OC (adequate Prog to suppress LH)
 - Metformin (build up dose to 1500- 2000mg/day)
- **Block T action** - Spironolactone 50mg bid
- **Future**
 - ? other AR blockers - flutamide (62.5mg/day)
 - shown to reduce total/abdominal adiposity, lipids.

CONTRIBUTORS - GCRC STUDIES

COLLABORATORS:

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Clinical Research Coordinators,

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