CURRENT UNDERSTANDING OF THE H-P-GONADAL AXIS

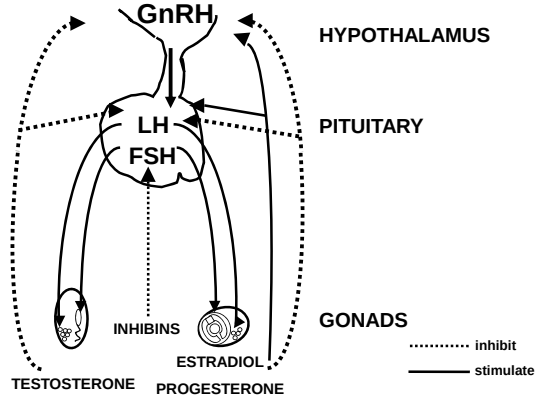
Normal maturation ⇨ PCOS

John C Marshall

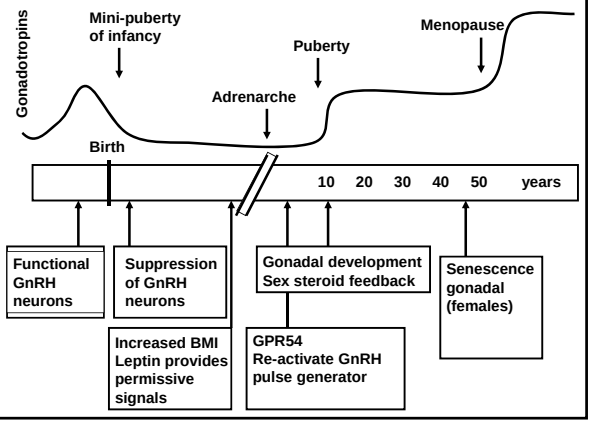
Center for Research in Reproduction.
Division of Endocrinology and Metabolism,
Department of Medicine
University of Virginia

Supported by Specialized Cooperative Centers Program for Research in Infertility and Reproduction,
U54 HD-28934

REPRODUCTION - BRAIN / PITUITARY / GONADS



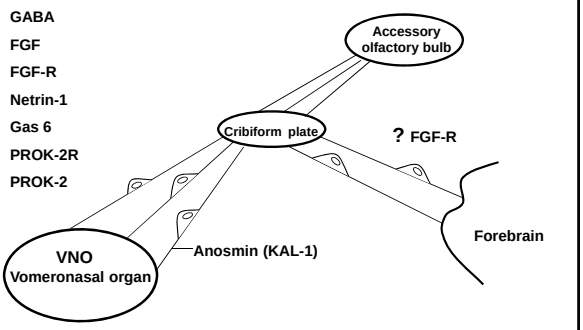
GONADOTROPINS THROUGHOUT LIFE



MUTATIONS CAUSING REDUCED GONADOTROPINS IN HUMANS

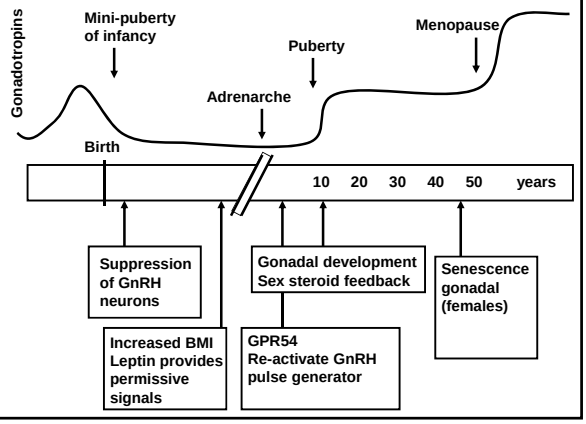
NEURONAL MIGRATION	KAL-1 (anosmin) FGF-R1 Prokineticin-2 (PROK2 / PROKR2) NELF (nasal embryonic LHRH factor)	Kallmann Syndrome
↓ GnRH SECRETION / ACTION	Neurokinin B GPR-54 GnRH-R Leptin, Leptin-R	- Normosmic Hypogonadotropism
PITUITARY DEVELOPMENT	PROP-1 LHX3 HESX1	- Combined Hypopituitarism
GONADOTROPINS	DAX-1 SF-1	- LH deficiency, Adrenal hypoplasia
	LH-ß subunit, LH-R FSH-ß subunit, FSH-R	- Hypogonadotropism

EMBRYONIC GnRH NEURONAL MIGRATION

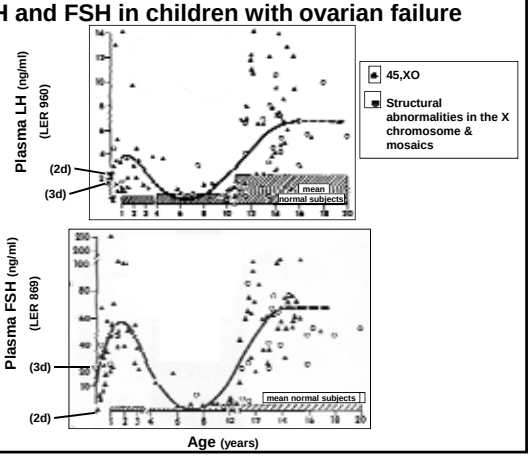


After Tobet, Schwarting Endocrinology 147:2006

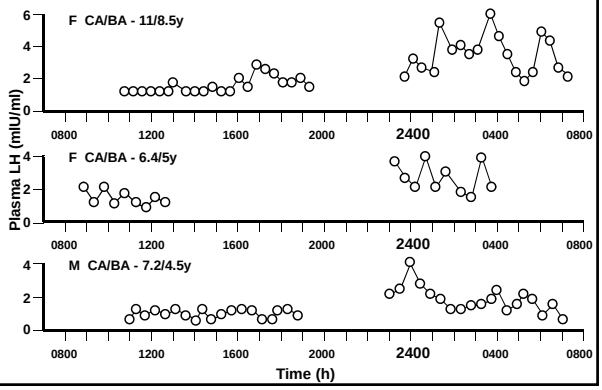
GONADOTROPINS THROUGHOUT LIFE



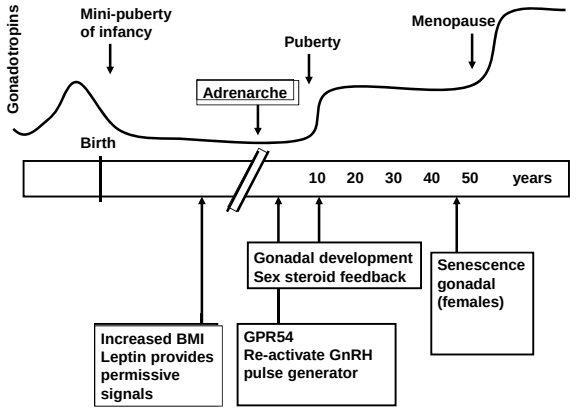
LH and FSH in children with ovarian failure



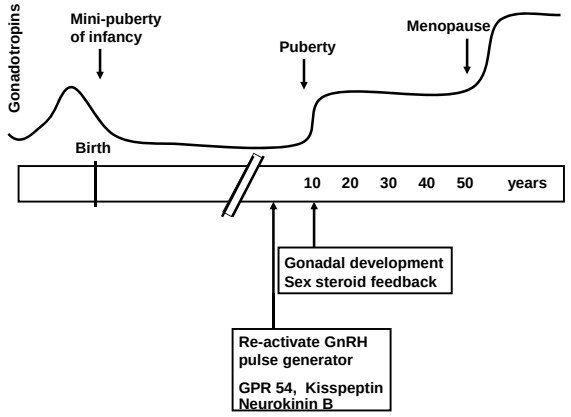
DAY / NIGHT LH PULSE SECRETION IN PREPUBERTAL CHILDREN



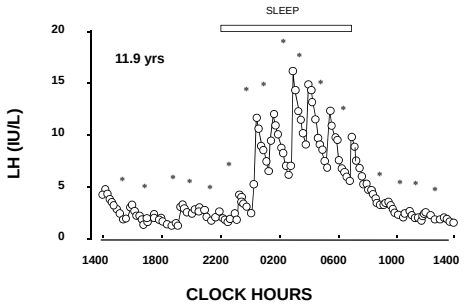
GONADOTROPINS THROUGHOUT LIFE



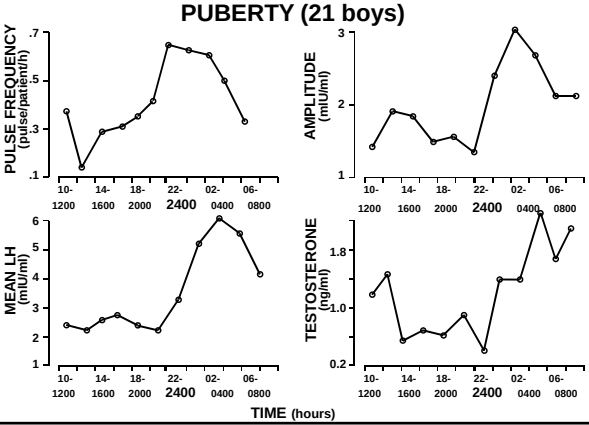
GONADOTROPINS THROUGHOUT LIFE



Plasma LH in Normal Girl (Tanner 3)



LH (GnRH) PULSE SECRETION IN EARLY PUBERTY (21 boys)



Neurokinin B and NK3R

Neurokinin B (NKB)
- Tachykinin family (Preprotachykinin-1 gene) Substance P, neurokinins.
- expressed in brain, hypothalamus, arcuate N human, monkey, rodents, sheep.
- colocalized with Kisspeptin in arcuate neurons

Neurokinin3 receptor (NK3R)
- G protein linked receptor (Gq)
- expressed widely in brain, ovary, uterus
- present on GnRH neurons

ACTION
- ? Release of GnRH

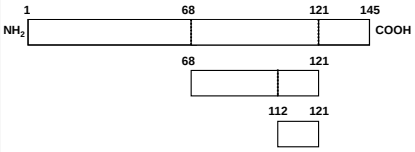
LOSS OF FUNCTION MUTATIONS - **HYPOGONADOTROPIC HYPOGONADISM**

(Nature Genetics 41: 354, 2008)

GPR 54

- **Orphan 7 transmembrane G-protein coupled receptor**
  - Rhodopsin receptor family
  - 45% homology to Galanin-R
  - 85% homology mouse-human
- **Expressed widely in brain**
  - hypothalamus, GnRH neurons
  - also pituitary, placenta, pancreas
- **Activates phospholipase C**
  - ↑ Ca^{++}, phosphotidylinositol
  - ERK, p38MAPK phosphorylation
- **Loss of function mutations**
  - **HYPOGONADOTROPIC HYPOGONADISM (mice and humans, 2003)**

KISSPEPTIN (METASTIN)



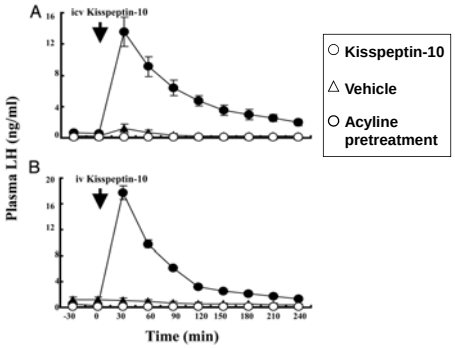
- KiSS-1 gene product
- KISSPEPTIN-54; METASTIN (I-54)
- KISSPEPTIN-10

KiSS-1
- Tumor suppressor gene

Kisspeptins
- Isolated from placenta (2001)
- Expressed in hypothalamus (arcuate, median eminence)
- Ligand for GPR54
- Activates GnRH neurons (c fos)
- Stimulates LH/FSH release (blocked by GnRH antagonist)

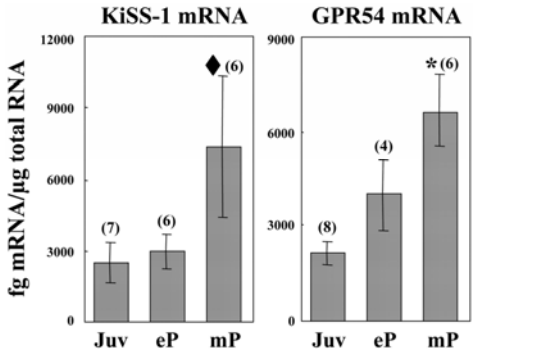
(not active in GPR54 -/-)

KISSPEPTIN-10 — STIMULATES LH SECRETION VIA GnRH (agonadal juvenile monkeys)



Shahab, et al. PNAS. 102, 2129 (2005).

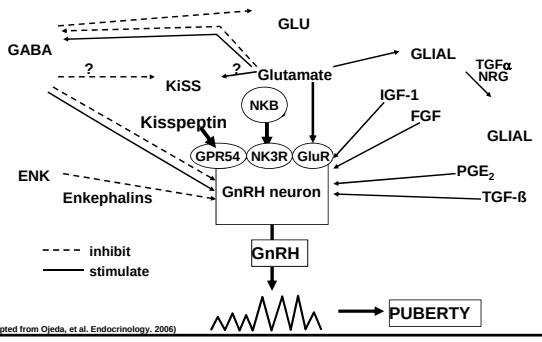
KiSS-1 and GPR54 mRNA content in MBH of intact female monkeys during pubertal development



Shahab, et al. PNAS. 102, 2129 (2005).

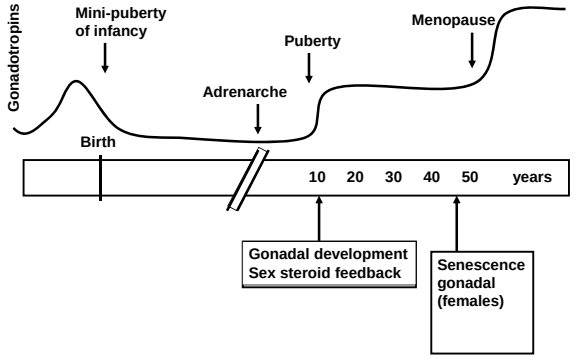
CENTRAL REGULATION OF GnRH PULSE SECRETION AT PUBERTY

INHIBITORY **EXCITATORY** **GLIAL MODIFIERS**

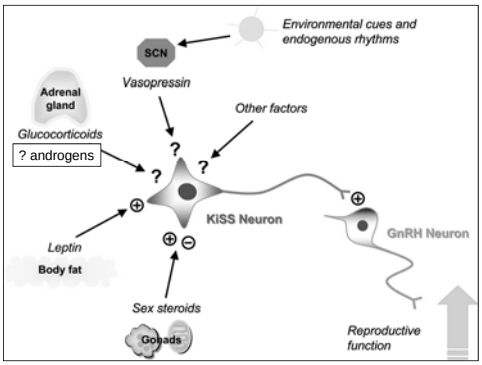


(adapted from Ojeda, et al. Endocrinology. 2006)

GONADOTROPINS THROUGHOUT LIFE

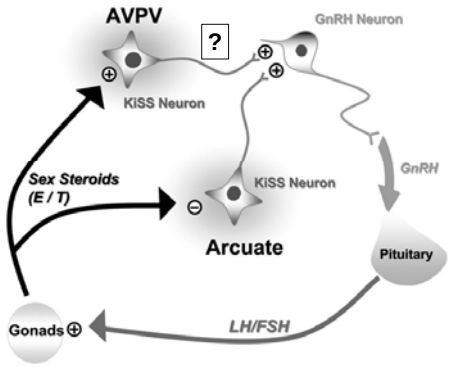


Kisspeptin neurons may act as central processors for relaying signals from the periphery to GnRH neurons



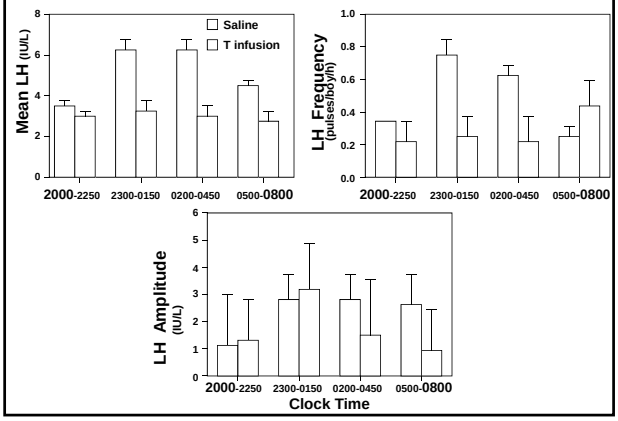
Dungan, et al. Endocrinology. 147: 1154 (2006).

Steroids differentially regulate KiSS-1 mRNA expression in forebrain nuclei (rodents)

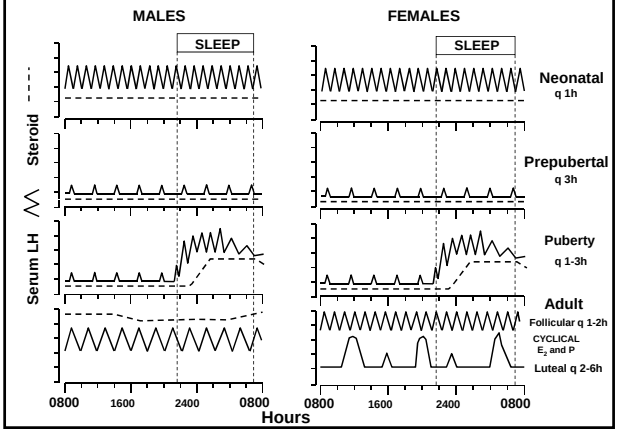


Dungan, et al. Endocrinology. 147: 1154 (2006).

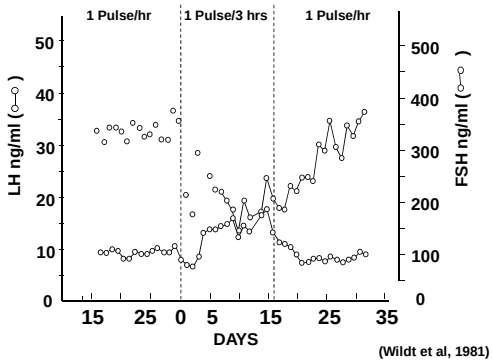
Testosterone inhibits O/N GnRH(LH) pulse secretion in boys



PULSATILE GnRH SECRETION DURING MATURATION

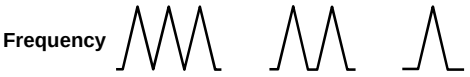


EFFECT OF GnRH PULSE FREQUENCY ON LH AND FSH SECRETION (monkey)



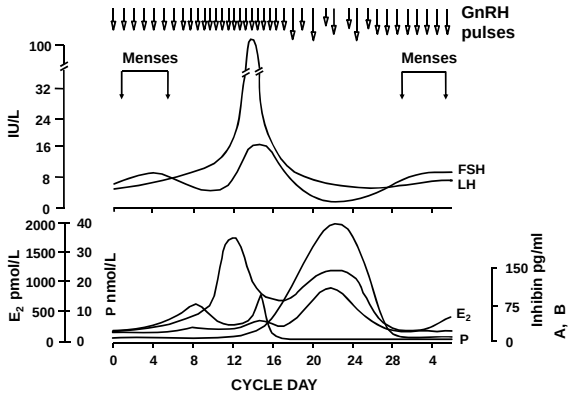
(Wildt et al, 1981)

GnRH PULSE STIMULI AND SUBUNIT mRNA EXPRESSION - FEMALE RATS (GnRH DEFICIENT)

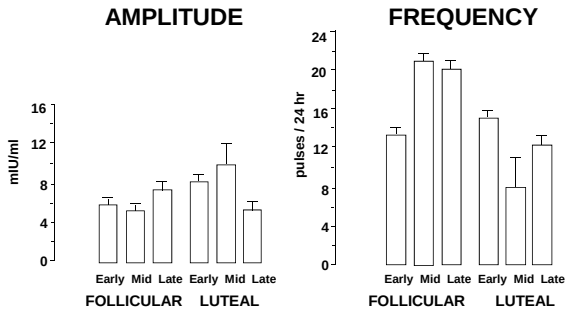


+	+	-	alpha
+	+	-	LH beta
±	+	+	FSH beta

GnRH SECRETION DURING THE MENSTRUAL CYCLE

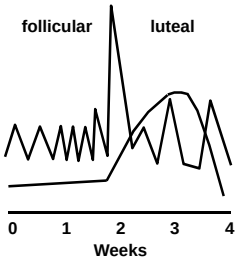


LH Pulses - during Ovulatory Cycles

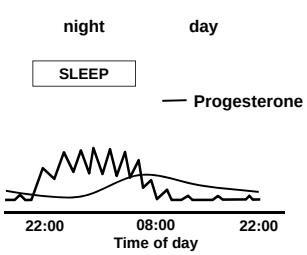


Regulation of GnRH pulse frequency

Ovulatory cycle:
P (with E_2) mediates follicular /luteal GnRH frequency.



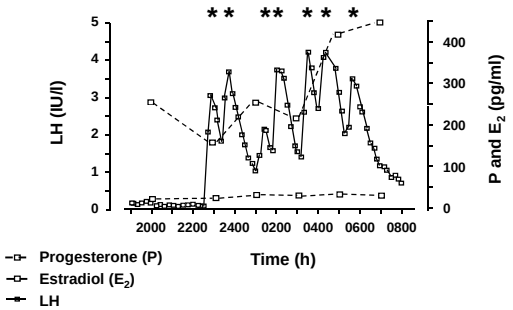
Pubertal maturation:
? P (with E_2) decreases daytime GnRH frequency.



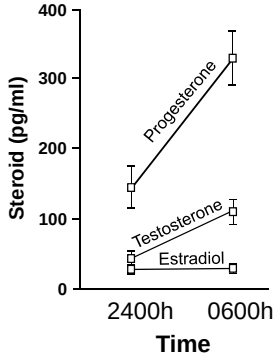
EARLY PUBERTY - OVERNIGHT LH, P and E_2

10 yo girl, Tanner stage 2

Total T - 0.50 pg/ml; SHBG - 50.8 nmol/l; Calc Free T - 4.7 pmol/l



Overnight Plasma Steroids in normal early pubertal girls



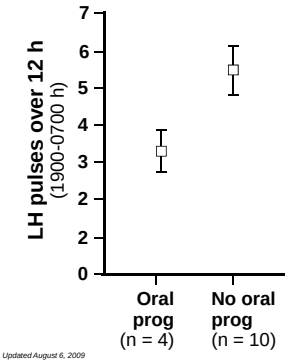
18 normal weight, early pubertal girls:

Tanner 1 (n = 5)
Tanner 2 (n = 6)
Tanner 3 (n = 7)

From MN to 6 a.m.:

- **P** increases **2.3-fold** (*P* < 0.0001)
- **T** increases **2.5-fold** (*P* = 0.0001)

Overnight LH pulses after oral progesterone in early to midpubertal girls (Tanner 2-3)



Normal pubertal girls
(**Tanner 2-3 only**)

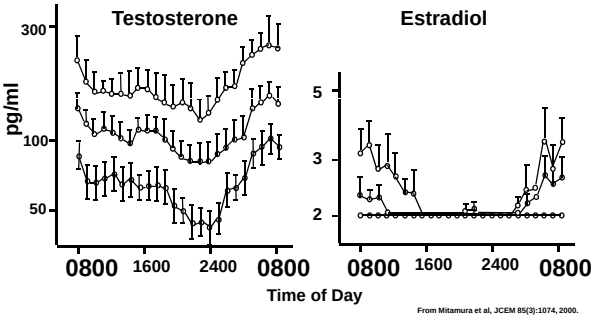
- **Progesterone given**
  (Tanner 2.5 ± 0.3,
  prog conc. 4.8 ± 0.7 ng/ml)
- **Progesterone not given**
  (Tanner 2.5 ± 0.2,
  prog conc. 0.3 ± 0.03 ng/ml)

41% fewer pulses in progesterone group

Updated August 6, 2009

PLASMA TESTOSTERONE AND ESTRADIOL DURING NORMAL PUBERTY IN GIRLS

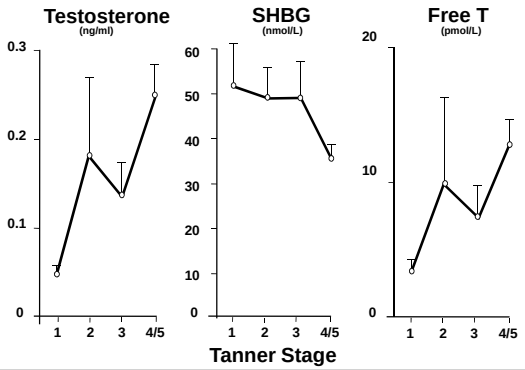
Breast Stage	° II (n = 4)	° I (II <1yr) (n = 6)	° I (II > 1 yr) (n = 7)



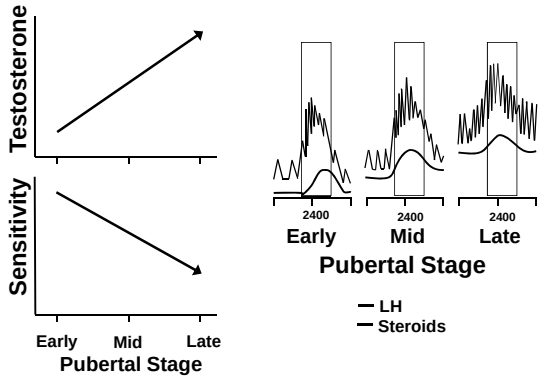
From Mitamura et al, JCEM 85(3):1074, 2000.

Testosterone during Normal Female Puberty (6-8am)

Normal weight (<85% BMI) n=5-11

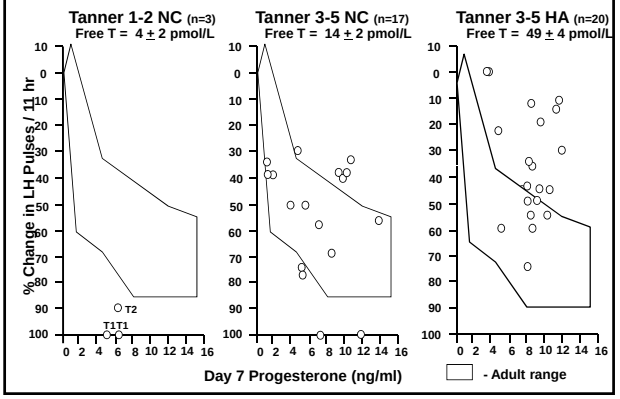


PUBERTAL GnRH SECRETION: Androgens reduce sensitivity to feedback inhibition by sex steroids



NORMAL AND HYPERANDROGENEMIC ADOLESCENT GIRLS

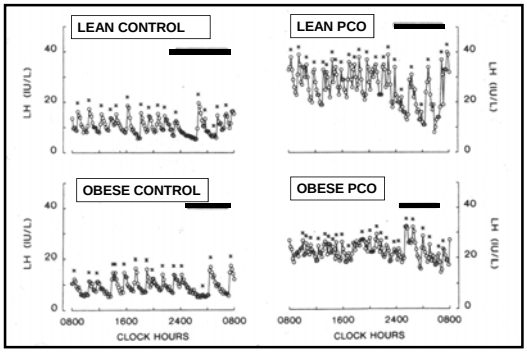
INHIBITION OF LH PULSE FREQUENCY BY PROGESTERONE (E_2 + P for 7 days)



Evolution of abnormal GnRH/LH secretion in PCOS

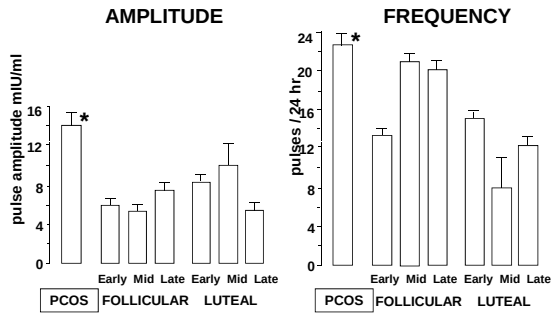
Role of hyperandrogenemia

LH Pulses in Lean and Obese PCOS (adults)



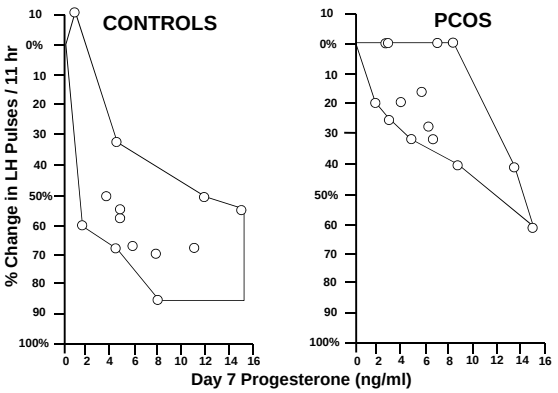
Morales et al, JCEM 81:2861, 1996.

LH Pulses - PCOS and Ovulatory Cycles



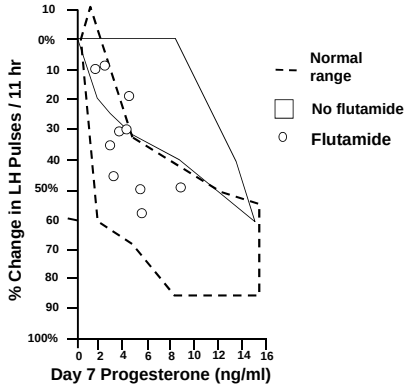
Normal and PCOS Adult Women

Inhibition of LH Pulse Frequency by Progesterone (E_2 + P for 7 days)

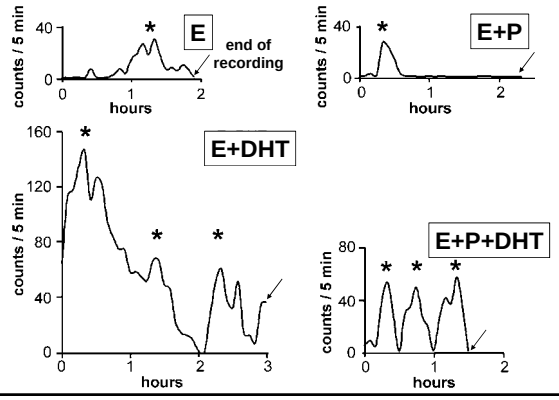


PCOS in Adult Women

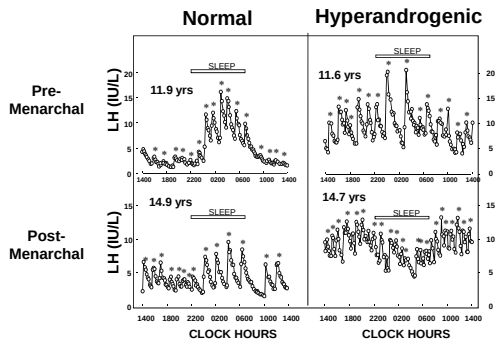
Flutamide for 5 weeks and E_2 + P for 7 days



P and DHT alter GnRH neuron activity

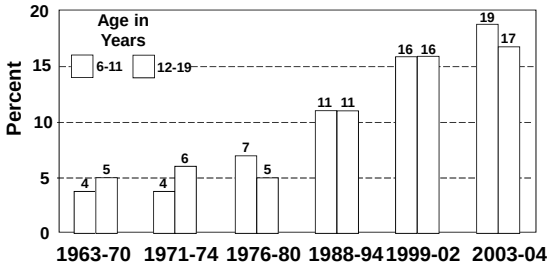


Plasma LH in Pre- and Post-Menarchal Normal and Hyperandrogenic Adolescent Girls



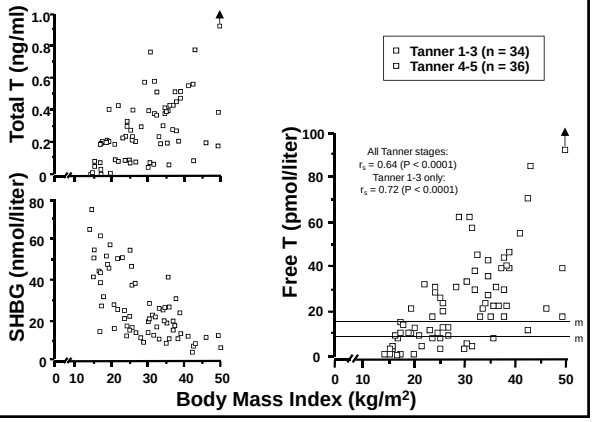
Apter et al JCEM, 79: 119,1994

PREVALENCE OF OVERWEIGHT AMONG CHILDREN AND ADOLESCENTS AGES 6-19 YEARS

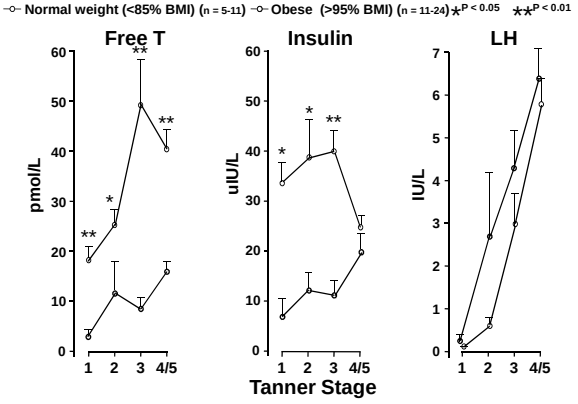


NOTE: Excludes pregnant women starting with 1971-74. Pregnancy status not available for 1963-65 and 1966-70. Data for 1963-65 are for children 6-11 years of age; data for 1966-70 are for adolescents 12-17 years of age, not 12-19 years.
SOURCE: CDC/NCHS, NHES and NHANES

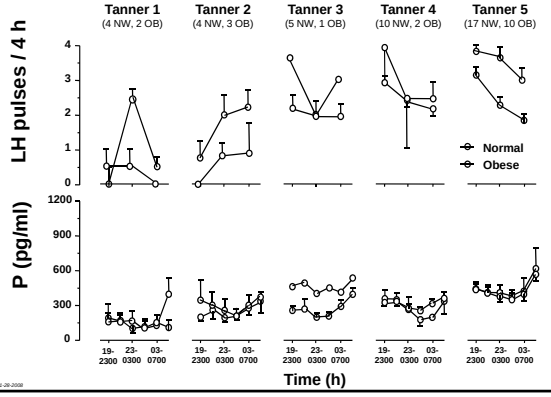
Adolescent Girls - Testosterone vs. BMI



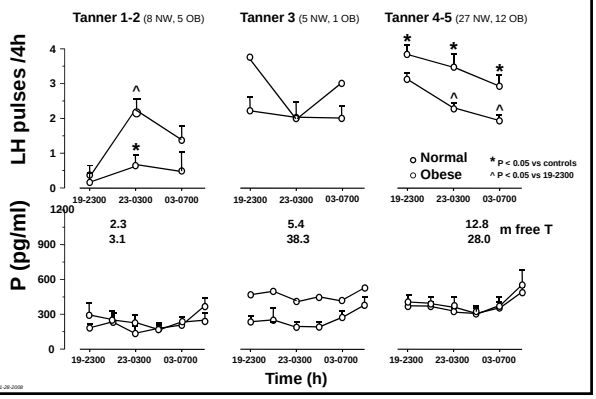
NORMAL WEIGHT VS. OBESE ADOLESCENT GIRLS (6-8am)



Progression of Day/Night Pulsatile LH and Progesterone Secretion During Puberty in Normal and Obese Girls

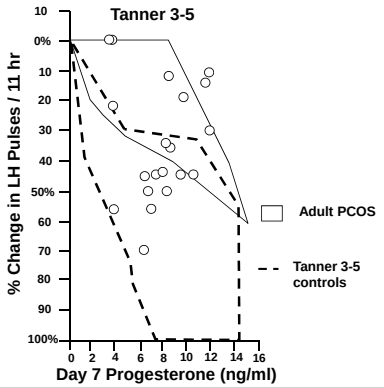


Progression of Day/Night Pulsatile LH and Progesterone Secretion During Puberty in Normal and Obese Girls(>95%)



Hyperandrogenic Adolescent Girls (n=20)

Inhibition of LH Pulse Frequency by Progesterone (E_2 + P for 7 days)



EVOLUTION OF ABNORMAL GONADOTROPIN/ ANDROGEN SECRETION IN PCOS

- POTENTIAL ROLE OF PREPUBERTAL EXPOSURE TO ANDROGENS IN SUSCEPTIBLE ADOLESCENT GIRLS

HYPOTHALAMIC EXPOSURE TO XS ANDROGENS ⇨ IMPAIRED E_2 + P INHIBITION OF GnRH PULSE FREQUENCY ⇨ PERSISTENT RAPID FREQUENCY OF GnRH SECRETION ⇨ ↑ LH ↓ FSH

In utero
?Prepubertal
? Pubertal

Pubertal nocturnal ↑ in ovarian steroids does not inhibit GnRH next day.

Favors ↑ LH, ↓ FSH synthesis & secretion

- ↑ androgen
- ↓ follicular maturation

CONTRIBUTORS - GCRC STUDIES

FELLOWS:

- Christine Eagleson
- Kathleen Prendergast
- Sandhya Chhabra
- Susan Blank
- Kristin Helm
- Karen Knudsen
- Jessica Collins

COLLABORATORS:

U Virginia - Chris McCartney
U Michigan - Carol Foster
UCSD - Jeff Chang
Yale - Sonia Caprio

RESEARCH ASSOCIATES:

- Amy Bellows
- Quirine Lamberts
- Carrie Cutchins
- Lauren Lockhart

GCRC:

U Virginia GCRC staff and nursing personnel