

# DYNAMICS OF THE FEMALE REPRODUCTIVE SYSTEM AND CHANGES WITH AGING

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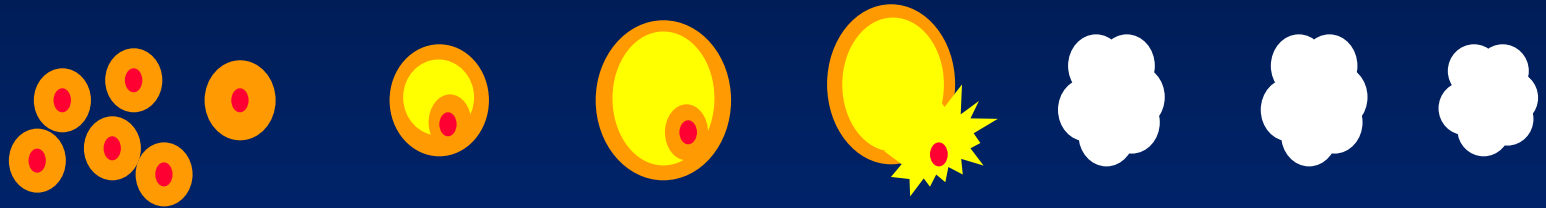
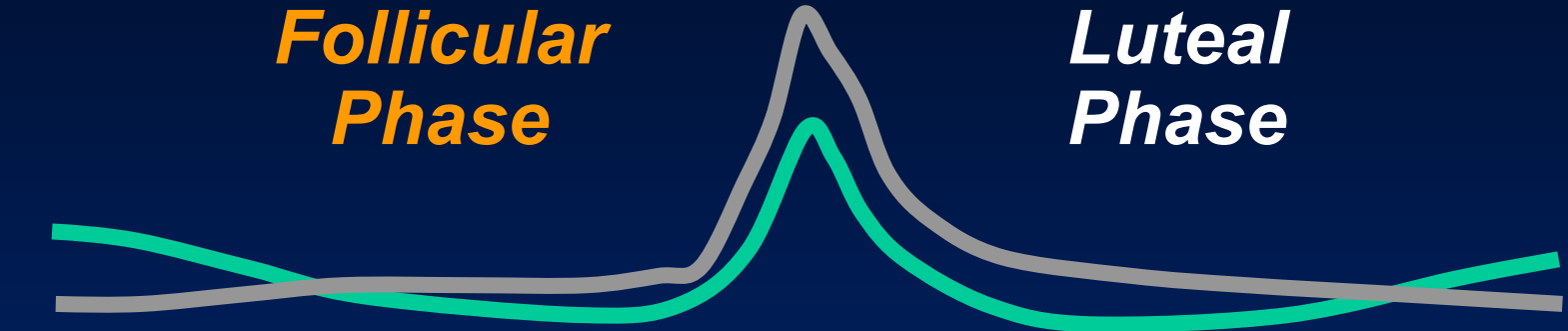
*Boston, MA*



*Follicular  
Phase*

*Luteal  
Phase*

**FSH**  
**LH**



**primary  
ovarian  
follicles**

**antral**

**dominant**

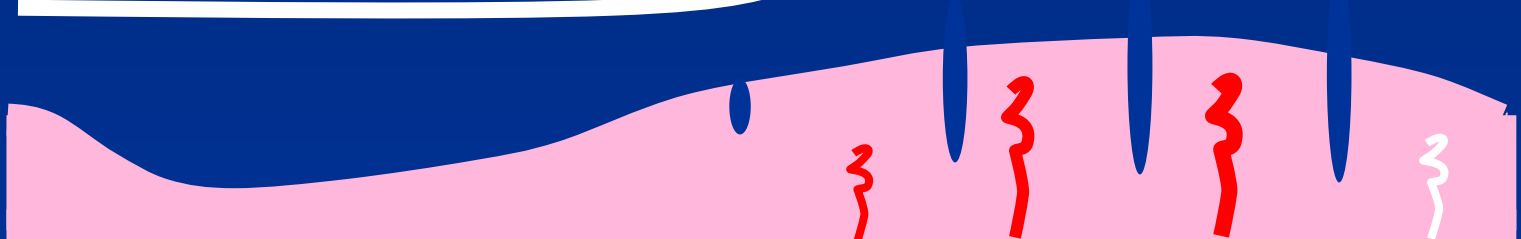
**ovulation**

**corpus  
luteum**

**E2**  
**Prog**

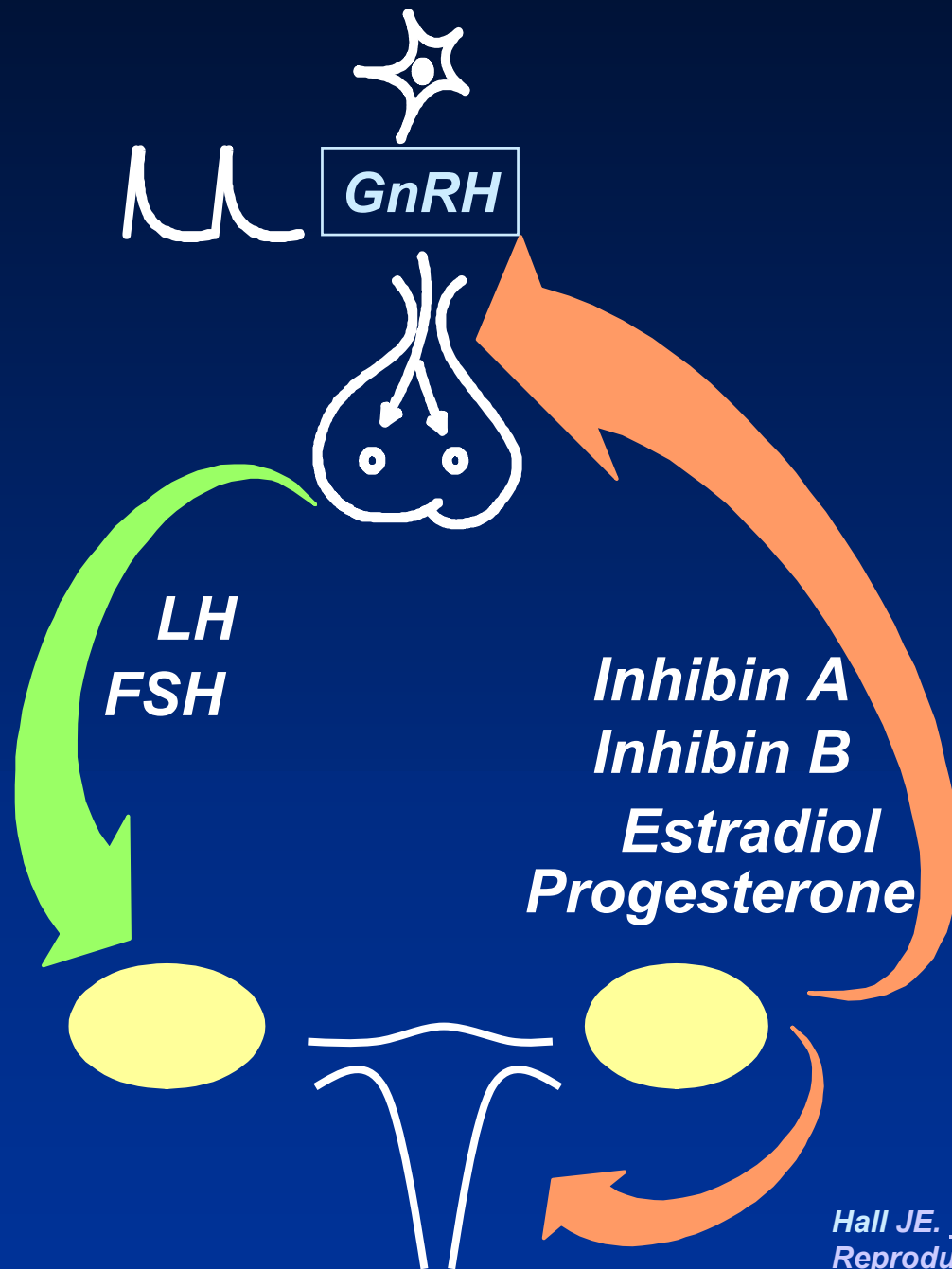


**Endo**



*Proliferative*

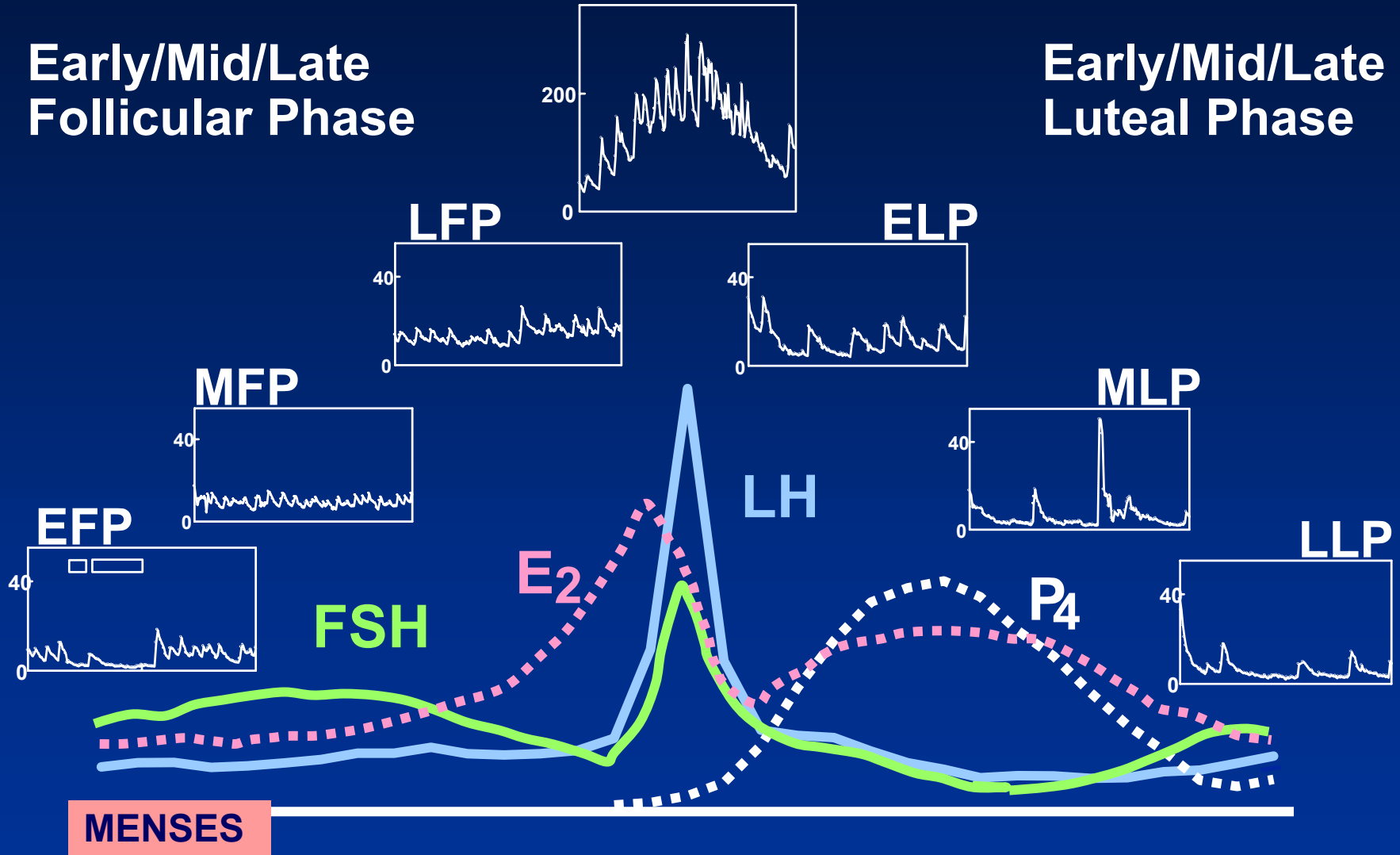
*Secretory*



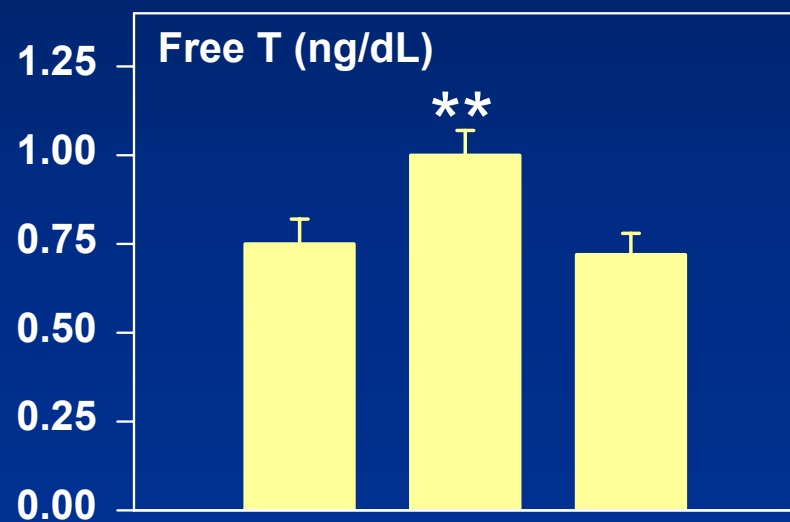
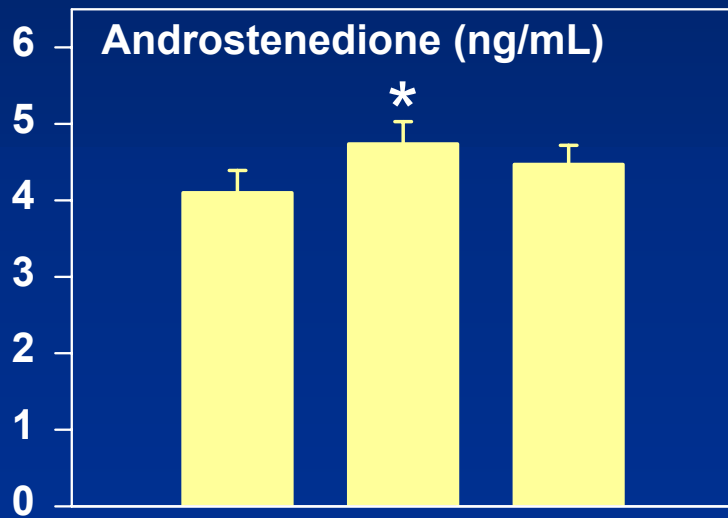
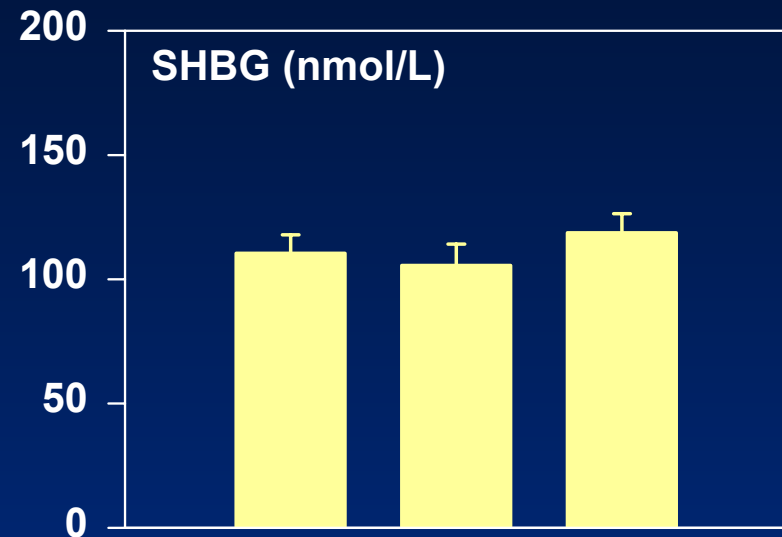
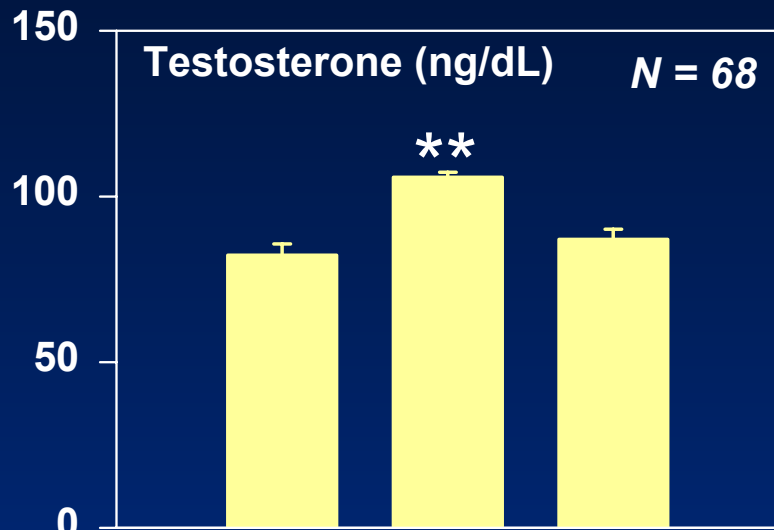
# Mid-Cycle Surge

Early/Mid/Late  
Follicular Phase

Early/Mid/Late  
Luteal Phase



# Variability in Androgen Levels Across the Menstrual Cycle



EFP

MCS

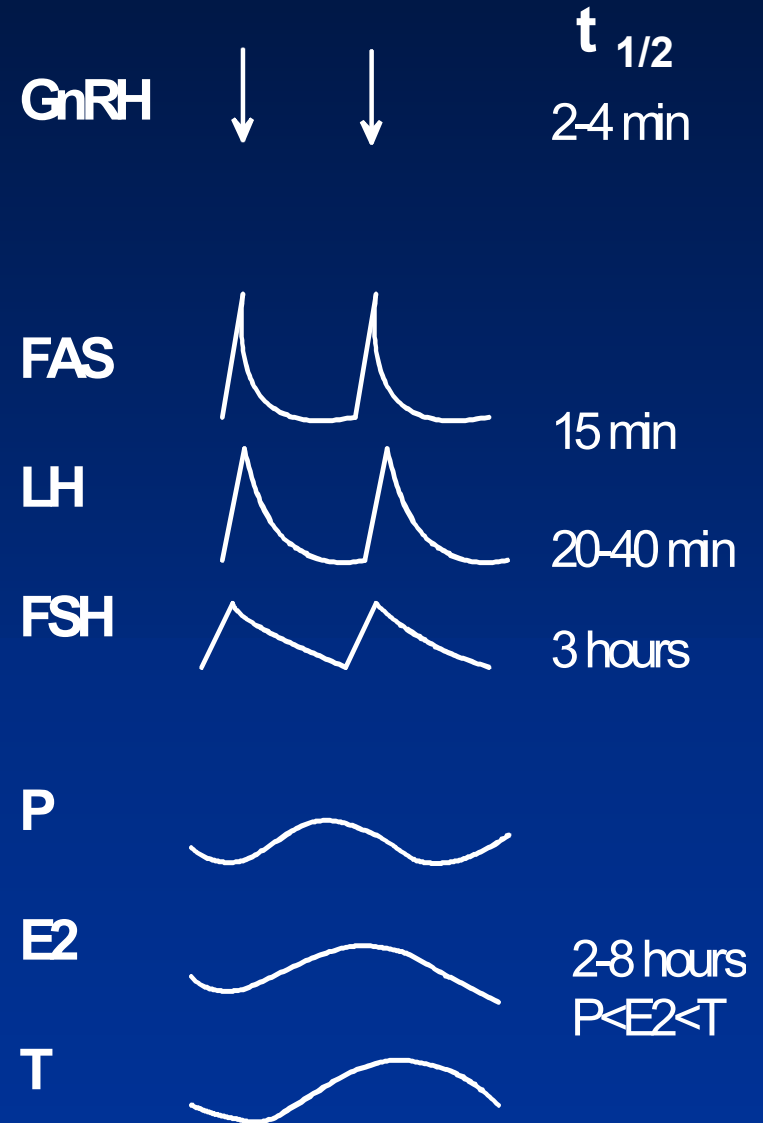
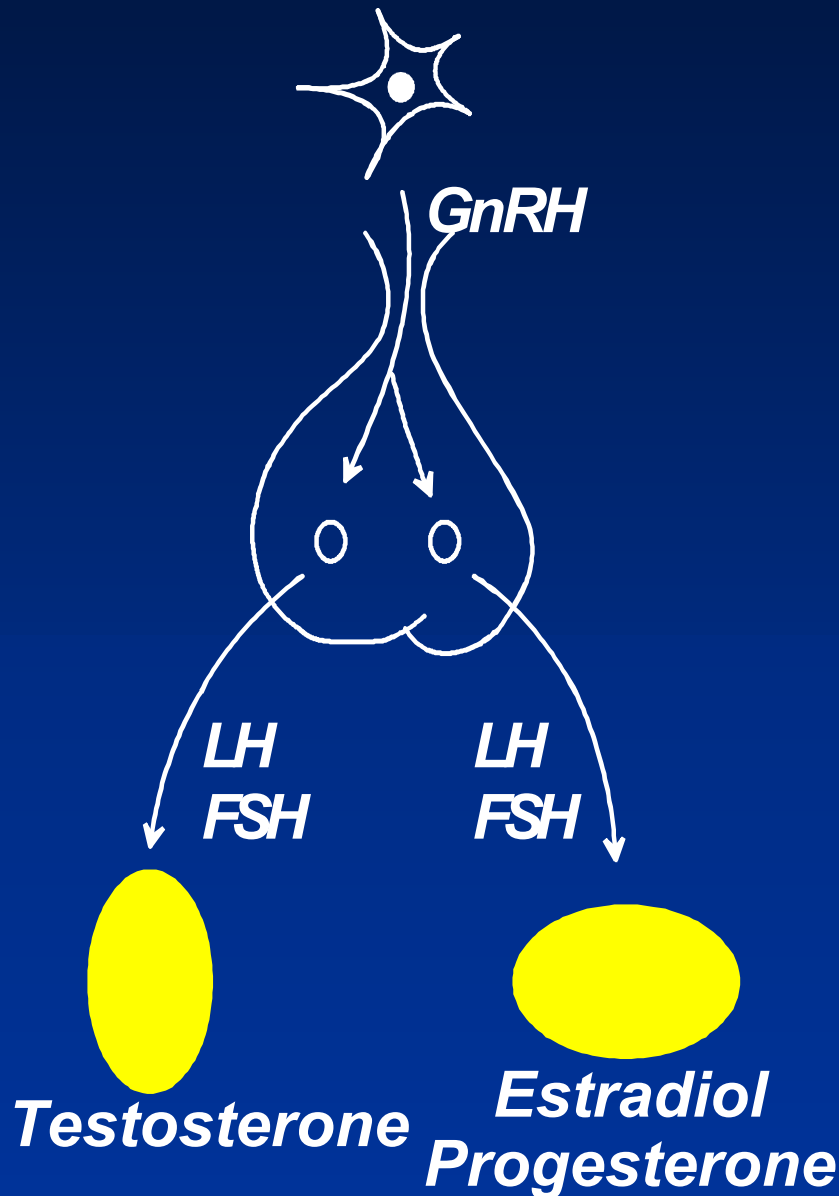
MLP

EFP

MCS

MLP

# Hypothalamic (*GnRH*), Pituitary (*LH*, *FSH*, free $\alpha$ -subunit) & Gonadal (*Steroid*) Hormone Secretory Dynamics



# Inhibin

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- Family of peptides consisting of varying combinations of an  $\alpha$  and several  $\beta$  subunits
- Two forms of inhibin important for reproduction in the human

## Inhibin A



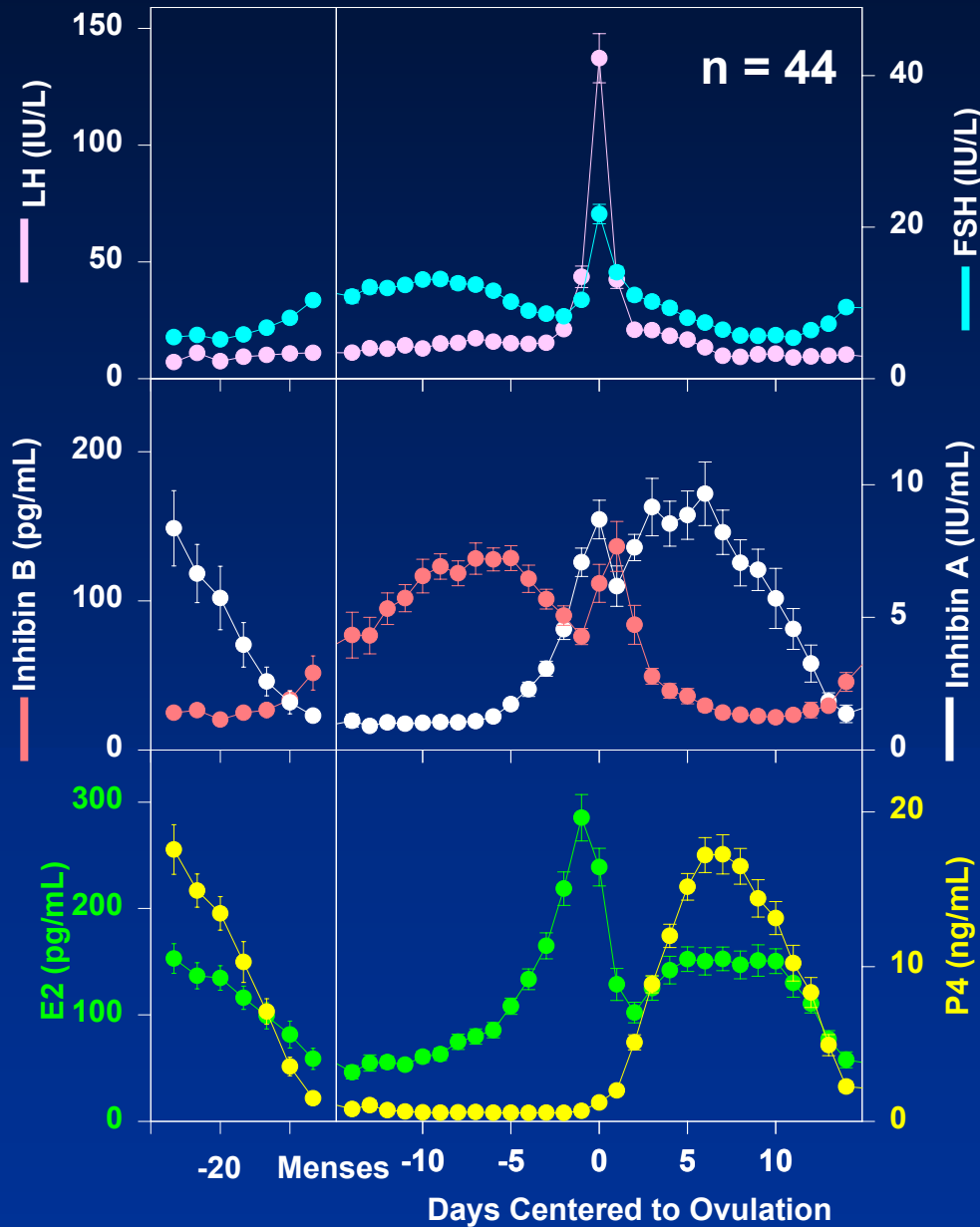
## Inhibin B



## Activin



# Differential Patterns of Inhibin A and Inhibin B across the Normal Menstrual Cycle





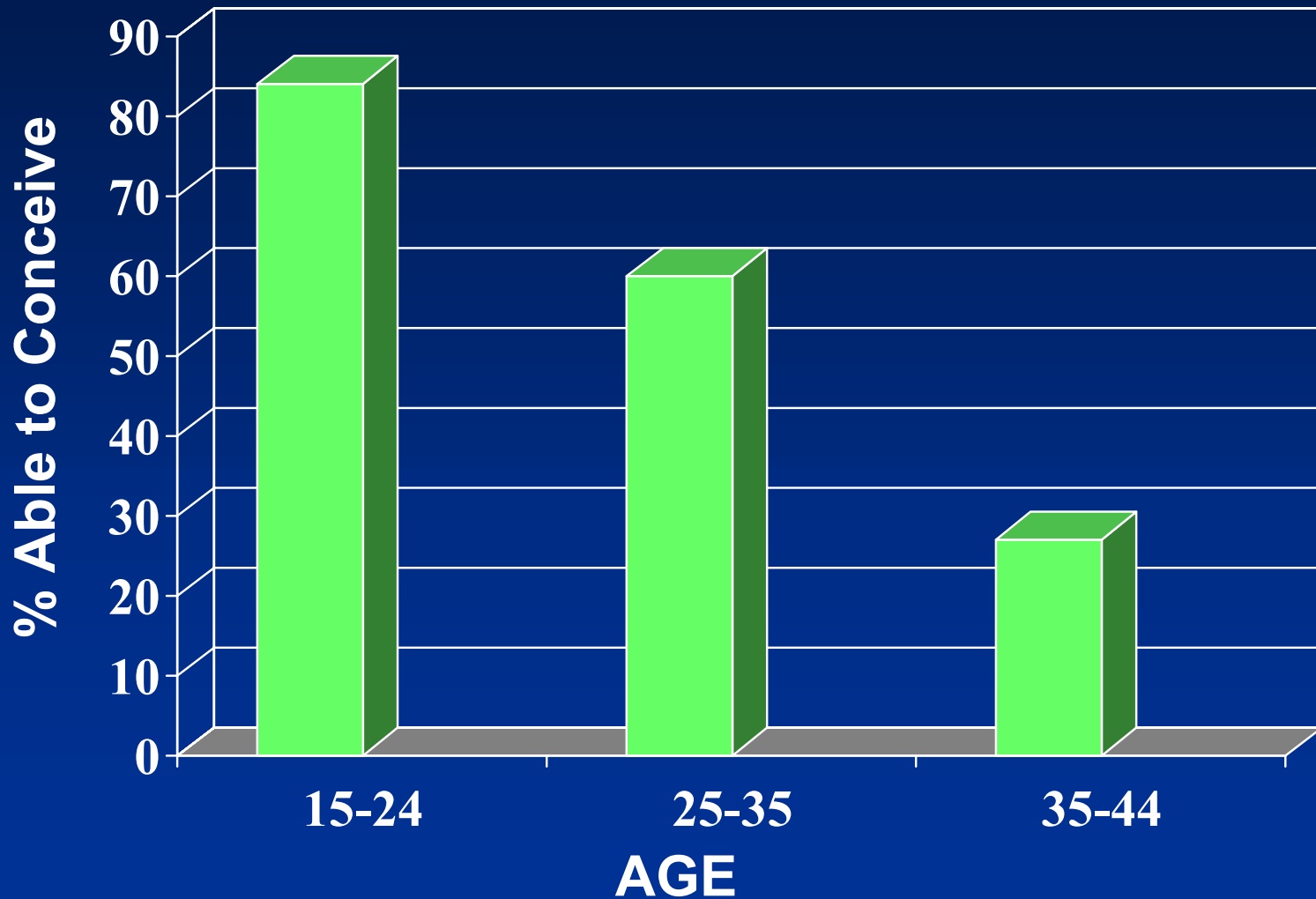
# Hormonal Dynamics of the Reproductive System

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- 1. Normal reproductive function requires precise integration of hypothalamic, pituitary and ovarian signals**
- 2. Normal reproductive function is associated with dynamic changes in gonadotropin secretion and ovarian steroids and peptides**
  - over a month
  - over hours to days

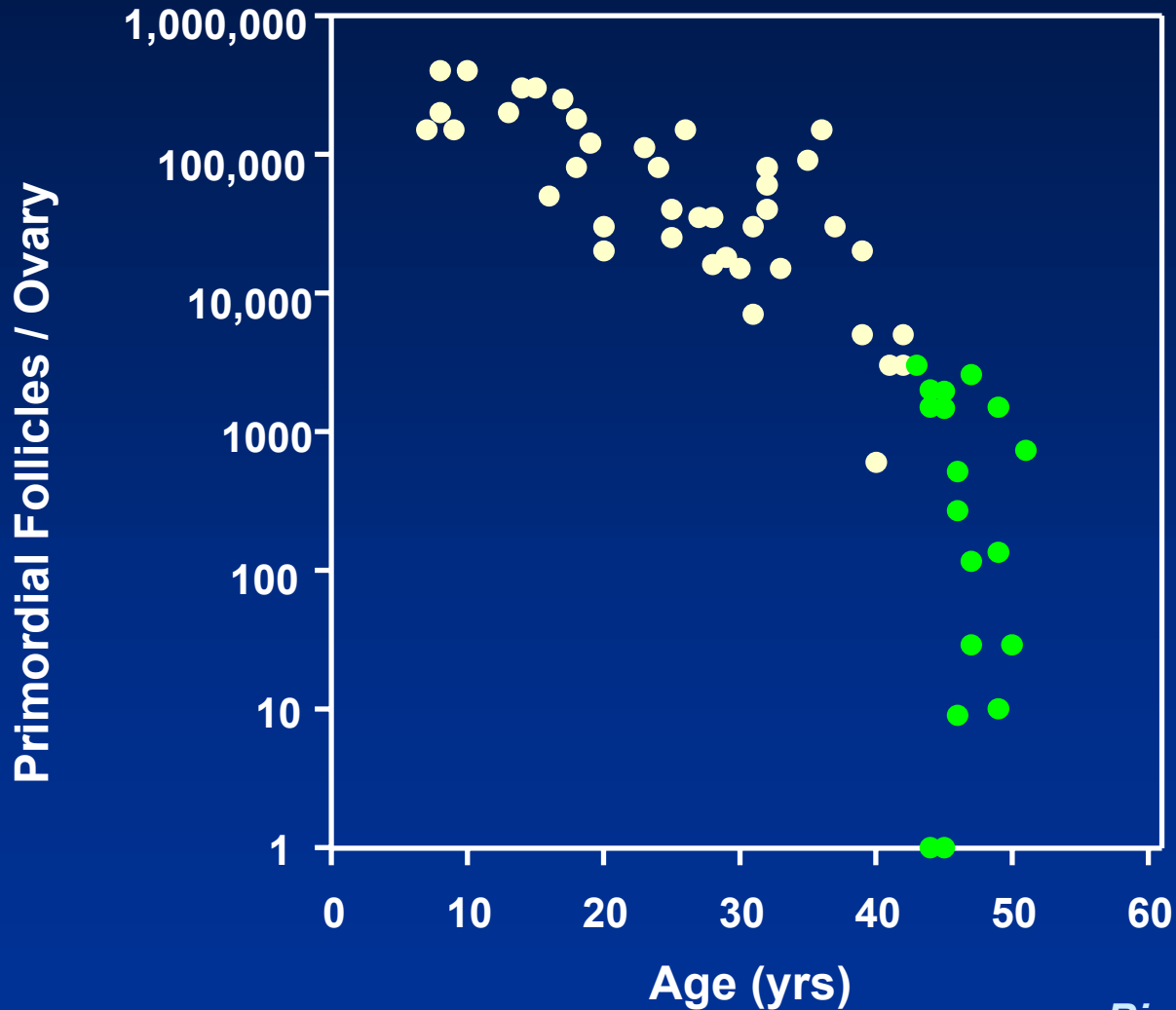
# Decreased Fecundity with Age

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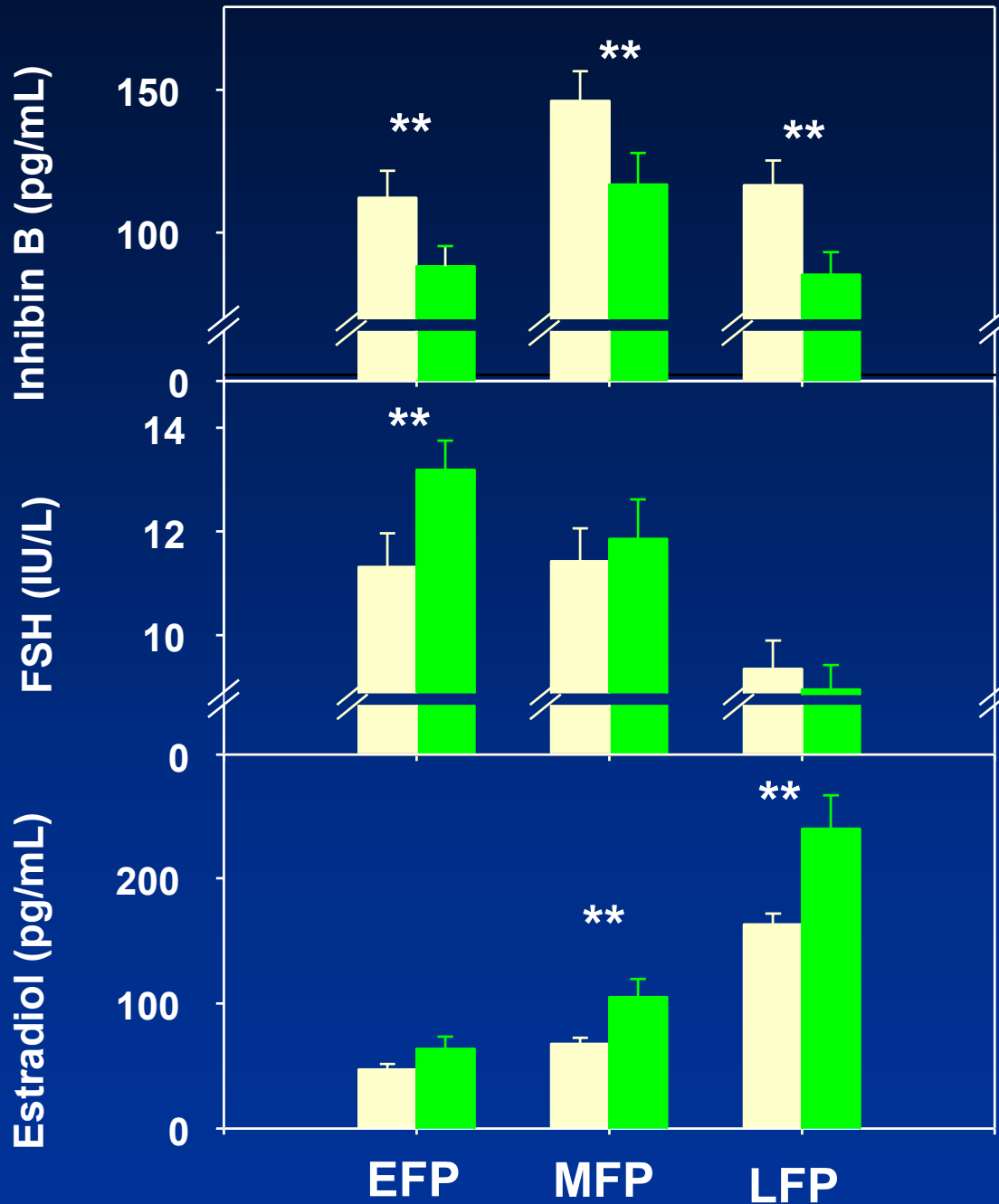


# Decline in Follicle Number with Age

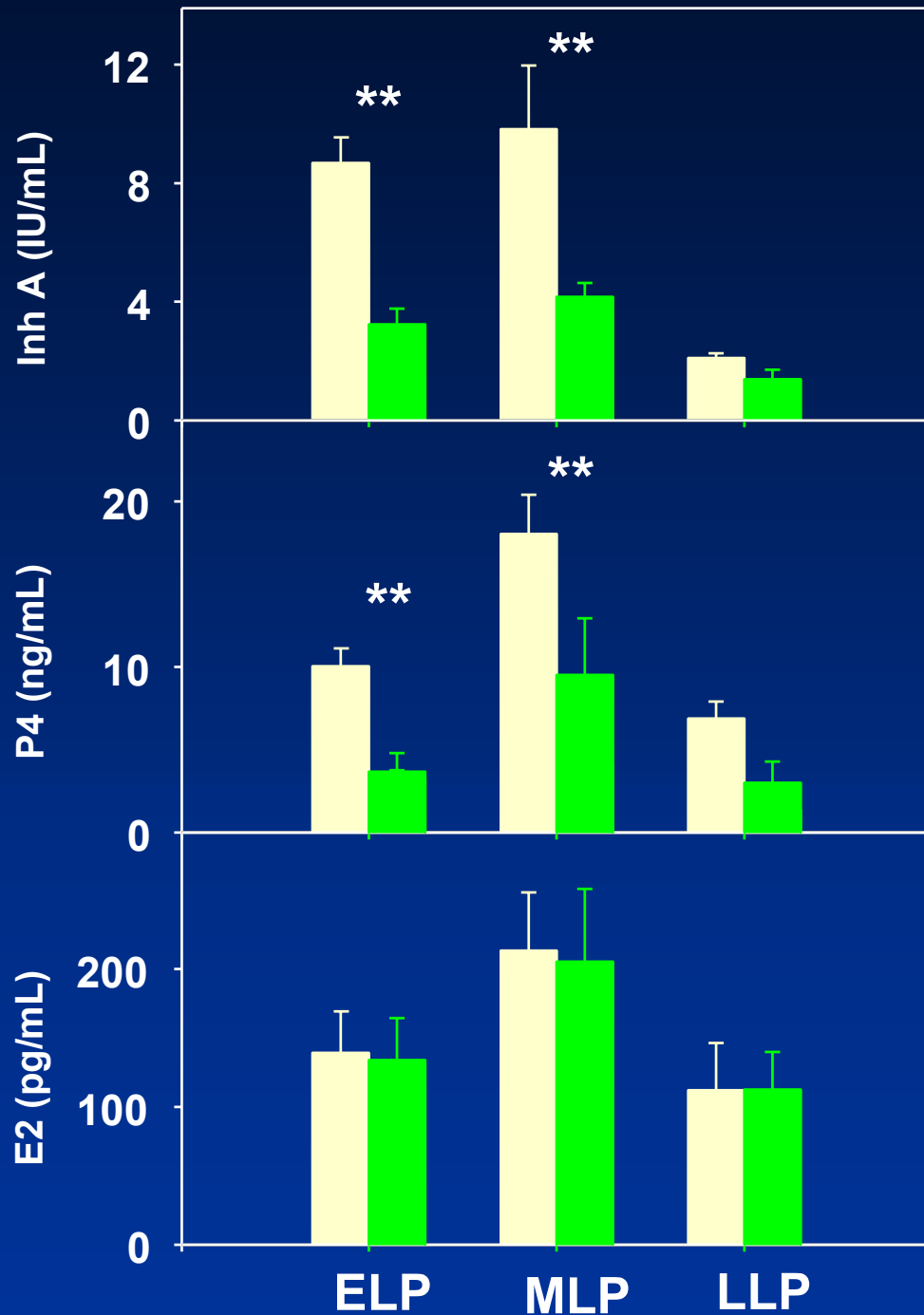
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# Mean Follicular Phase Levels

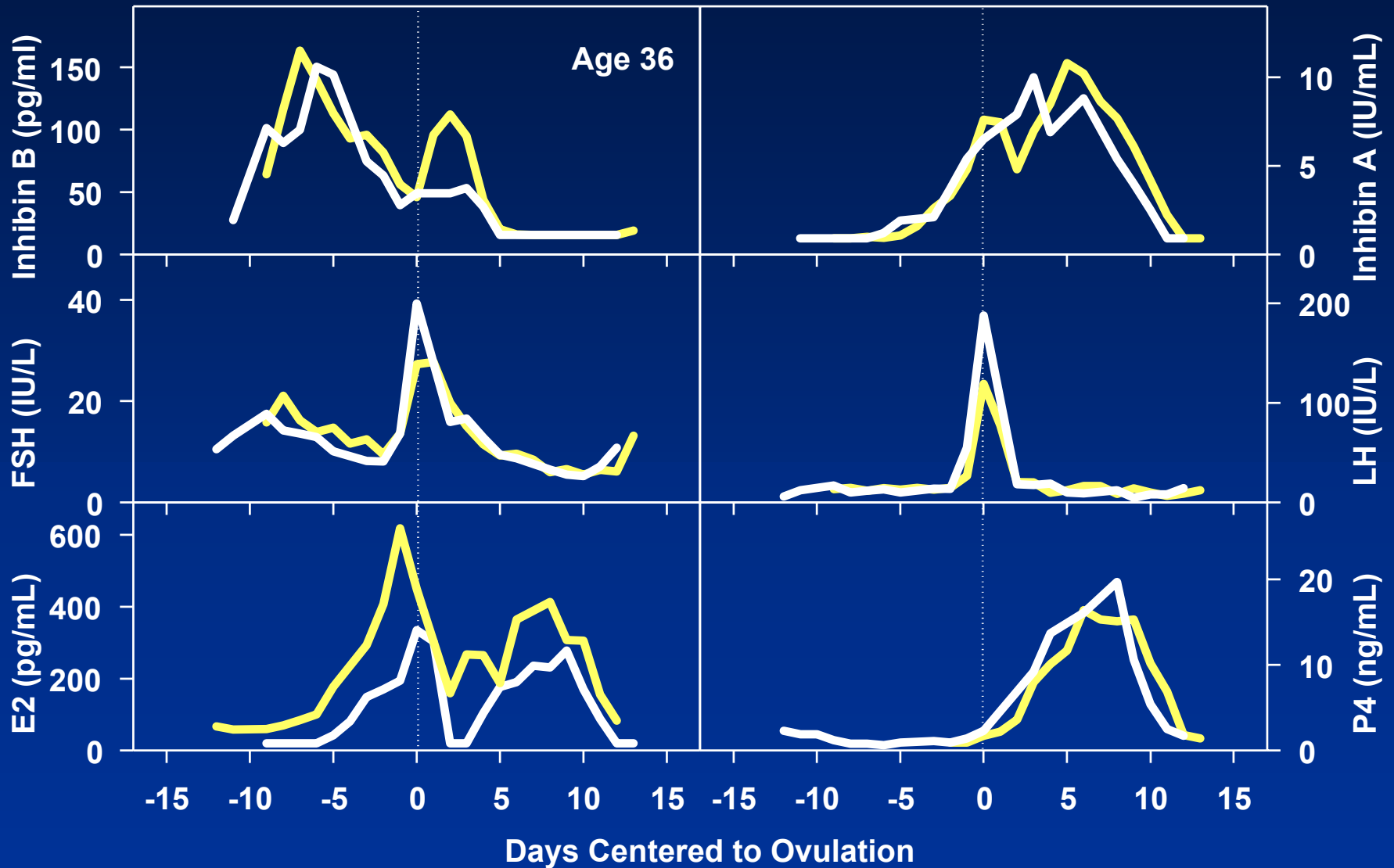


# Luteal Phase Longitudinal Changes

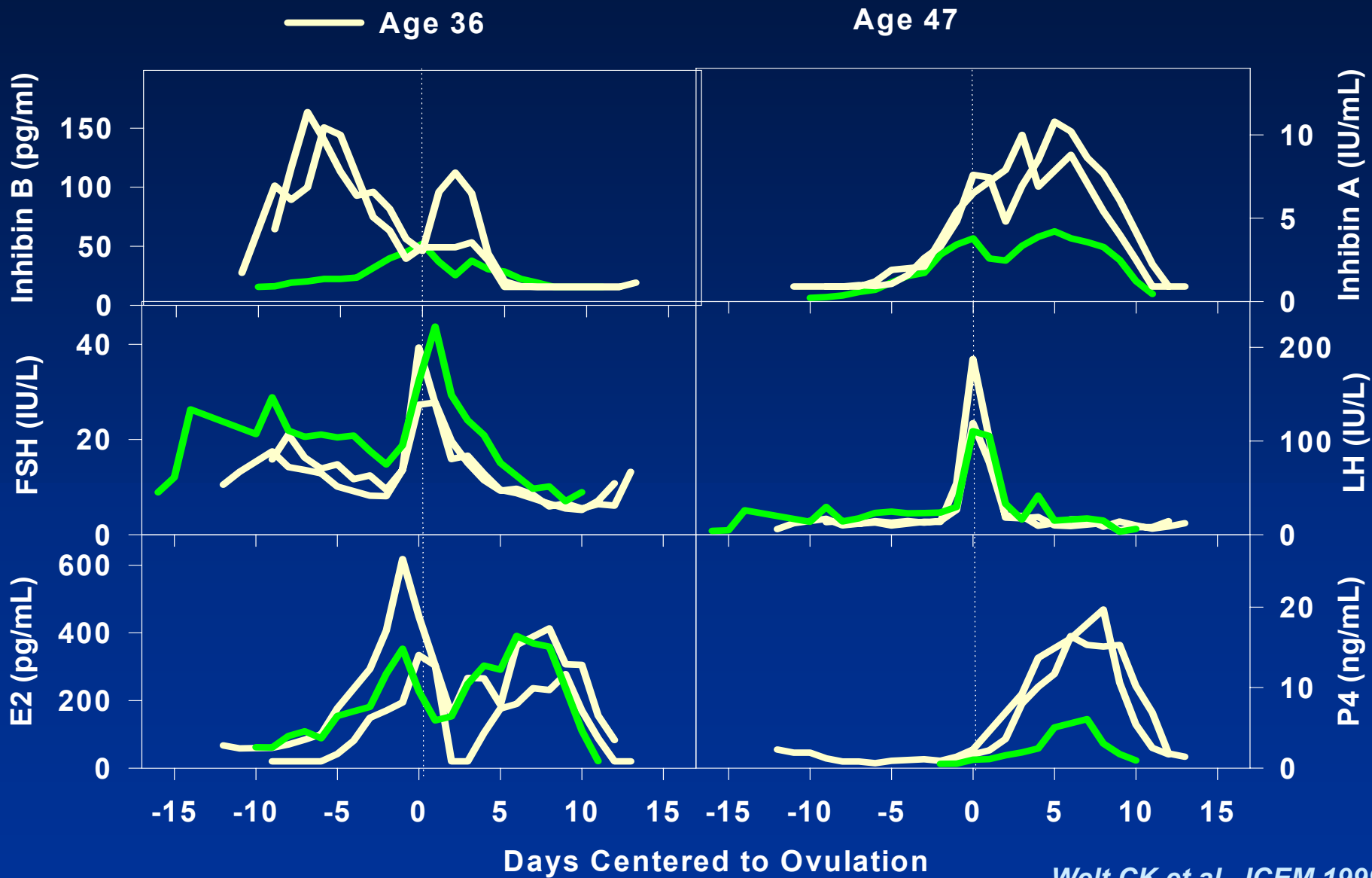


Younger Cycles  
Older Cycles

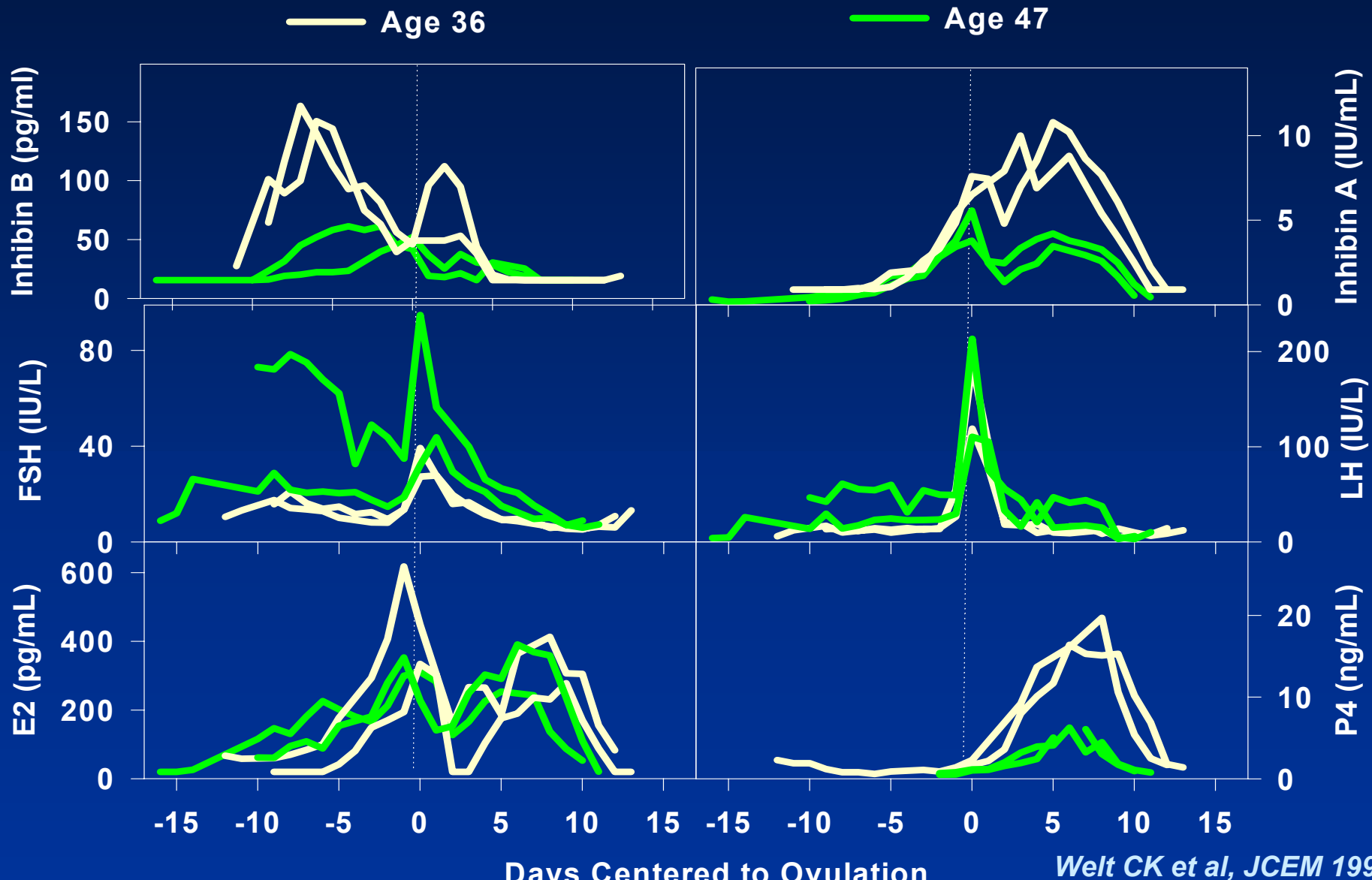
# Reproductive Hormone Levels



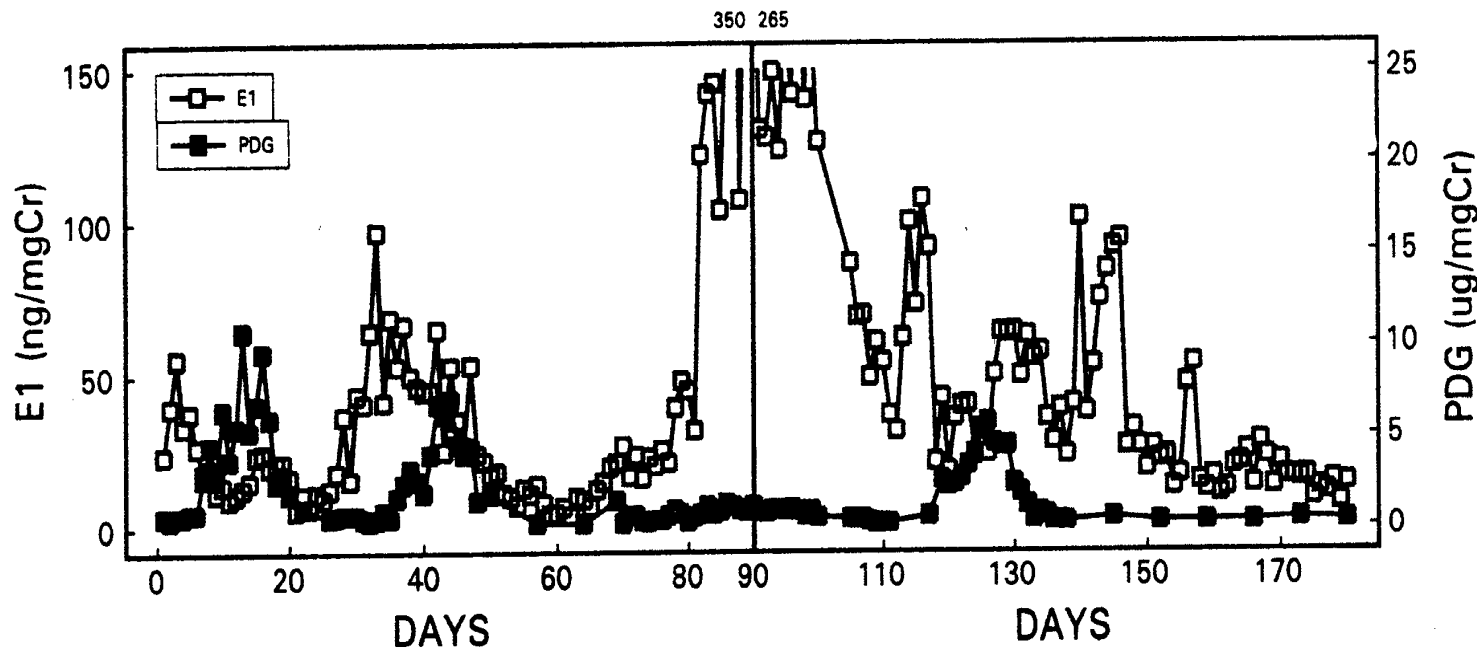
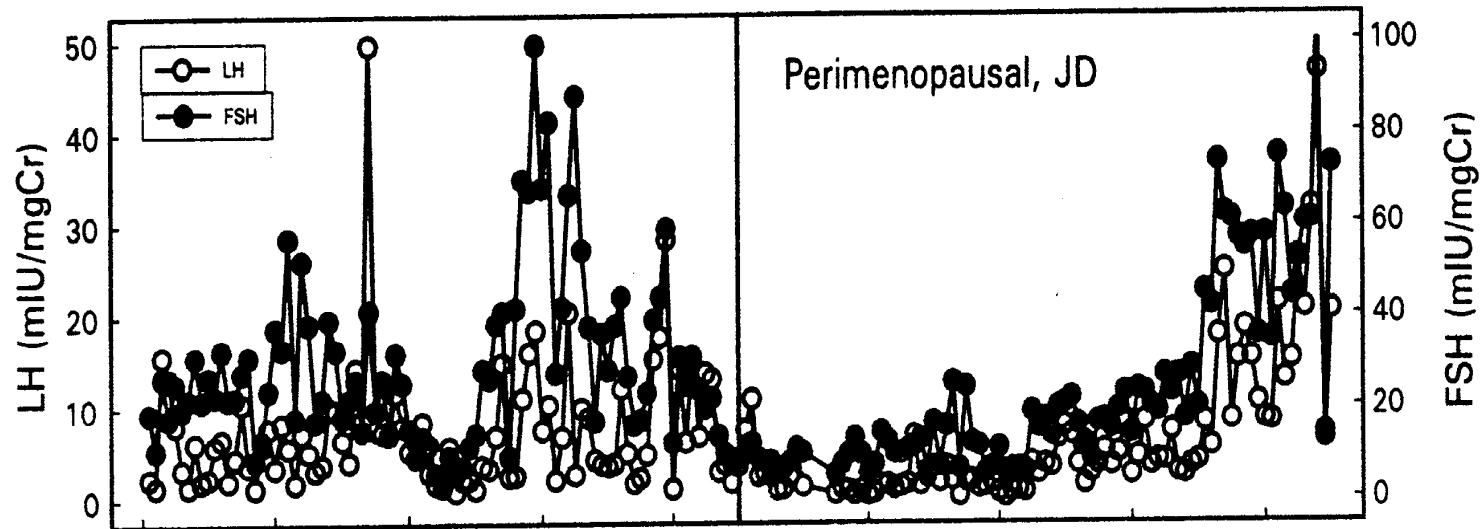
# Longitudinal Changes in Reproductive Hormones



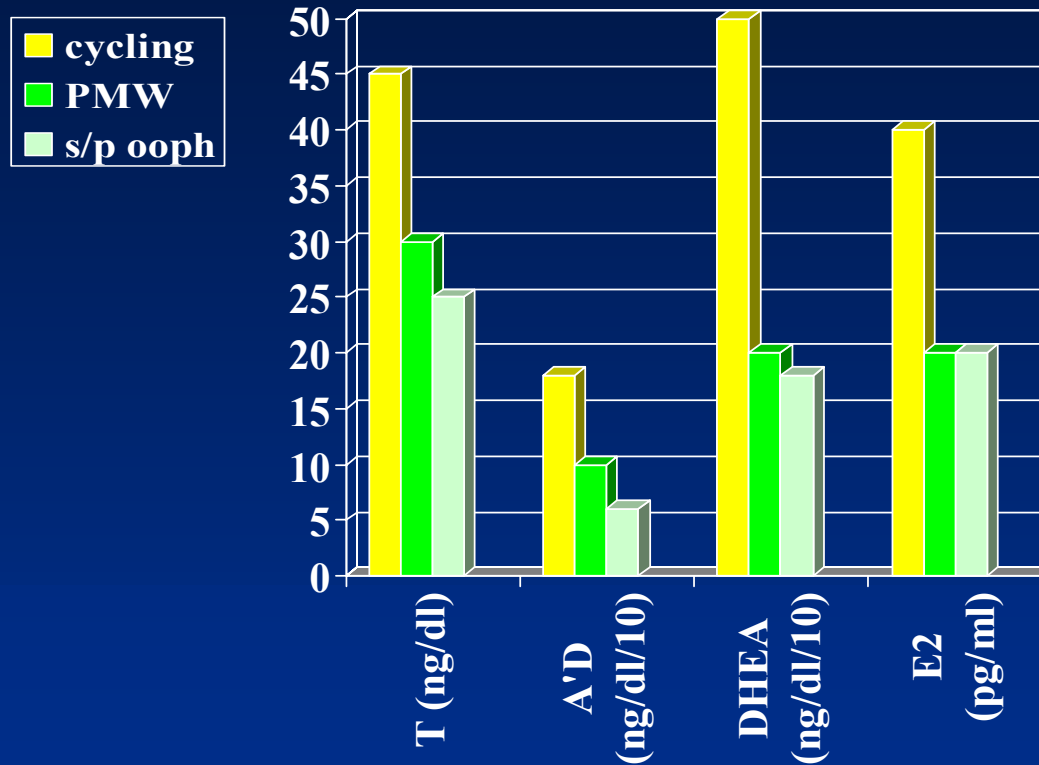
# Variability in Reproductive Hormone Levels with Aging







# Androgens and Estrogens with Loss of Ovarian Function



## Couzinet et al, 2001

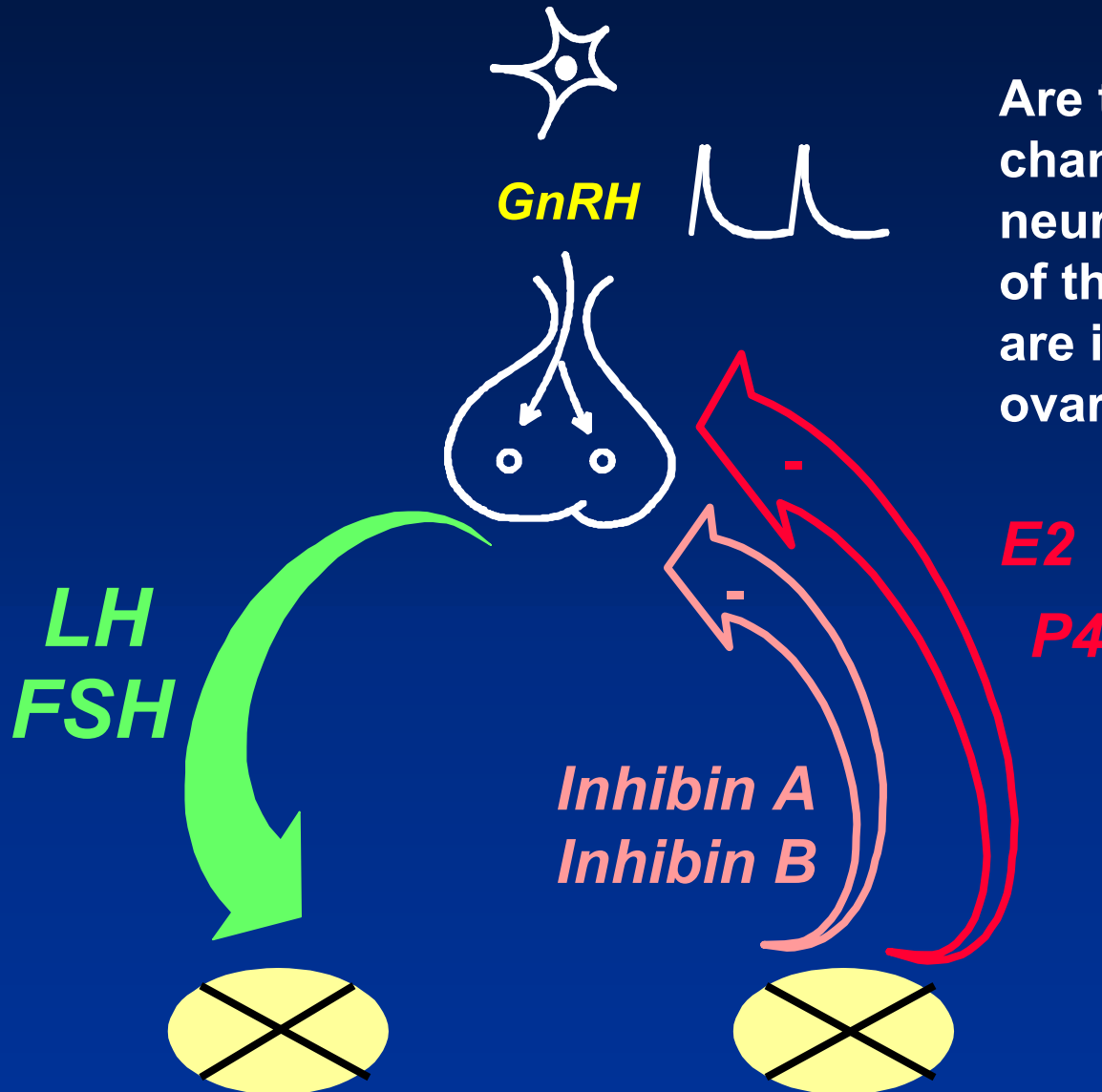
- PMW + adrenal insufficiency - absent androgens
- virtual absence of steroidogenic enzymes in the PM ovary
- absence of LHR and FSHR in the PM ovary

# Hormonal Dynamics of the Reproductive System: Transition to Menopause

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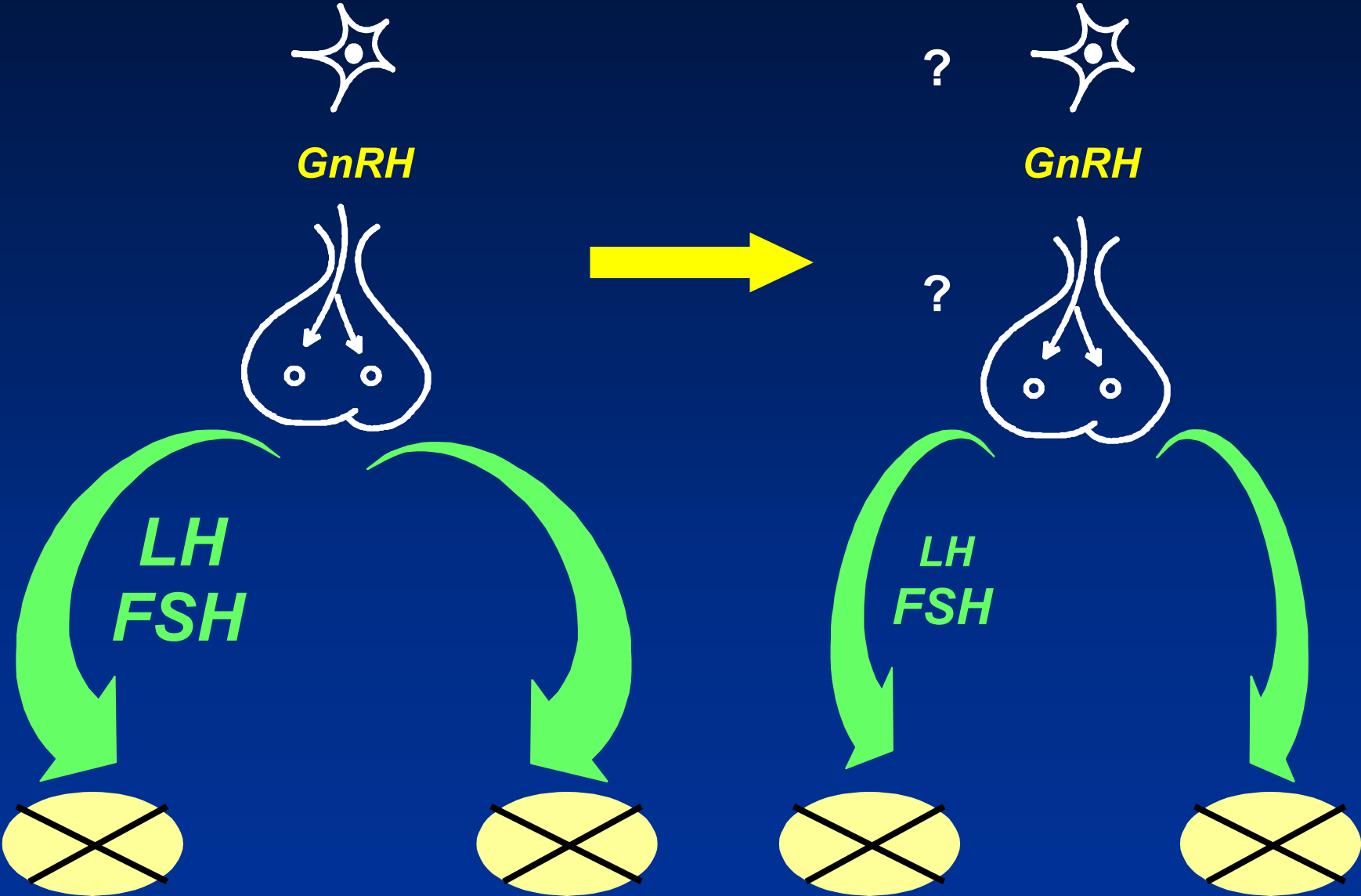
- 1. Decreased ovarian function is accompanied by decreased levels of inhibin, increased FSH and early increased in estradiol.**
- 2. The transition to menopause is characterized by dramatic fluctuations in hormone levels**
- 3. Hormonal secretion from the postmenopausal ovary is probably negligible**
  - improved assays for testosterone and estradiol are required to understand the effects of these steroids on non-reproductive tissues**

# Postmenopausal Women: a unique model in which to examine the effects of aging on the brain

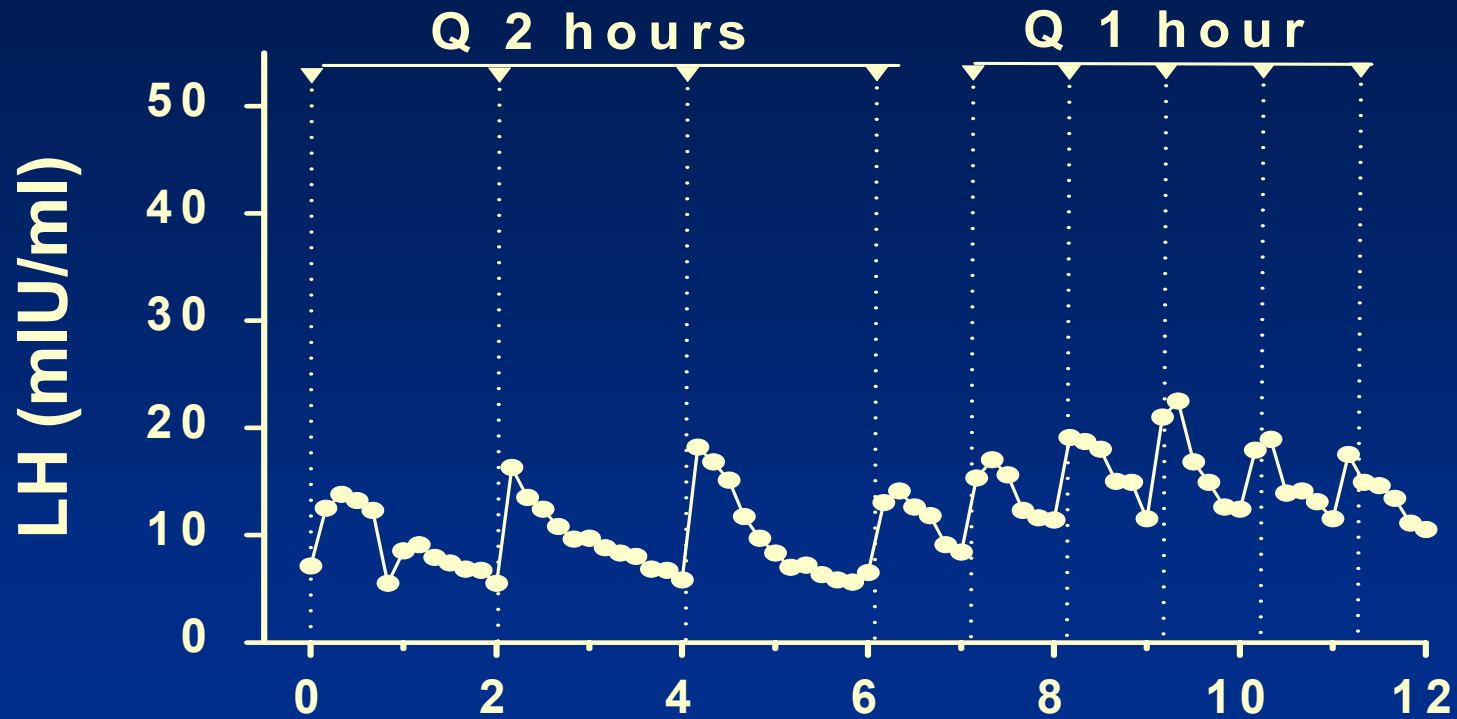


Are there age-related changes in the neuroendocrine components of the reproductive axis that are independent of changing ovarian feedback?

# Hypothalamic vs Pituitary Site of Age-Related Decrease in Gonadotropins

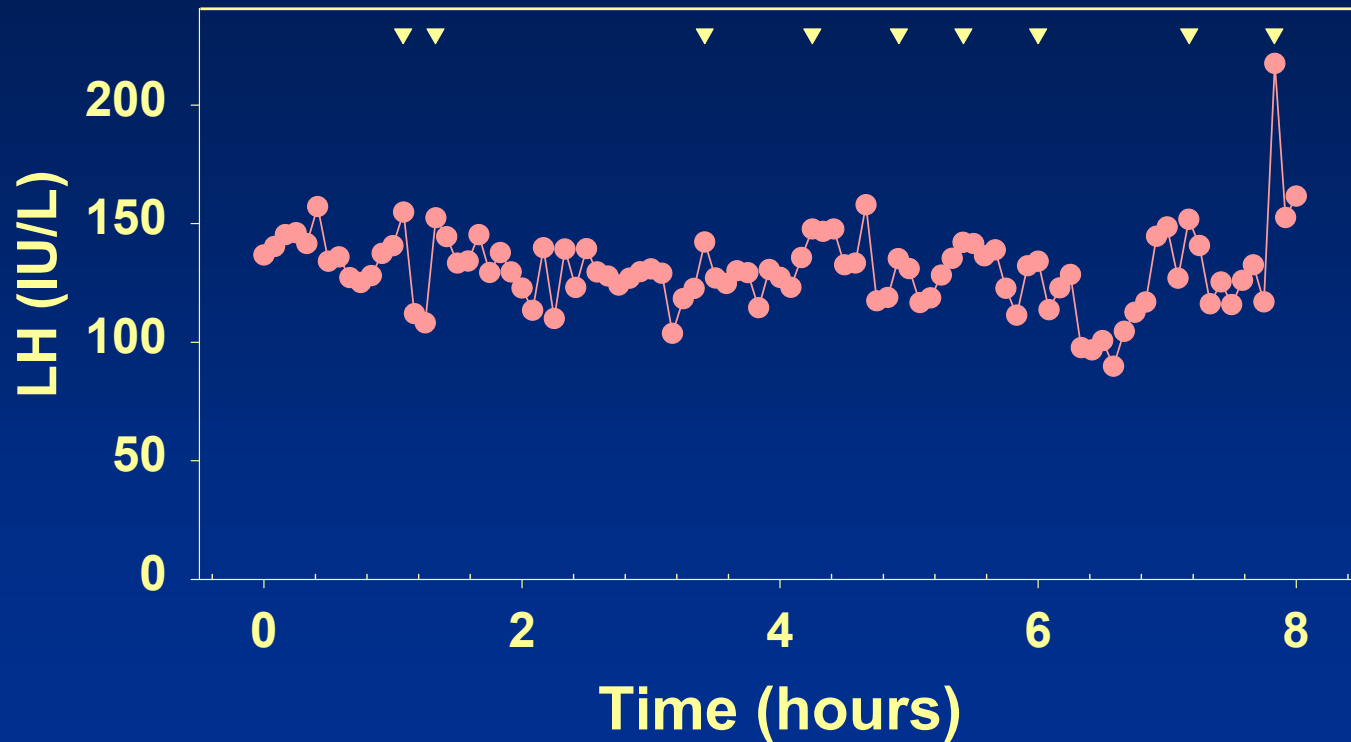


# Markers of Pulsatile GnRH Secretion

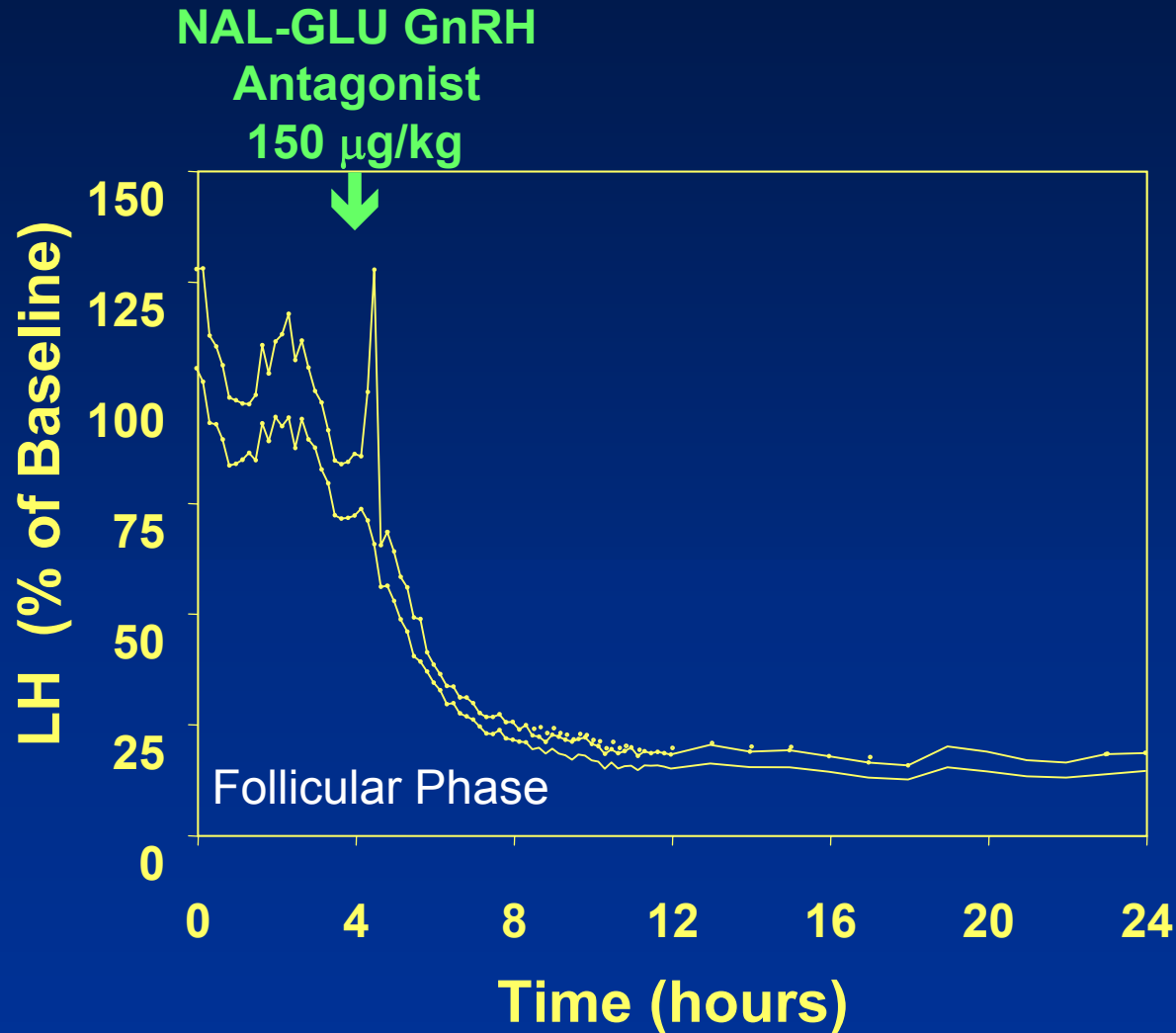


# LH Pulses in a Young Postmenopausal Woman

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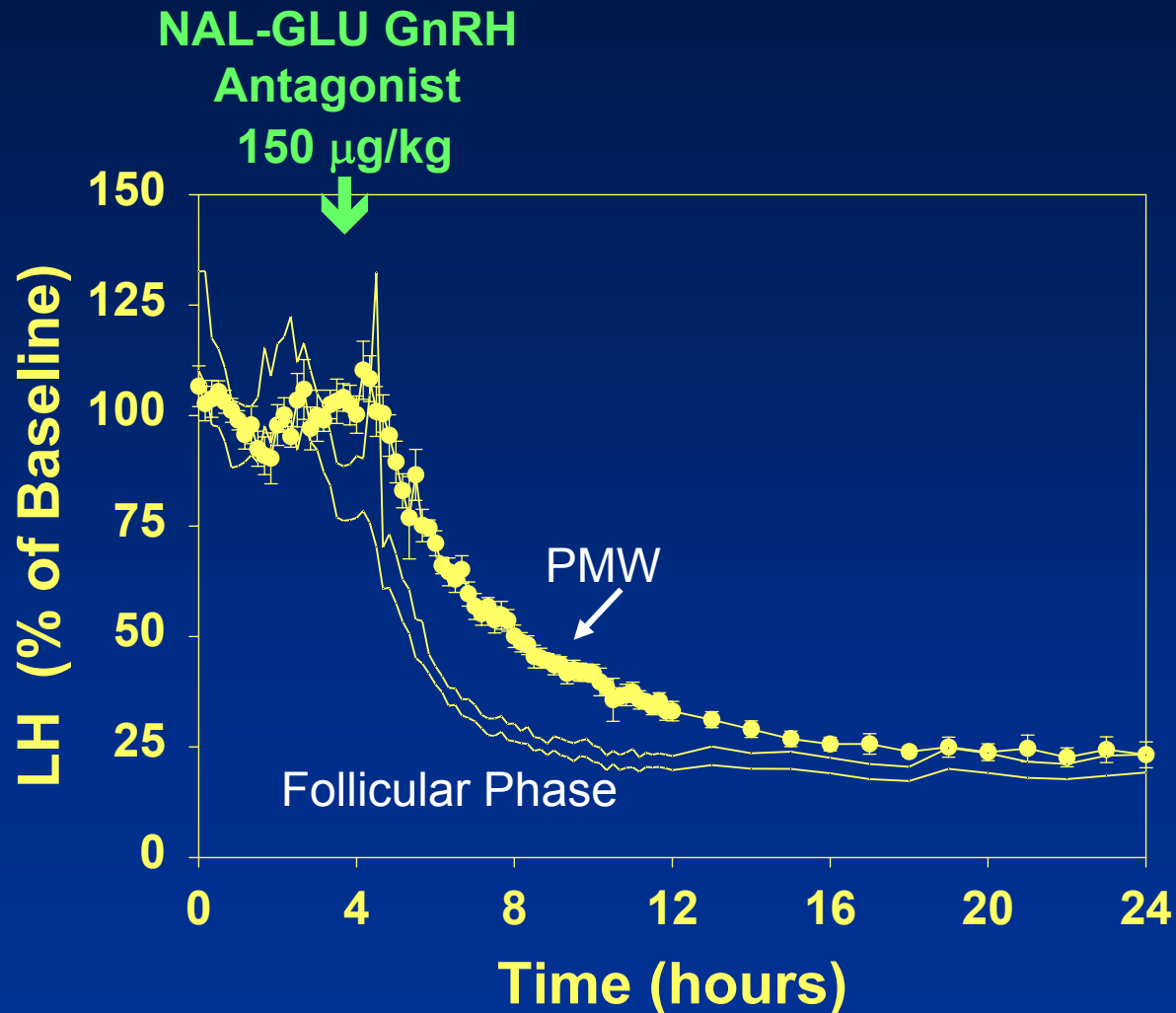


# GnRH Receptor Blockade: Plasma Disappearance





# Prolonged Disappearance of Endogenous LH in Postmenopausal vs Normal Women



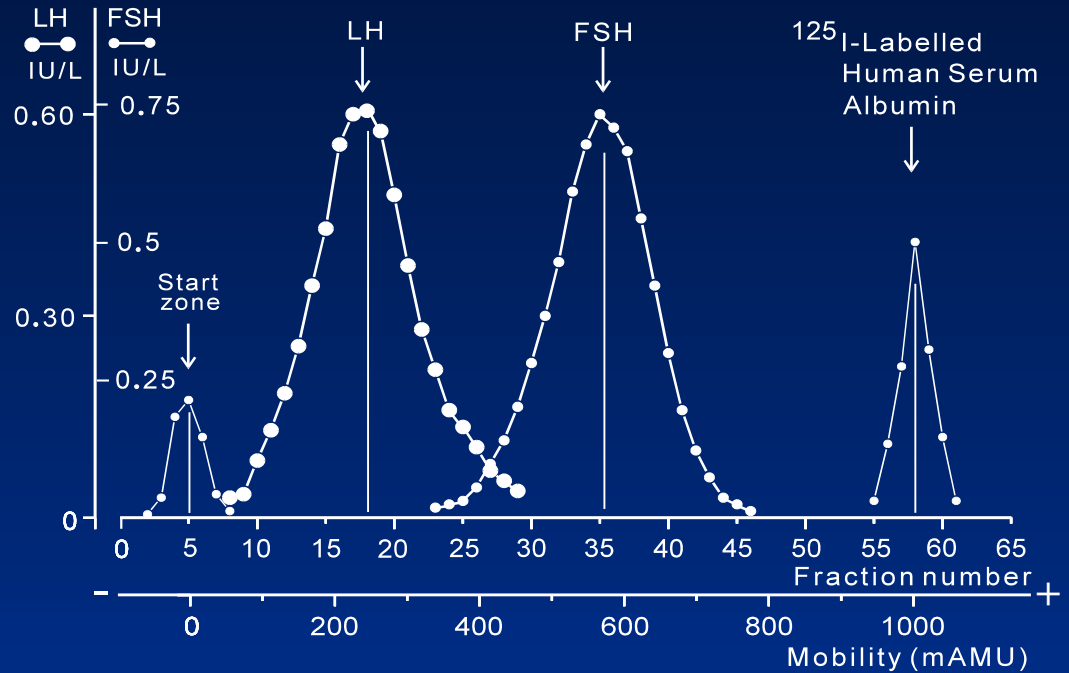
# Prolonged Disappearance of Endogenous LH in Postmenopausal vs Normal Women

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	LH	
	Baseline(IU/L) mean+/-sem	T1/2 (min) mean+/-sem
Postmenopausal	62+/-3	139+/-35
EFP, LFP	10+/-1	57+/-28
MCS	56+/-11	78+/-20

# Microheterogeneity of LH and FSH

- Multiple isoforms of LH and FSH differing in their carbohydrate structure in pituitary and serum

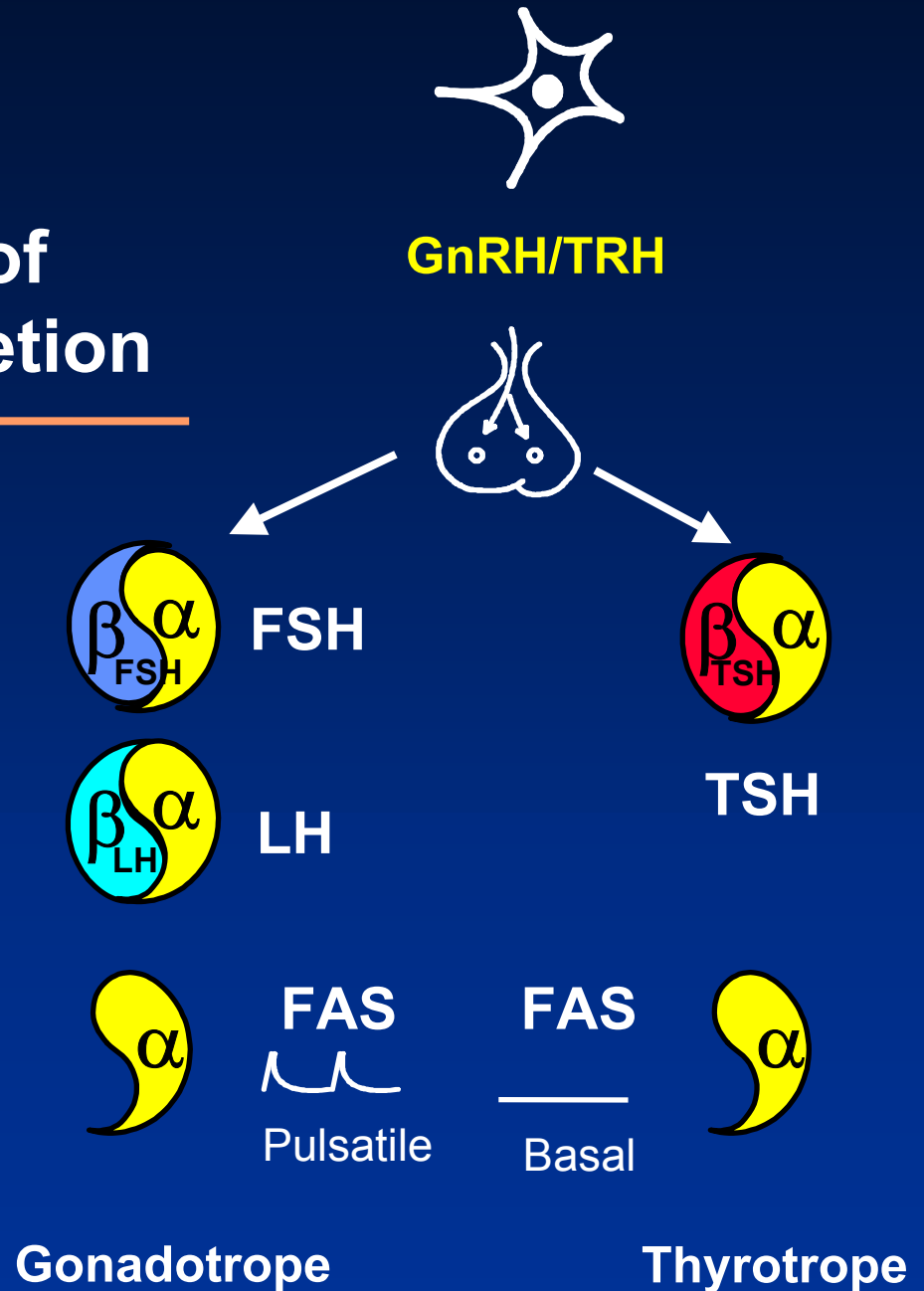


Wide & Naessen, 1994

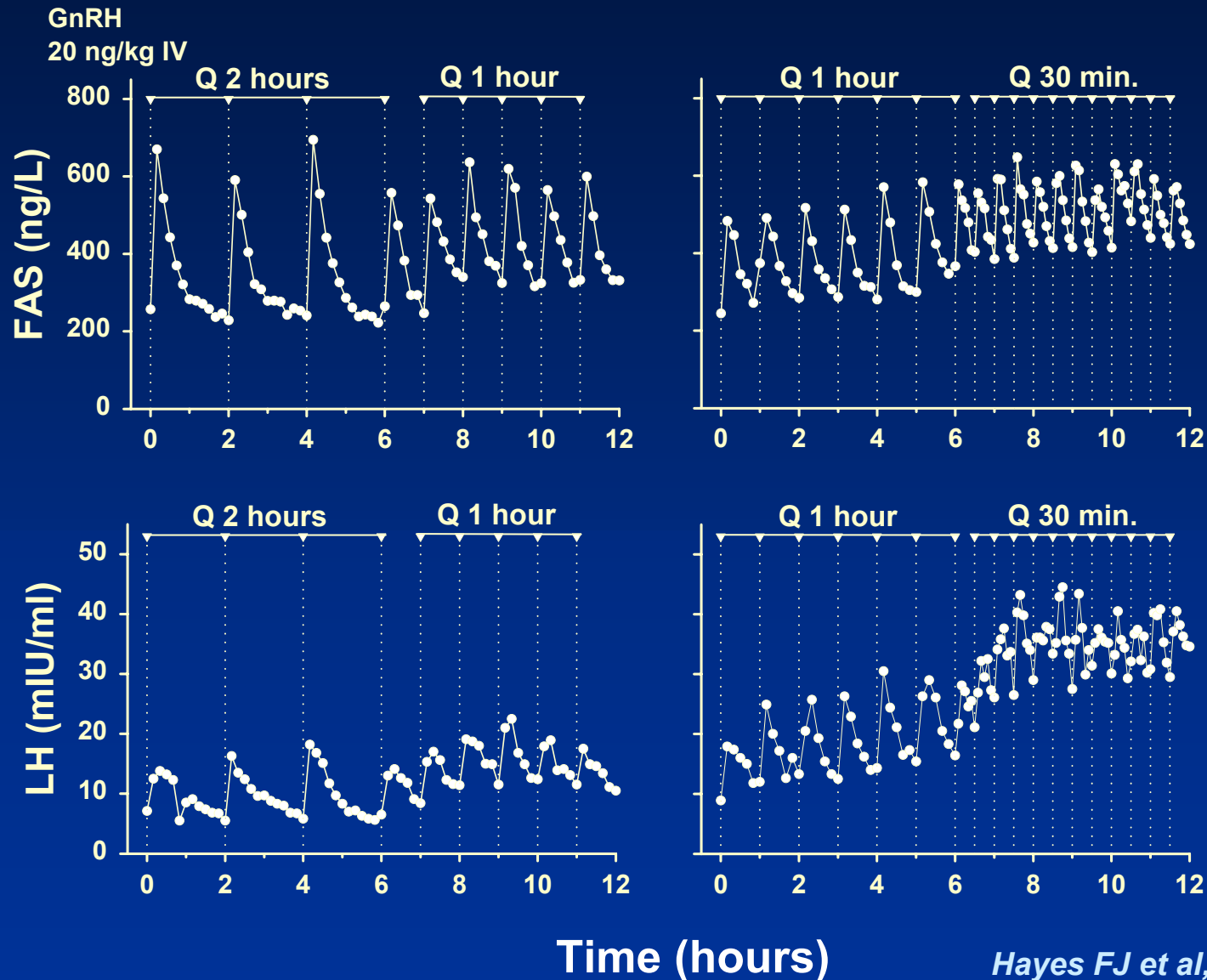
- biologic and immunologic activity may vary in relation to changes in carbohydrate structure
  - more basic isoforms are associated with shorter half-lives and increased 'in vitro' bioactivity

# FAS as a marker of pulsatile GnRH secretion

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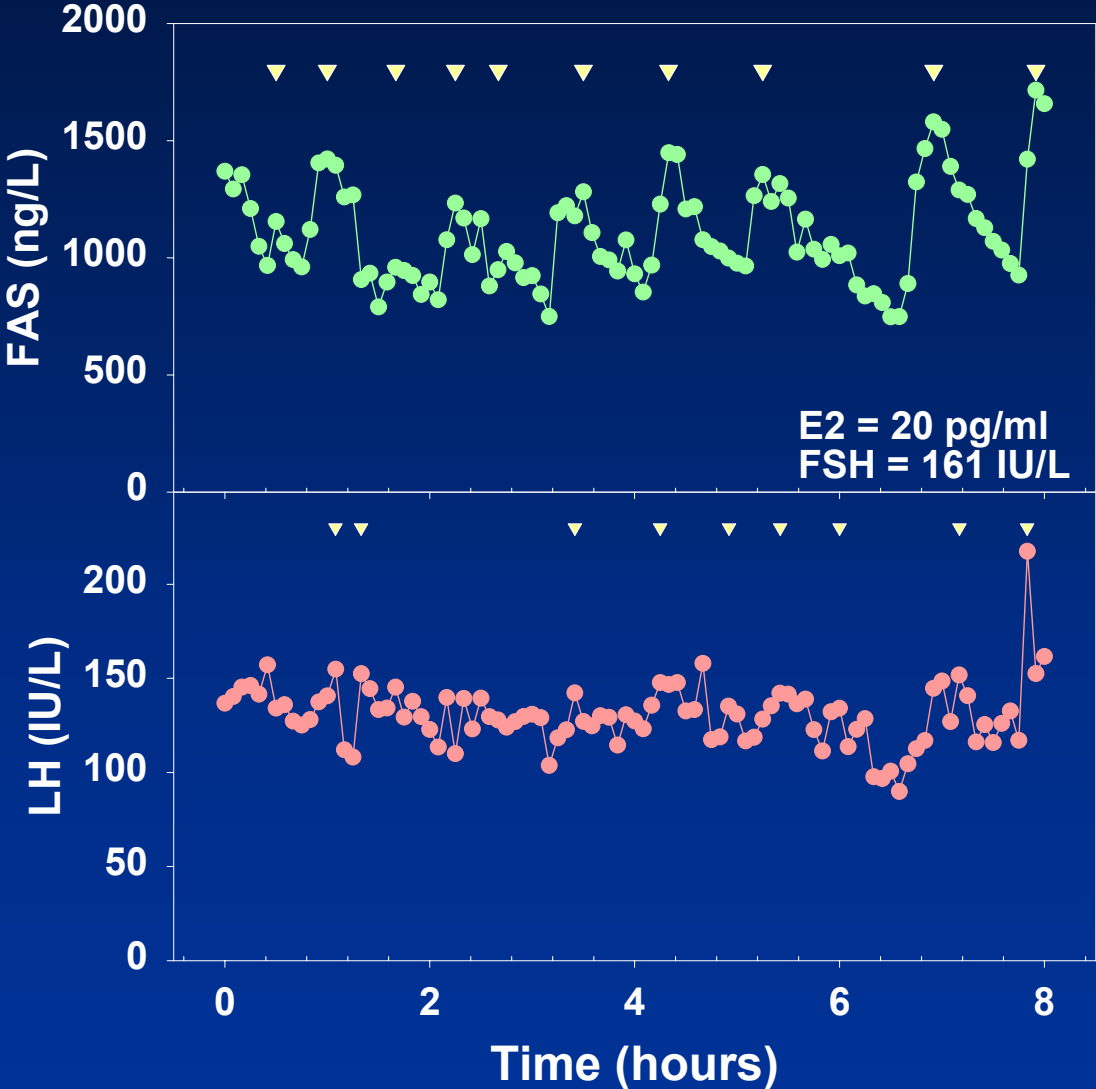
# FAS and LH in Response to Increasing Frequencies of Pulsatile GnRH in a GnRH-Deficient Man



# Prolonged Disappearance of Endogenous LH but not FAS in Postmenopausal vs Normal Women

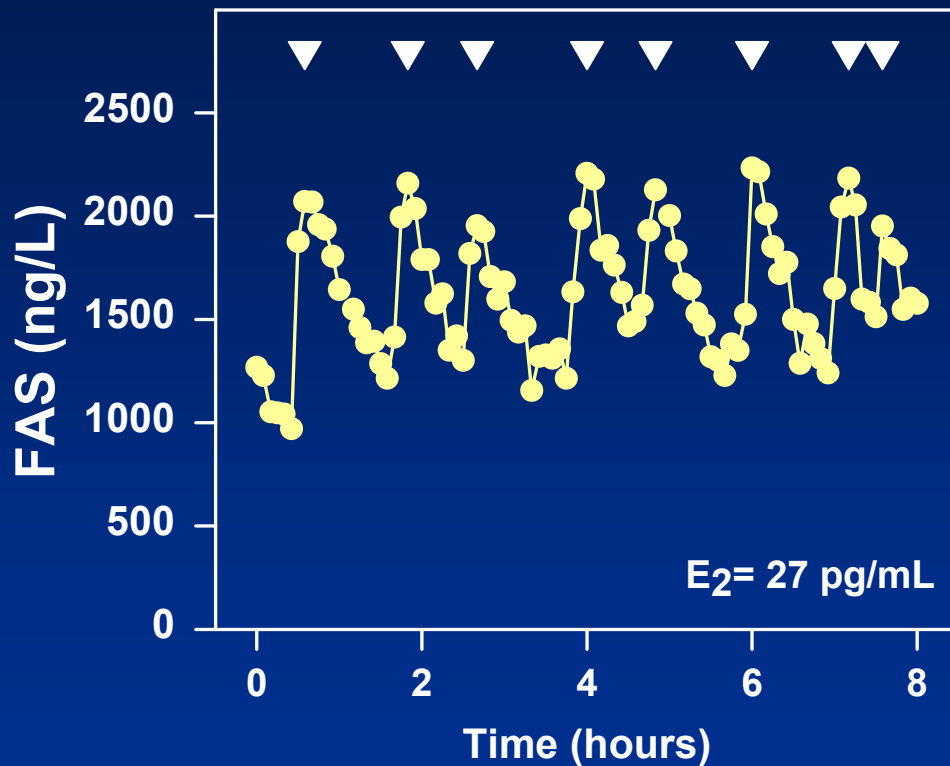
	LH		FAS	
	Baseline(IU/L) mean+/-sem	T1/2 (min) mean+/-sem	Baseline (pg/mL) mean+/-sem	T1/2 (min) mean+/-sem
Postmenopausal	62+/-3	139+/-35	774+/-45	51+/-26
EFP, LFP	10+/-1	57+/-28	266+/-44	41+/-12
MCS	56+/-11	78+/-20	627+/-122	41+/-19

# FAS and LH Pulses in a Young Postmenopausal Woman

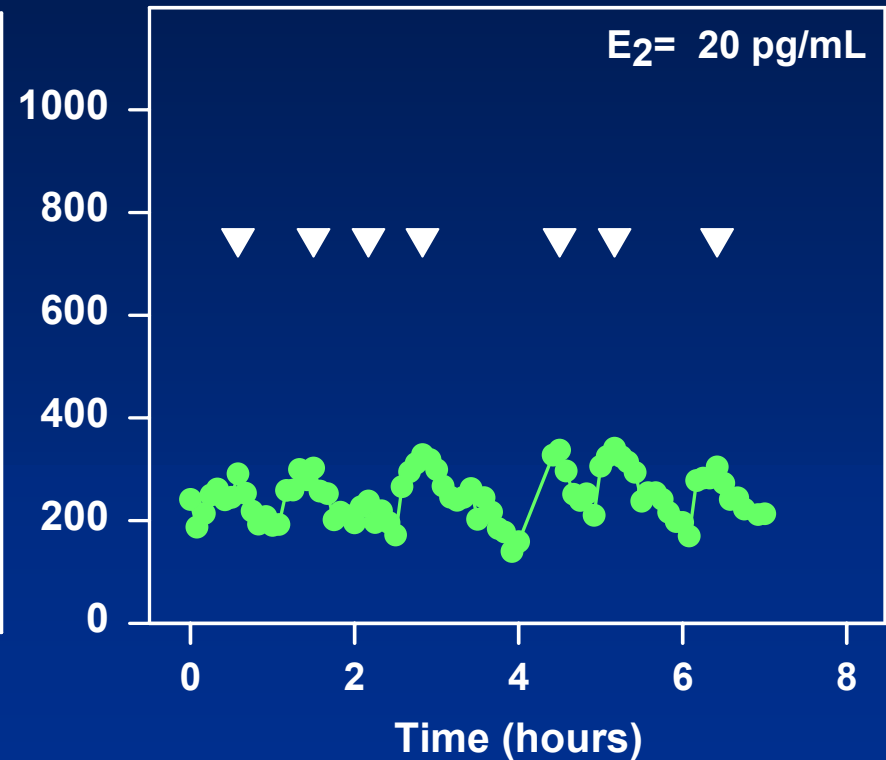


# Decreased FAS Pulsatility with Aging: Decreased Activity of the GnRH Pulse Generator

YOUNG PMW

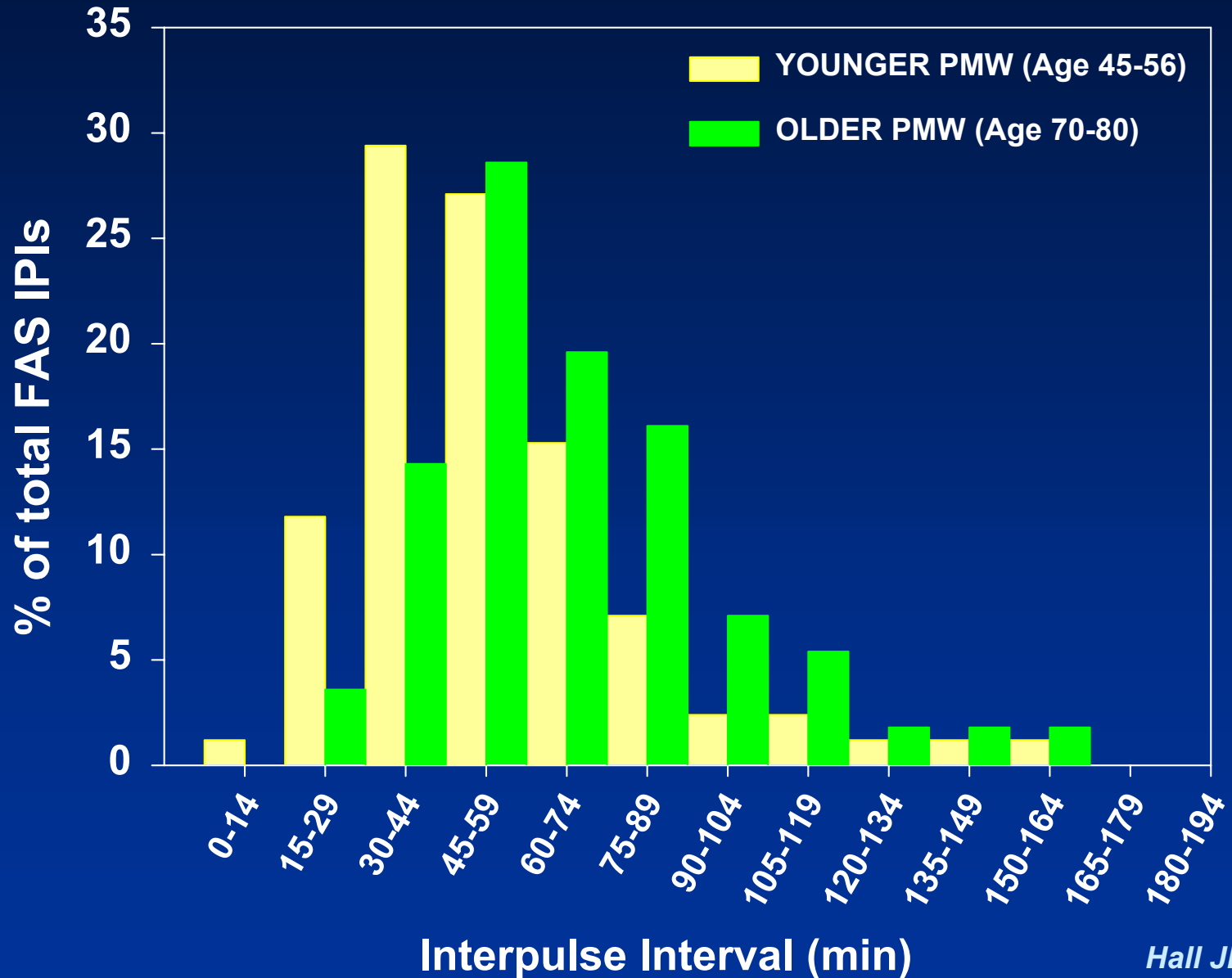


OLD PMW





# Longer Interpulse Intervals with Aging



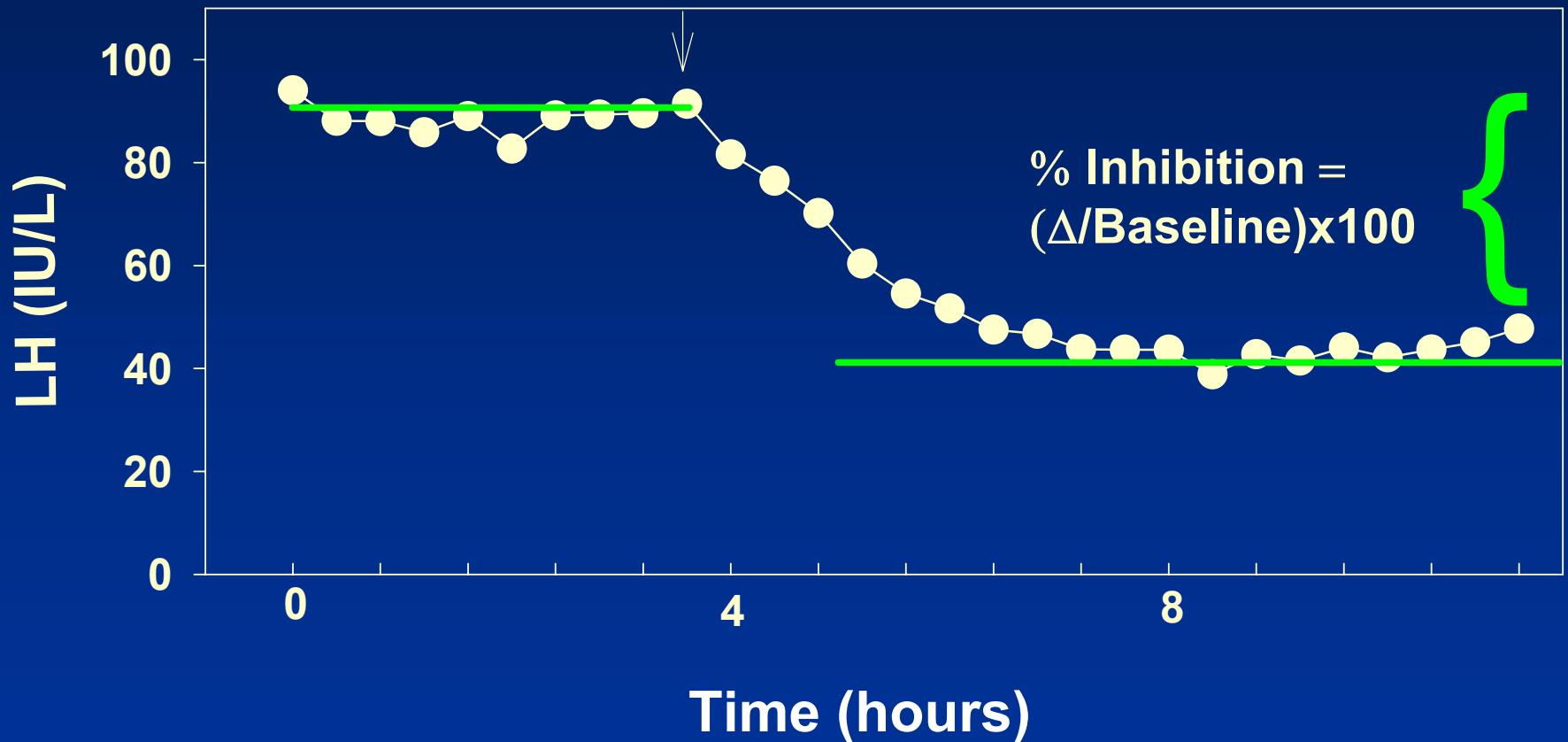
# Indirect Assessment of GnRH Secretion in Human Studies

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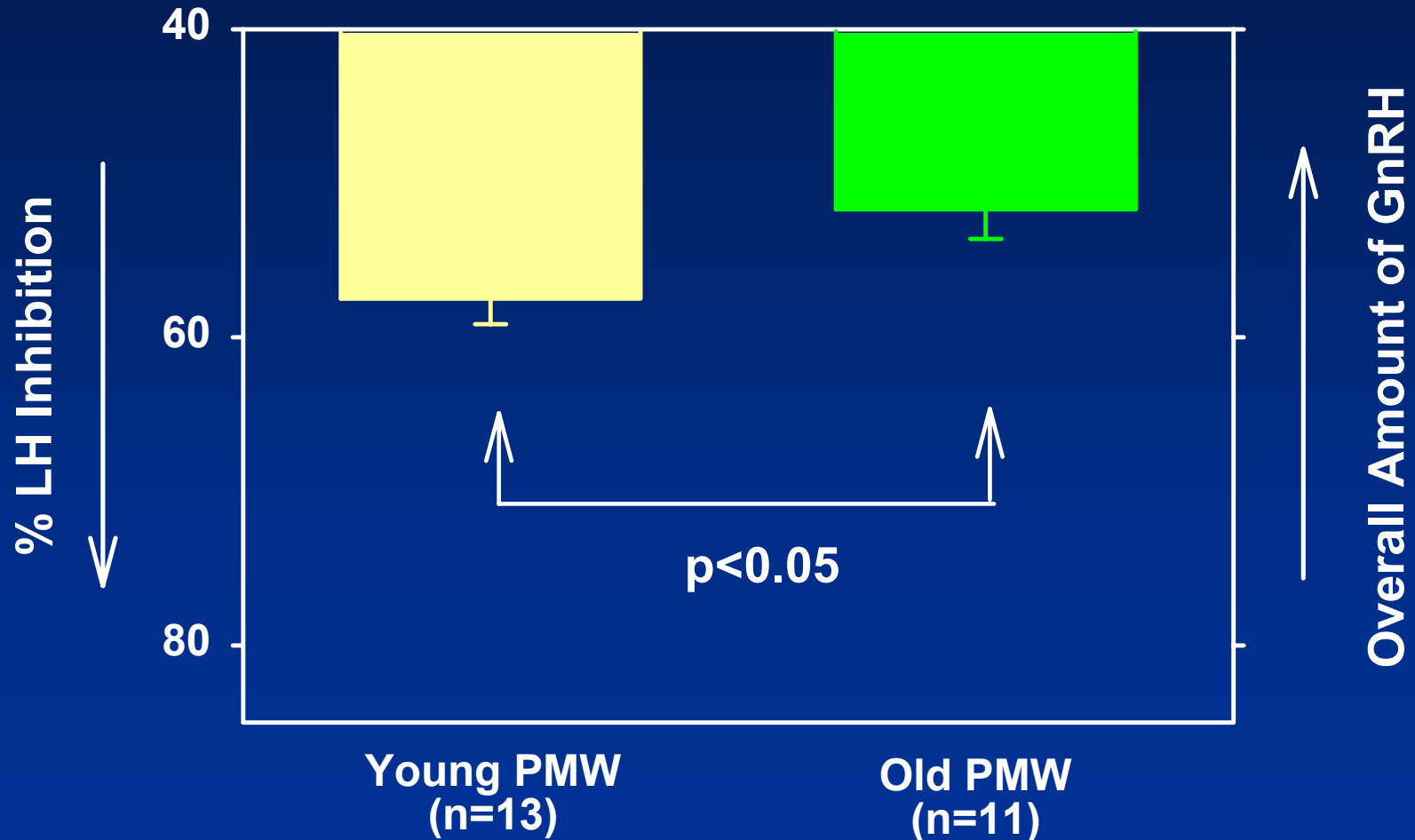
- Competition at the GnRH receptor between GnRH and GnRH antagonist provides a semi-quantitative estimate of overall quantity of endogenous GnRH
- At submaximal NAL-GLU GnRH antagonist dose (5  $\mu\text{g}/\text{kg}$ ):
  - less LH suppression implies more GnRH
  - more LH suppression implies less GnRH

# Calculation of % Inhibition from Baseline

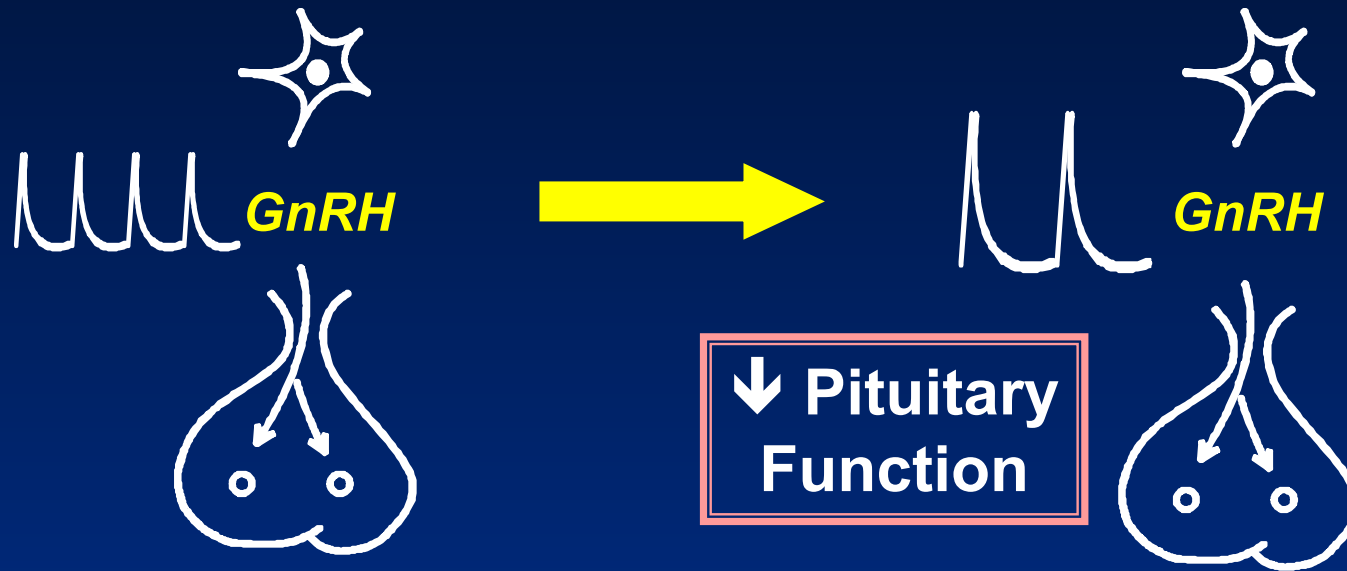
**NAL-GLU GnRH Antagonist  
5  $\mu\text{g}/\text{kg}$**



# Less LH Suppression with GnRH Antagonist = More Endogenous GnRH Secreted in Older vs Younger PMW



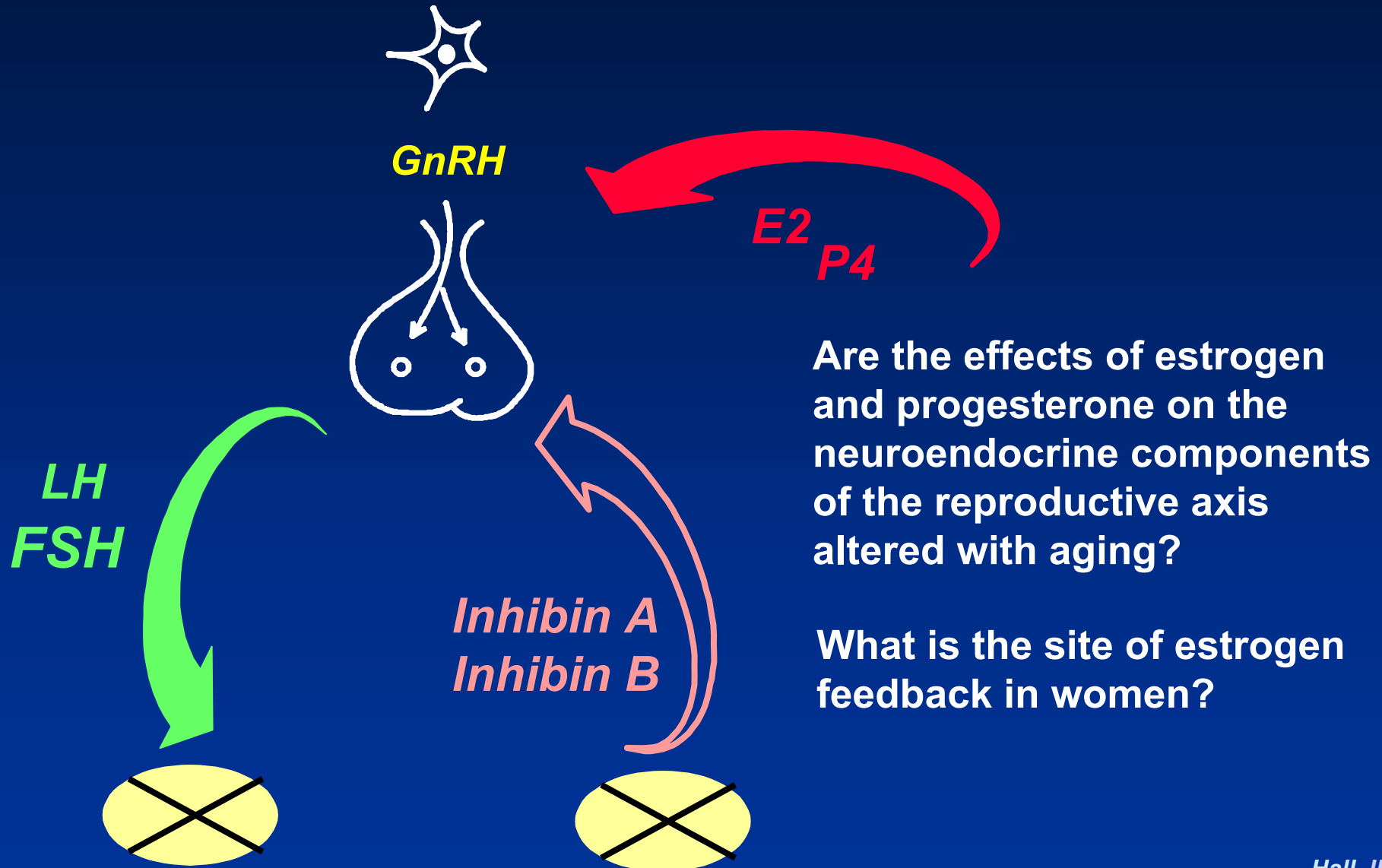
# Neuroendocrine Changes with Aging



- Slowing of GnRH pulse frequency
  - Increase in overall amount of GnRH secretion
- ⇒ neuronal plasticity into the 8th decade
- ⇒ significant effect of aging at the pituitary level

# Postmenopausal Women: a unique model in which to examine the effects of aging on the brain

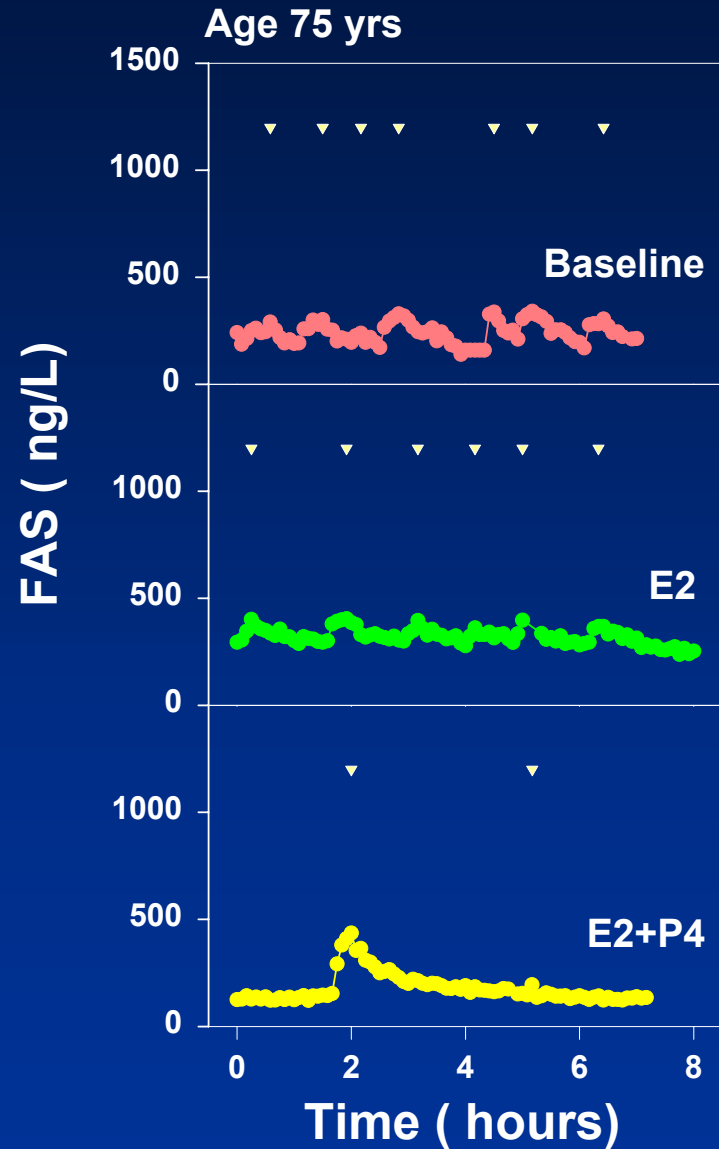
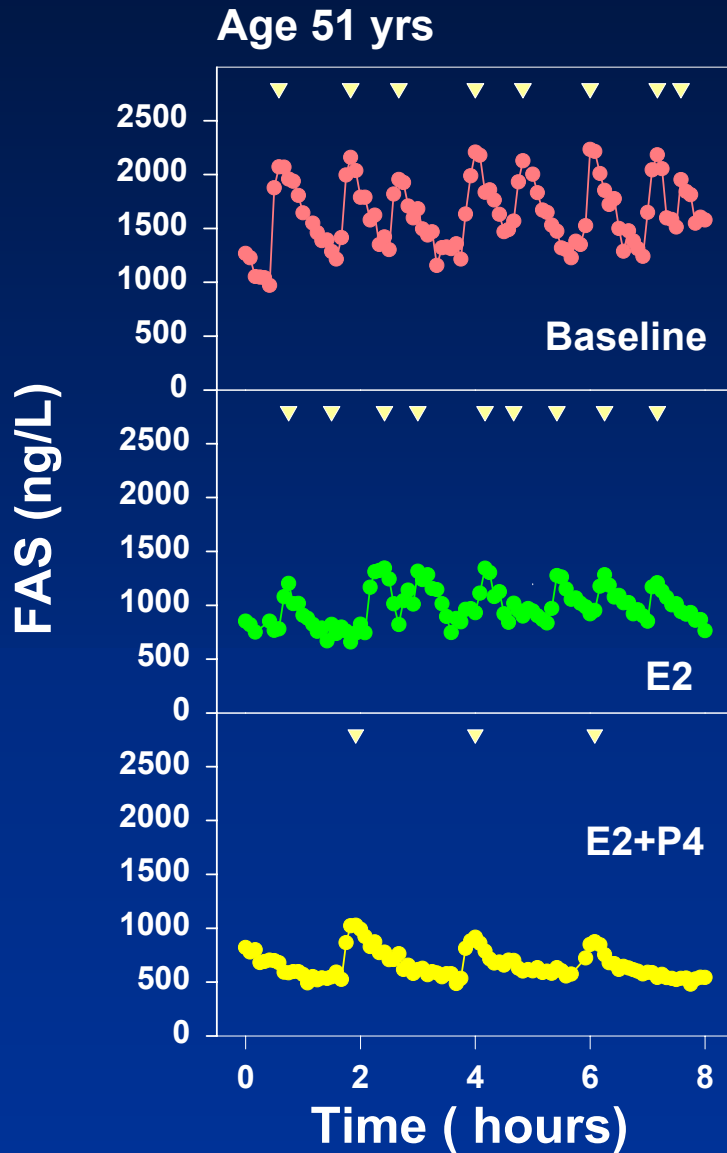
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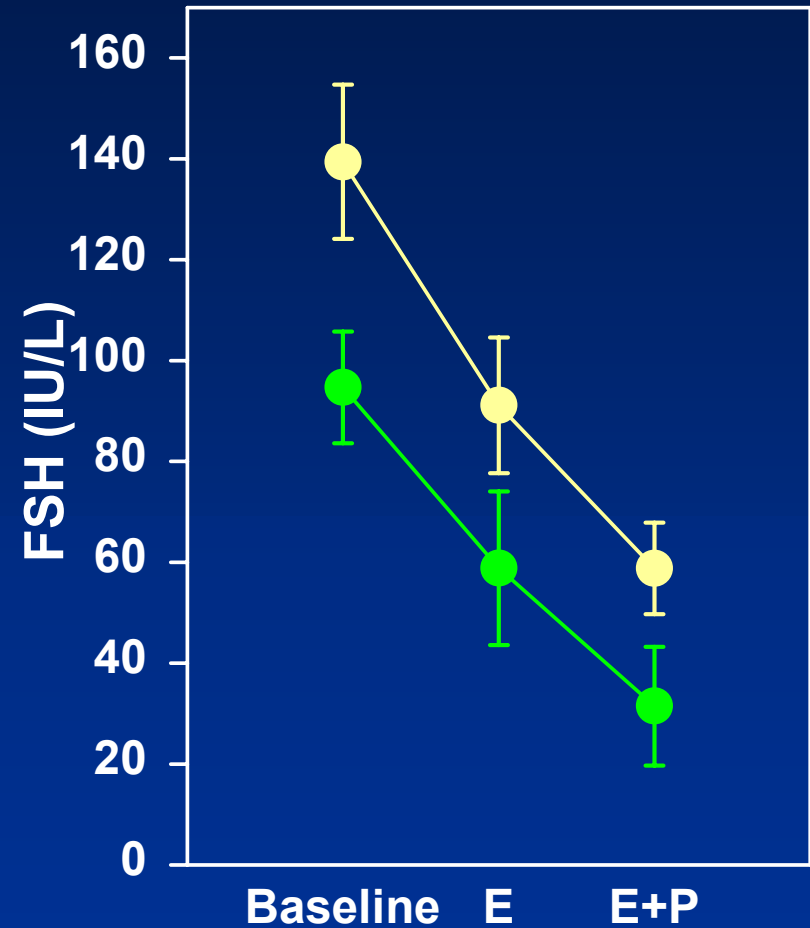
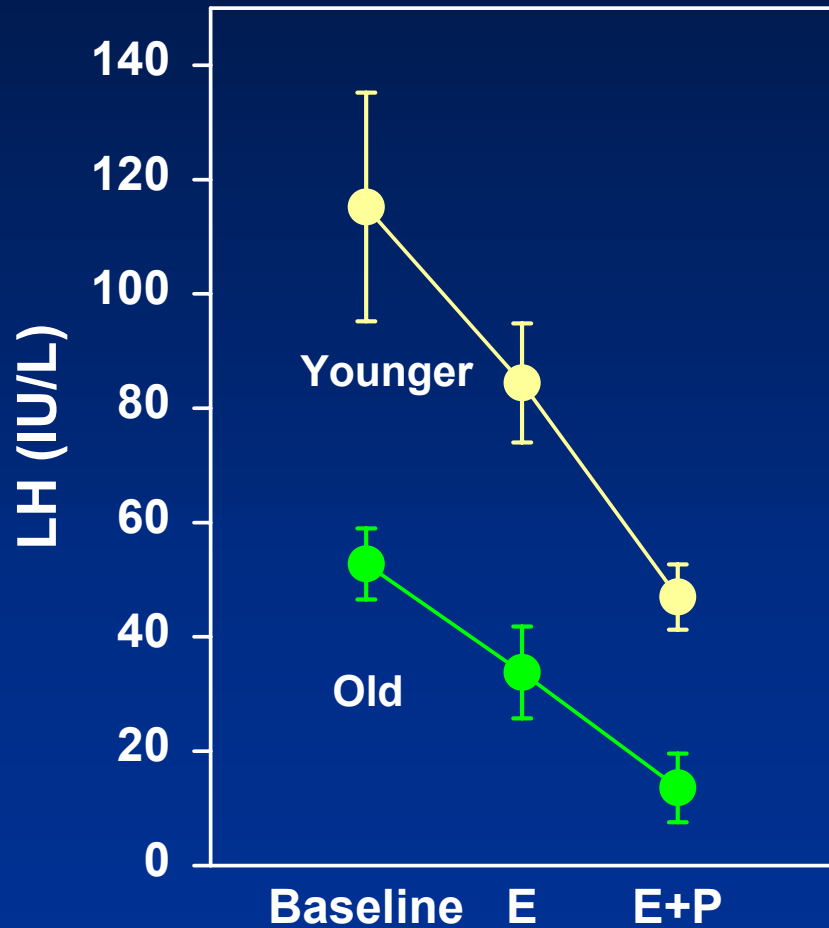
Are the effects of estrogen and progesterone on the neuroendocrine components of the reproductive axis altered with aging?

What is the site of estrogen feedback in women?

# Response to Gonadal Steroids in Postmenopausal Women

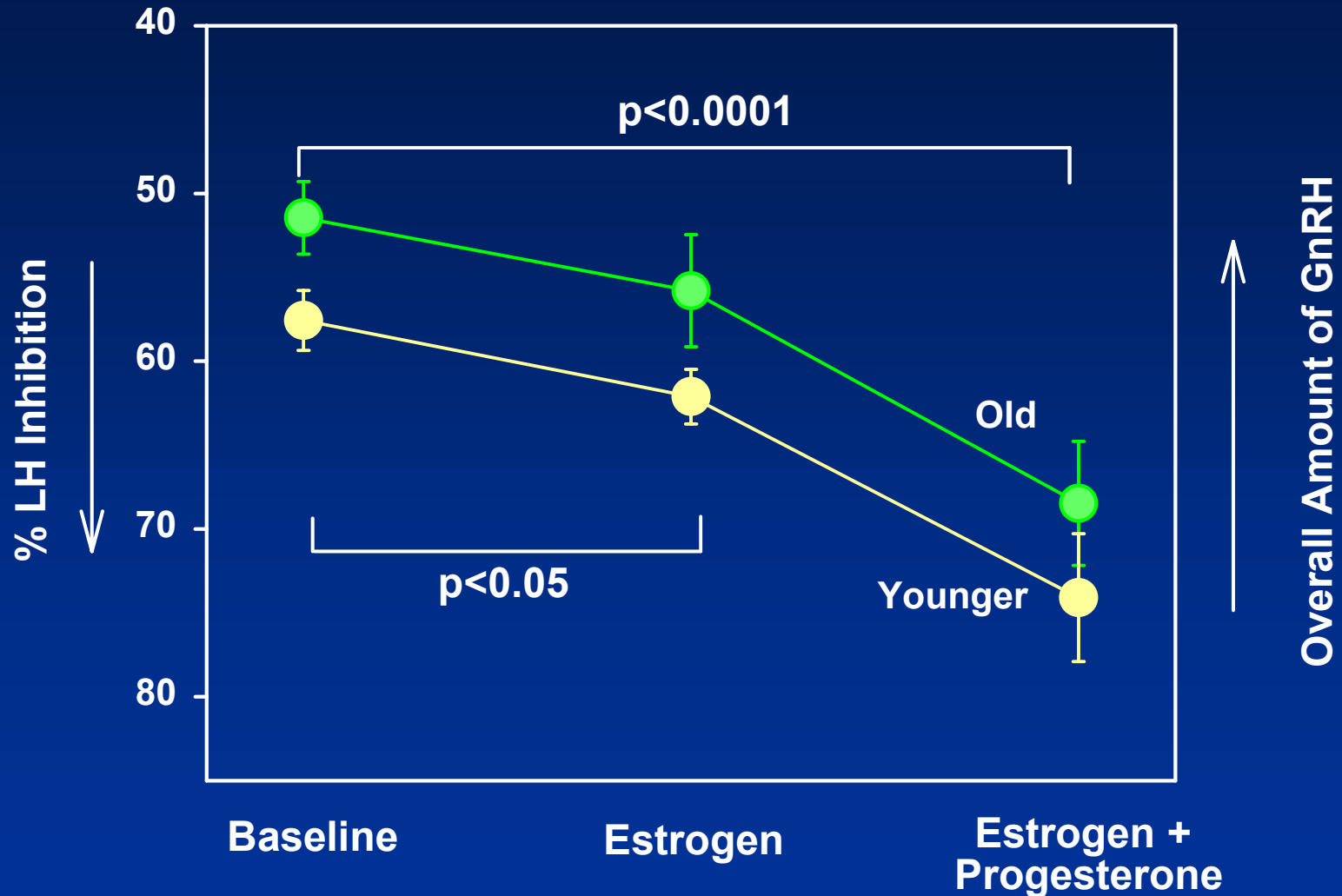


# Negative Feedback of Gonadal Steroids on Gonadotropins is Preserved with Aging





# Negative Feedback of Gonadal Steroids on the Overall Amount of GnRH Secreted is Preserved with Aging



# Hormonal Dynamics of the Reproductive System: Changes with Aging

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- 1. Changes in the hypothalamic and pituitary components of the reproductive axis occur with aging in women**
  - do these contribute to the ultimate loss of reproductive function?
  - Do these changes in gonadotropin secretion and function have effects outside the reproductive system?
- 2. The reproductive axis in women provides a unique window through which to examine the effects of aging on the brain**
  - the brain remains sensitive to estrogen effects well into the 8th decade
  - opportunity to examine the effects of estrogen, SERMS and phytoestrogens