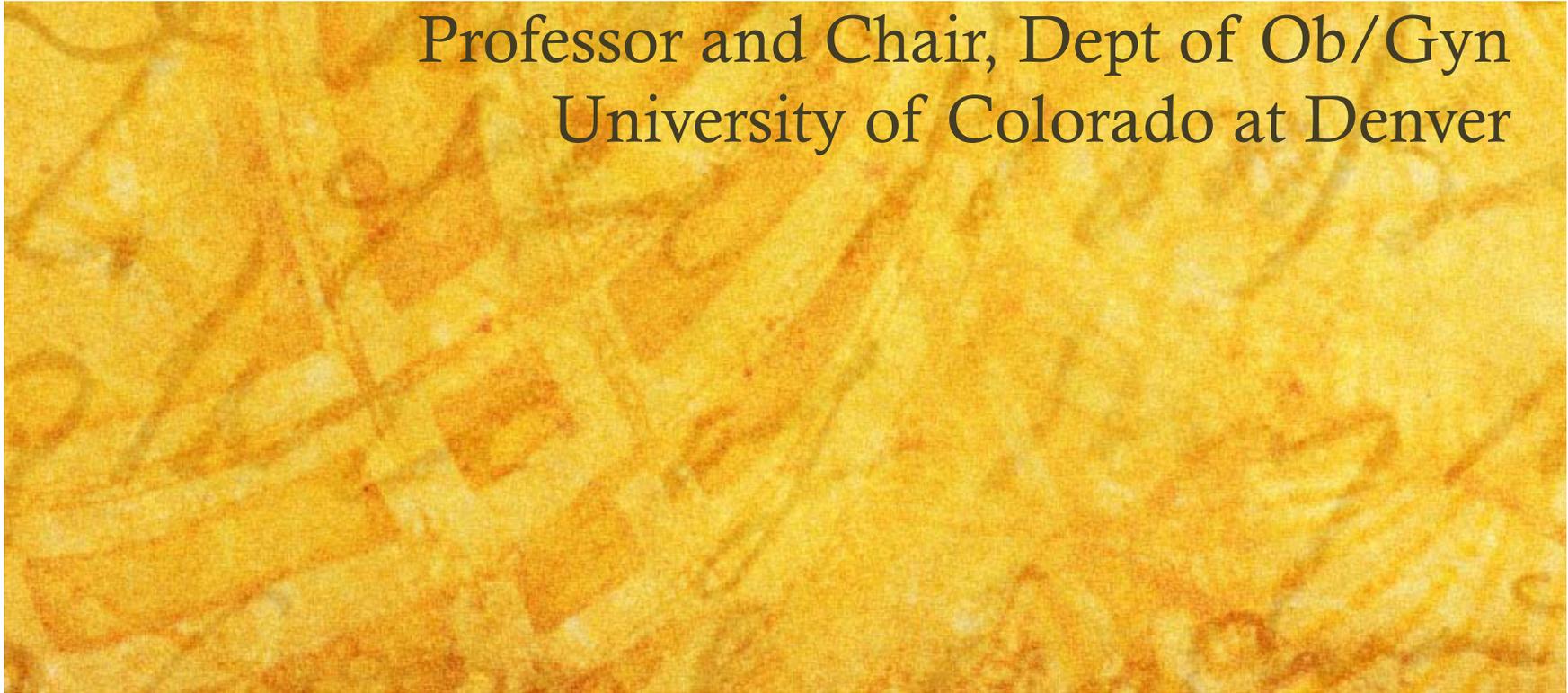




Reproductive Hormonal Changes with Aging

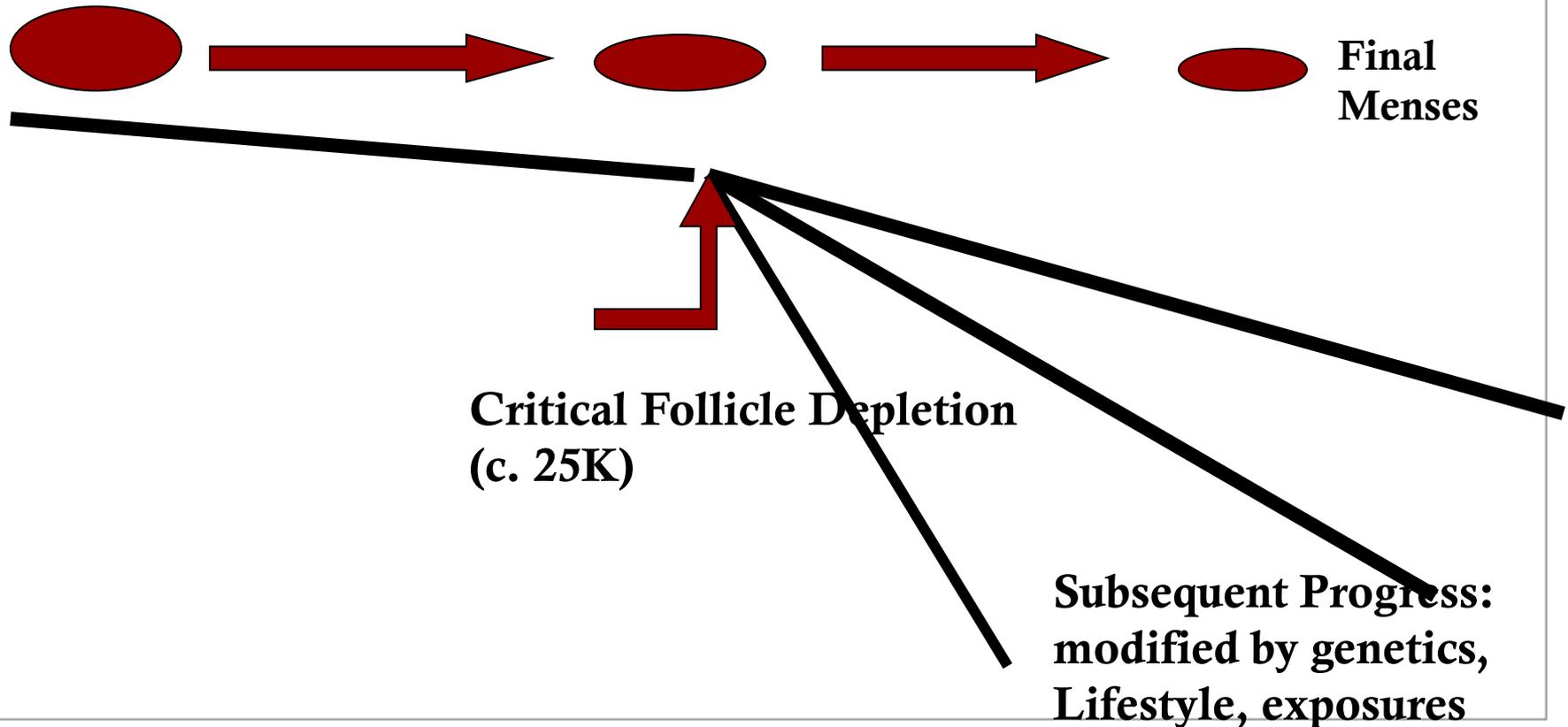
Nanette Santoro, MD

Professor and Chair, Dept of Ob/Gyn
University of Colorado at Denver



Ovarian Aging--Modifying Factors

**Midreproductive years:
Ovarian function stable**



Puberty Reproductive Yrs Transition Postmenopause



Final Menstrual Period (FMP)

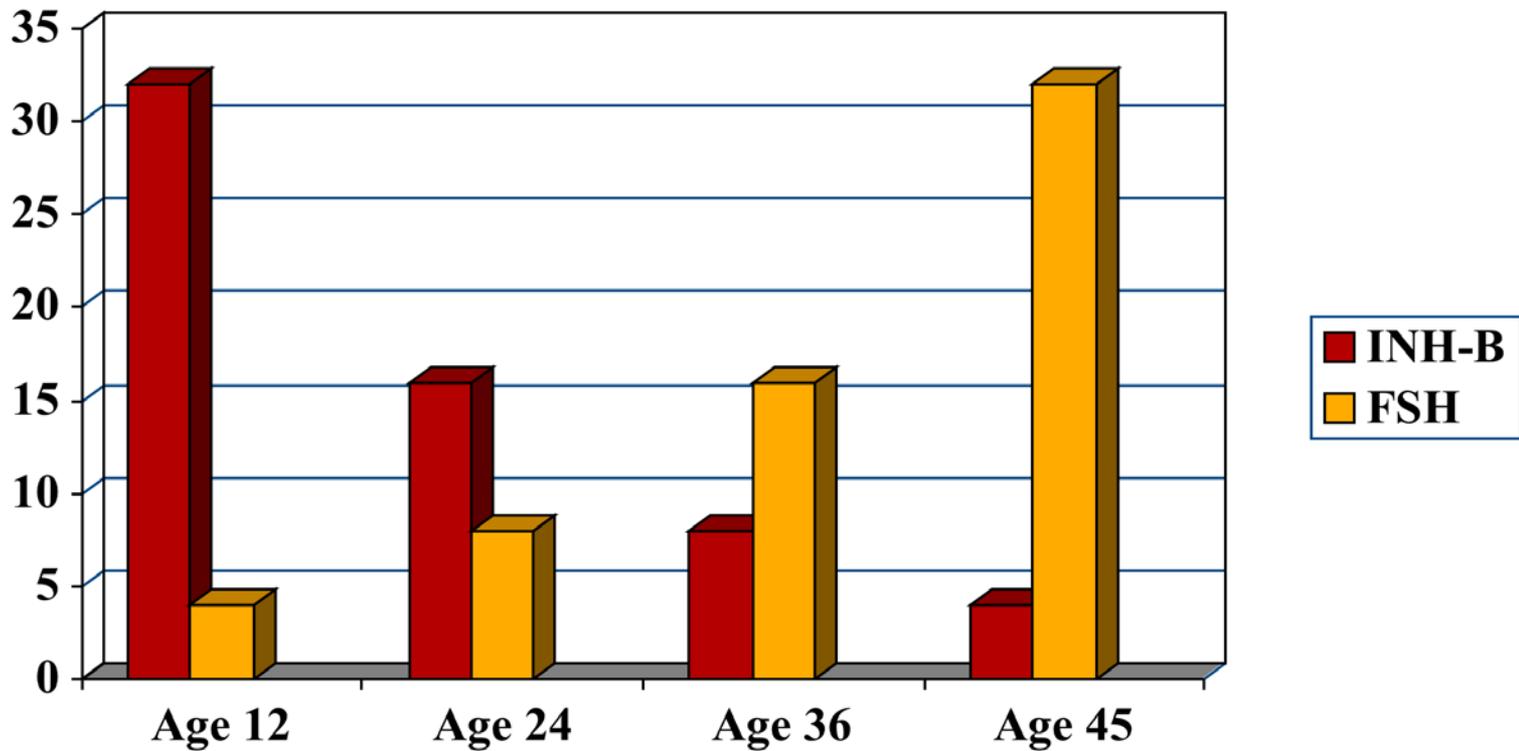


<i>Stages:</i>	-5	-4	-3	-2	-1	0	+1	+2
<i>Terminology:</i>	Reproductive			Menopausal Transition			Postmenopause	
	Early	Peak	Late	Early	Late*		Early*	Late
				Perimenopause				
<i>Duration of Stage:</i>	variable			variable		a 1 yr	b 4 yrs	until demise
<i>Menstrual Cycles:</i>	variable to regular	regular		variable cycle length (>7 days different from normal)	≥2 skipped cycles and an interval of amenorrhea (≥60 days)	Amen x 12 mos	none	
<i>Endocrine:</i>	normal FSH		↑ FSH	↑ FSH			↑ FSH	

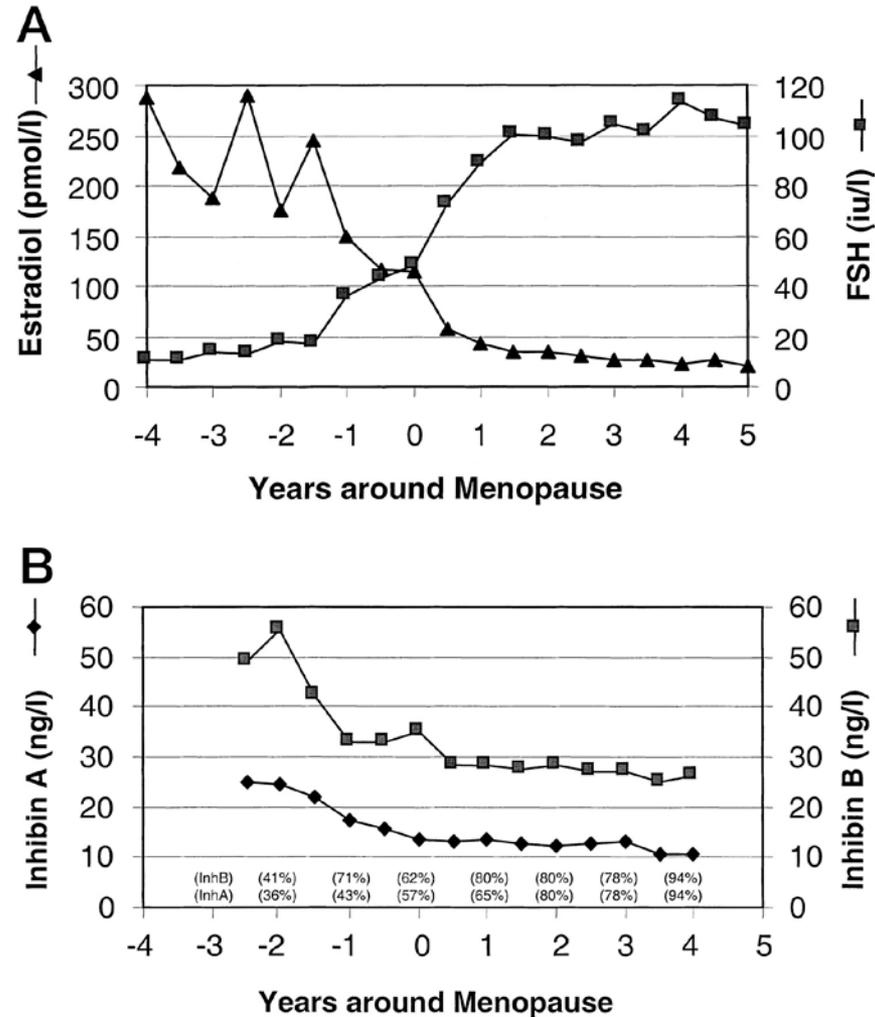
*Stages most likely to be characterized by vasomotor symptoms

↑ = elevated

The Inhibin Hypothesis



E2 and Inhibin Changes in Relation to FMP

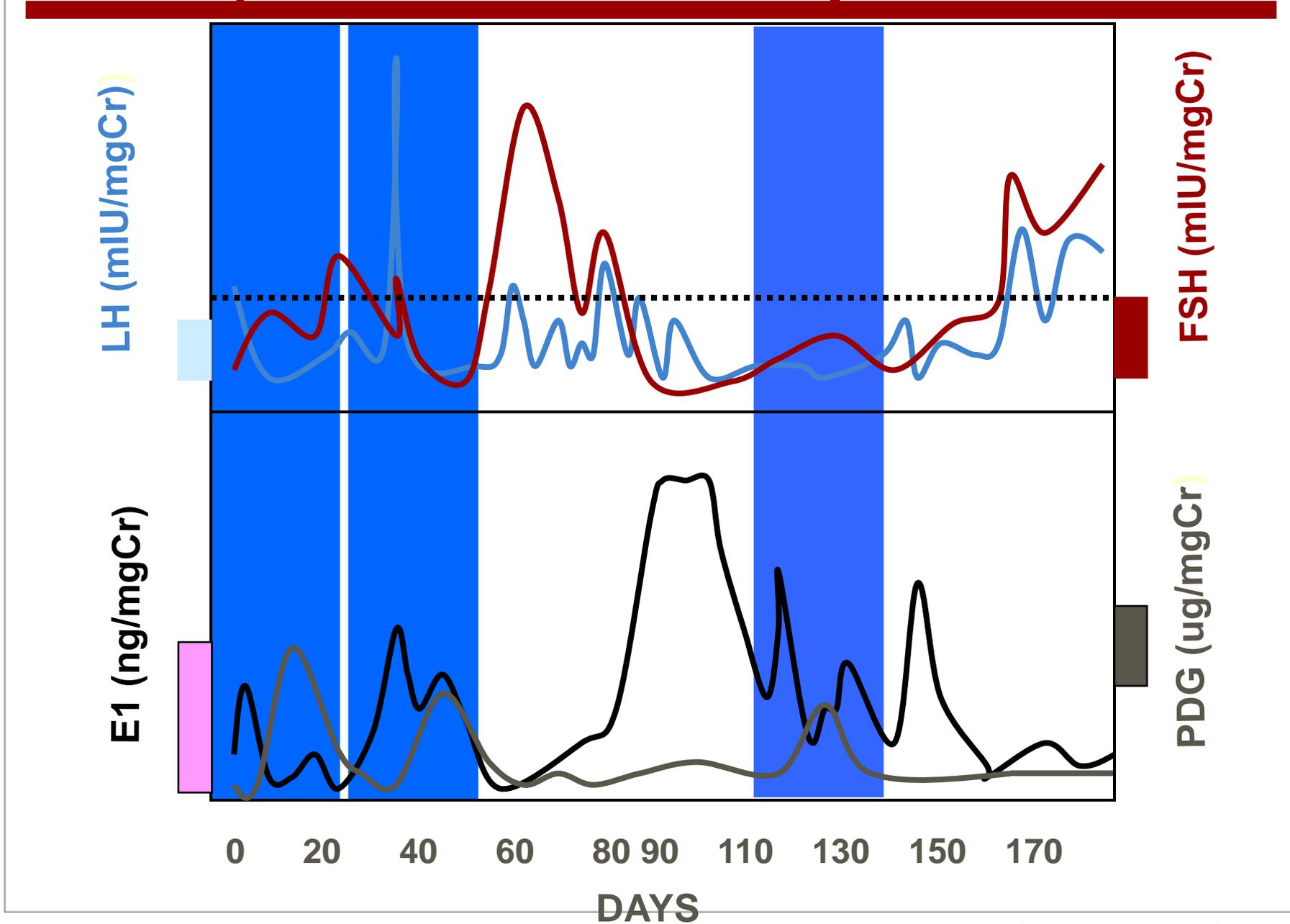


Burger, H. G. et al. J Clin Endocrinol Metab 1999;84:4025-4030

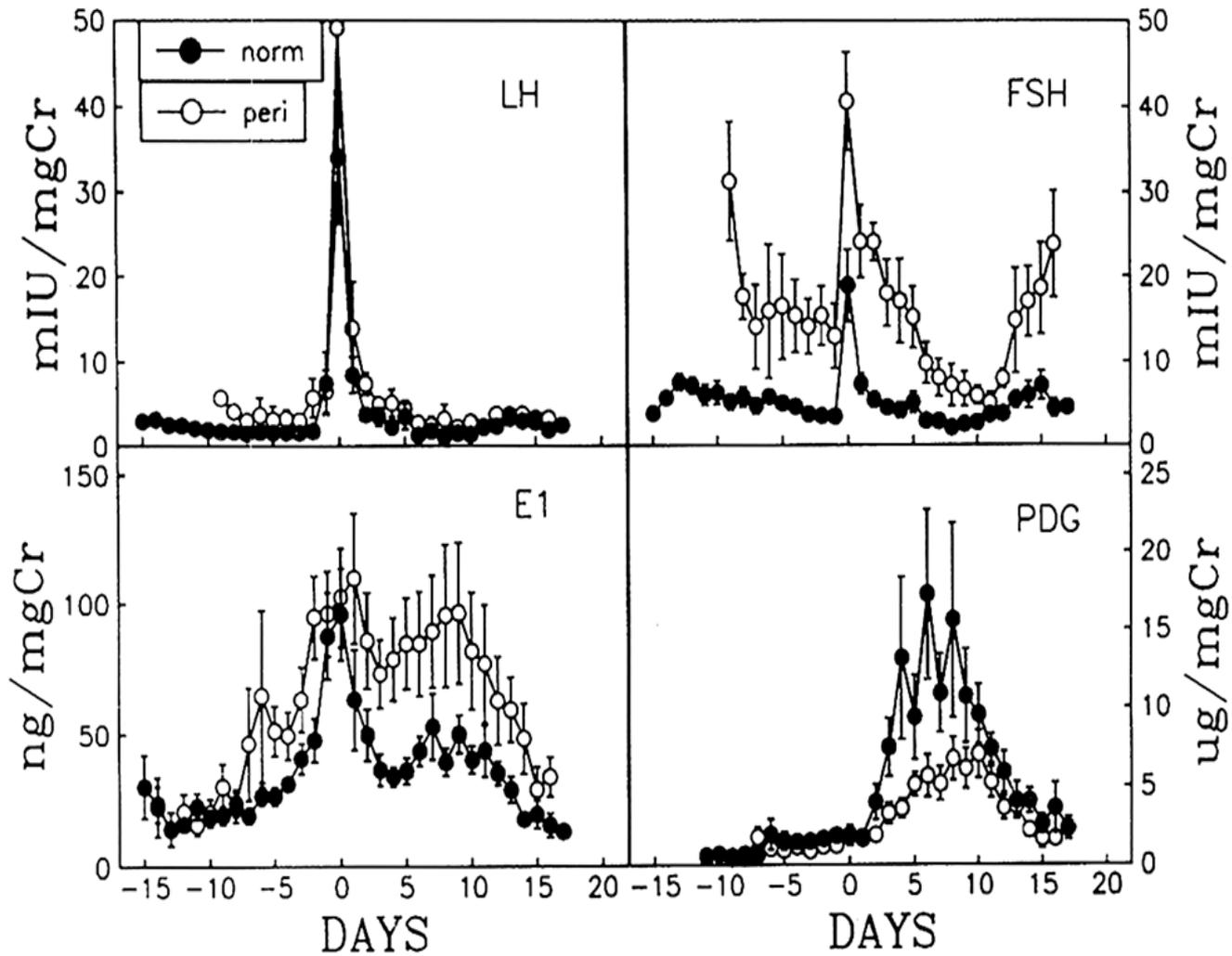
My Early Career

- Obsessed with POF—etiology and treatment
- K08 award to describe endocrine characteristics of women with POF, perimenopause and postmenopause
- Urinary hormone measurement: non-invasive and appropriate for long-term longitudinal hormonal assessments

Perimenopausal Woman – urinary hormones x 6 mo



Transition Hormone Patterns



DOR: Sentinel Diagnosis

- May herald entry into POF/POI or early menopause
- May be a harbinger of genetic disease
- May be a harbinger of future health challenges
- Diagnosis goes beyond fertility concerns

Change of Focus

- New insight into physiology and symptomatology
 - The transition is NOT uniformly hypoestrogenic
 - The transition is NOT gradual—it's saccadic
 - Hormone patterns explained symptoms/cycles
- Re-oriented to 'go where the money is'
 - Re-evaluation of hormonal changes and influences

Strategy for Further Study

- Mechanistic models
 - Physiologic probing of the system
 - Animal models
- Epidemiological models
 - Large scale studies
 - Detect associations and inform causal inference

Opportunity Knocks 1994

- SWAN, the Study of Women's Health Across the Nation
 - RFA issued in 1994
 - Independent assessment of the need for epidemiologic investigation of the menopausal transition
 - Longitudinal study cohort assembly
 - Long-term follow up planned from the start

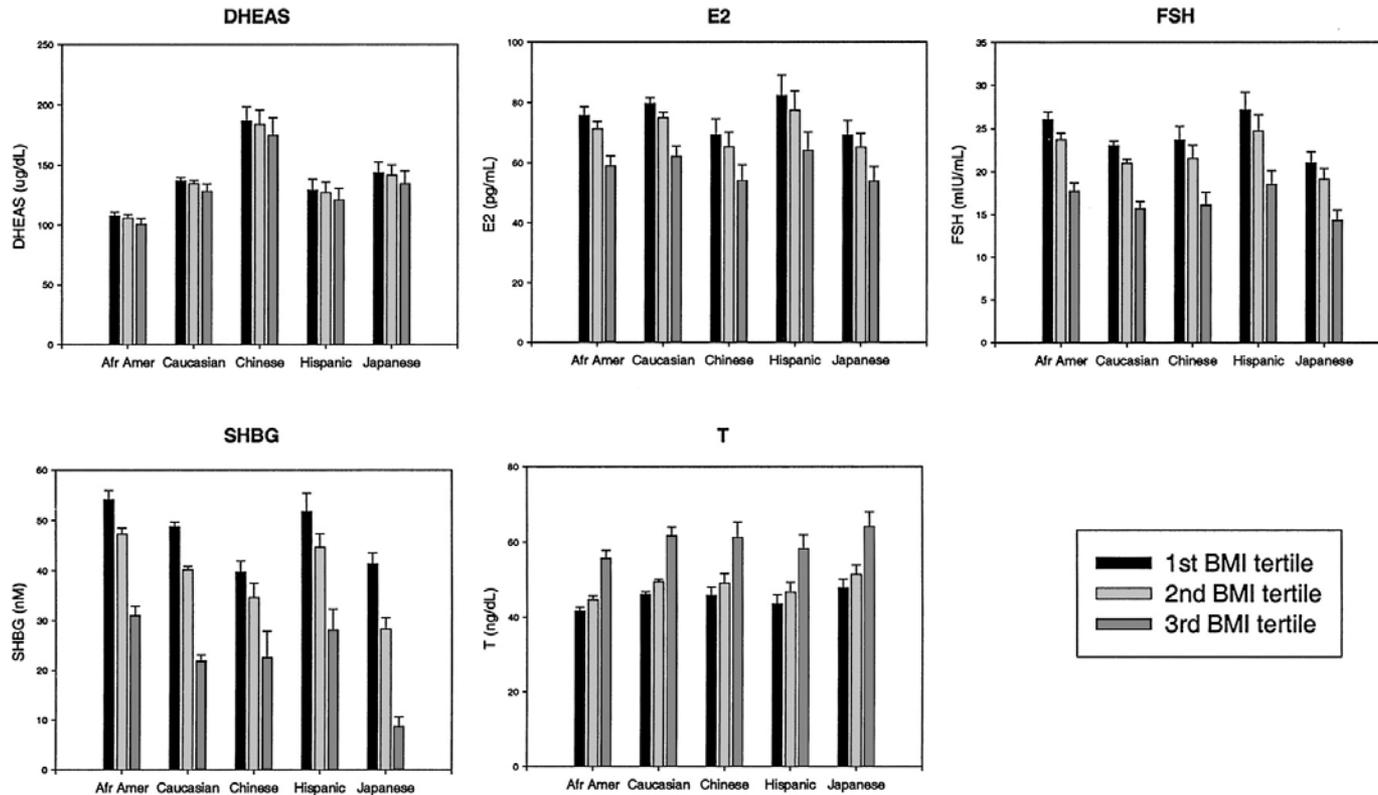
Strategy for SWAN

- Develop a local cohort
- Assess gynecologic/endocrine outcomes
- Nothing proceeded as originally planned or expected

How Epidemiology Helps

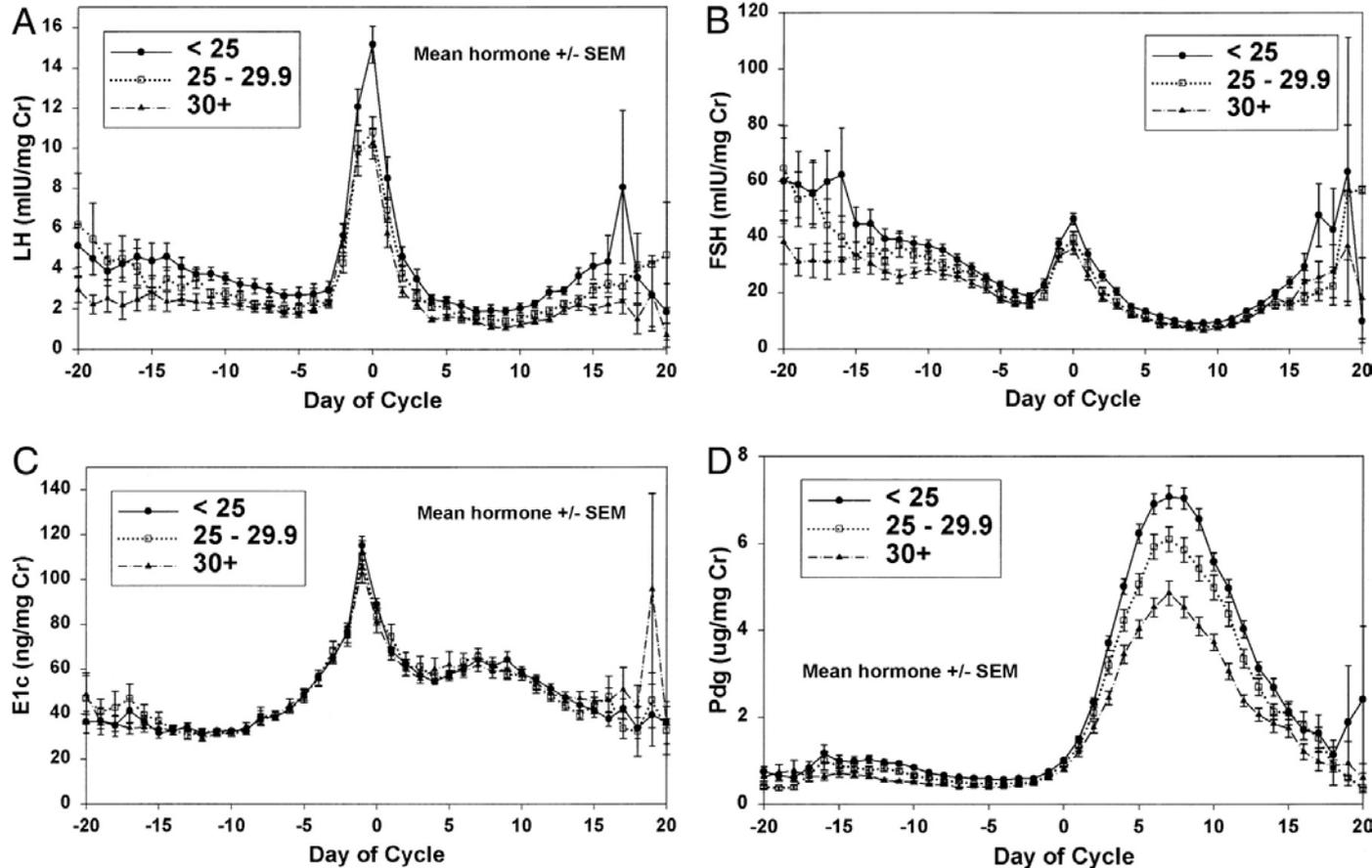
- SWAN: Daily Hormone Study
 - Volunteer subcohort (n=990) collected daily urine for one cycle or up to 50 days (whichever came first)
 - All samples measured for LH, FSH, E1c Pd_g and creatinine
- Initial analyses yielded previously unappreciated findings

Serum FSH and E2 Decrease with Increasing BMI in Women



Randolph, J. F. et al. *J Clin Endocrinol Metab* 2003;88:1516-1522

Daily urinary hormones in women with BMIs <25 kg/m², 25-29.9 kg/m², and ≥30 kg/m²



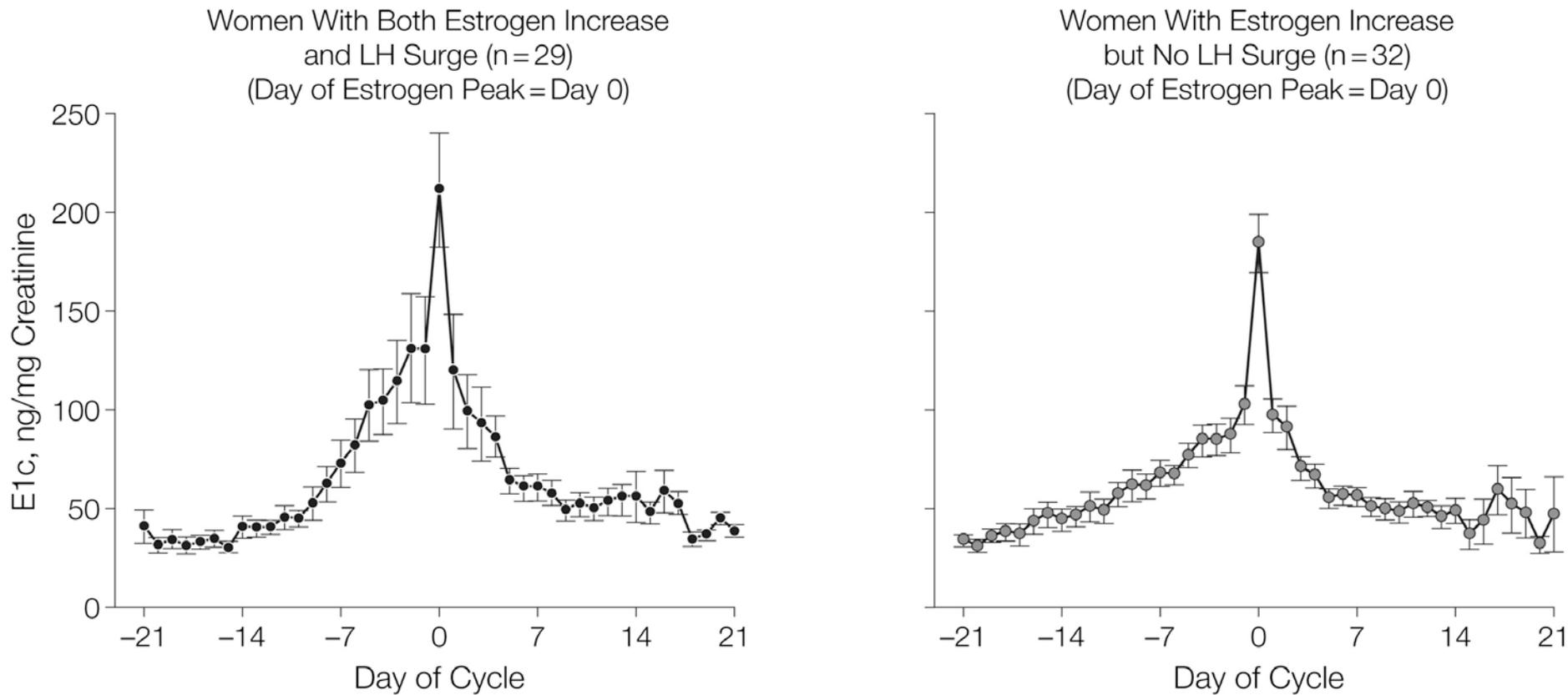
Santoro, N. et al. J Clin Endocrinol Metab 2004;89:2622-2631

What About the Mechanisms?

- Animal models
 - Difficult to establish
 - Currently being worked on in basic science labs (Gore, Neal-Perry, Rance)
- Physiologic probing in humans
 - Difficult to probe CNS mechanisms
 - Reproductive hormonal aberrations do not seem to lead to increased bleeding—Hypothesis not correct
 - Regrouping



Figure 2. Daily Urinary E1c Levels in Anovulatory Older Reproductive-Age Women With Estrogen Increases



Comparison of E1c levels (estrone conjugates) in women who had an LH surge (group 1) (left panel) vs those who did not (group 2) (right panel). E1c levels (mean [SEM]) for women with both estrogen increases and LH surges are shown here, where day 0 is the day of maximum E1c.

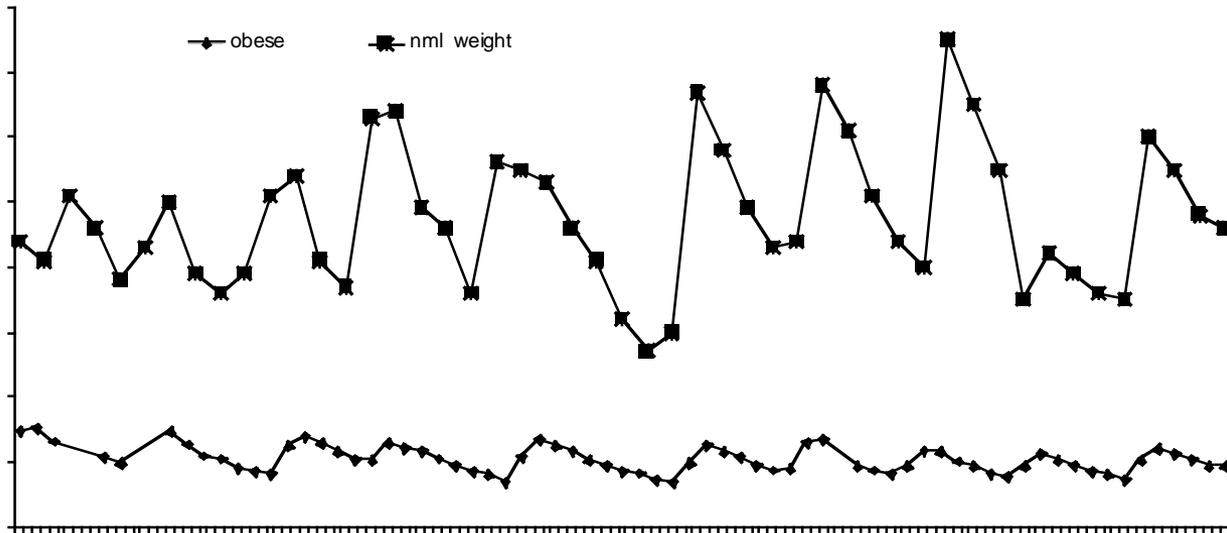
K24 Mid-Career Award

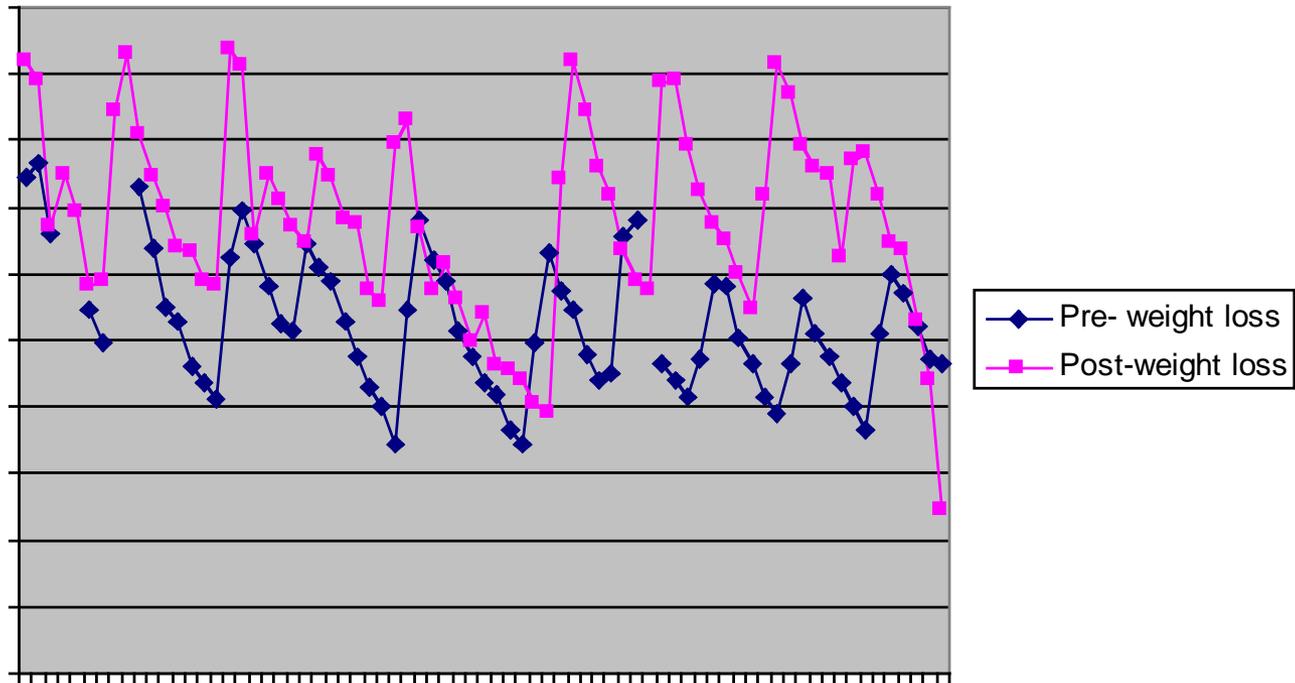
- Most productive grant I've ever had
- 27 publications in first funding period
- 27 proteges trained on the proposal
- Must have primary NIH grant as PI to qualify
- Renewable x 1

Opportunity Knocks 2004

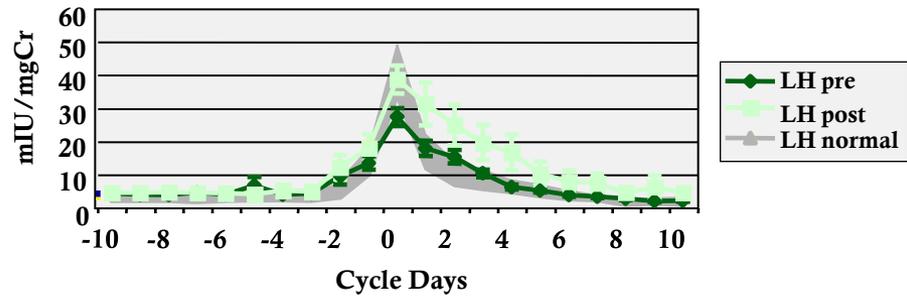
- Link between reproductive hormones and obesity beginning to be appreciated
- Fertility severely compromised in obese women (Gesink-Law, Polotsky)
- Obesity epidemic gaining major attention
- Exploratory grant to examine effects of weight loss on hormone profiles

Representative LH Pattern in Normal Weight vs Obese Woman

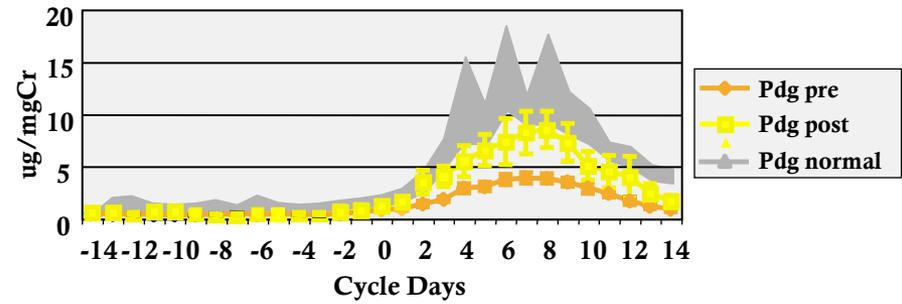




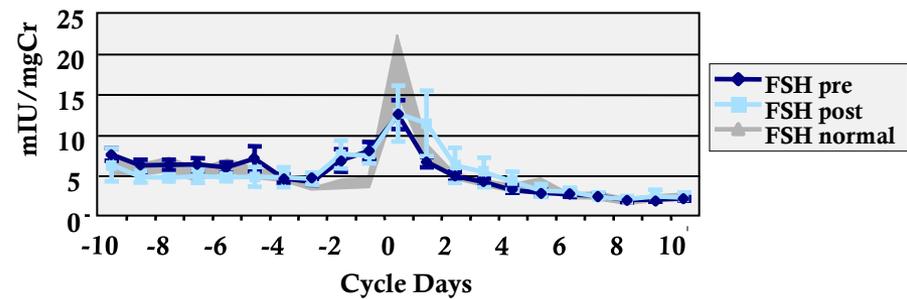
LH



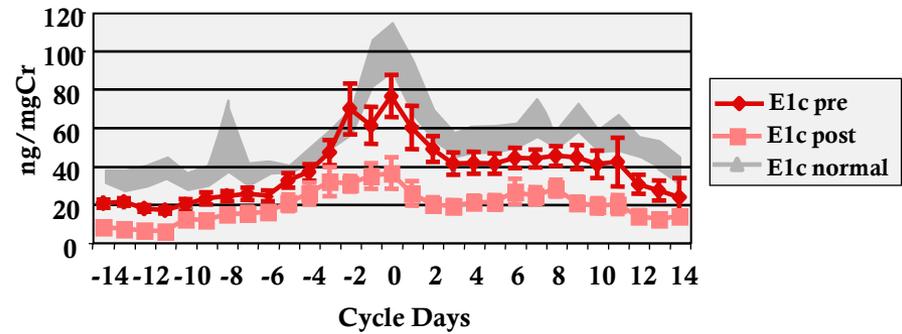
Pdg



FSH



E1c



Role of Estrogen Feedback

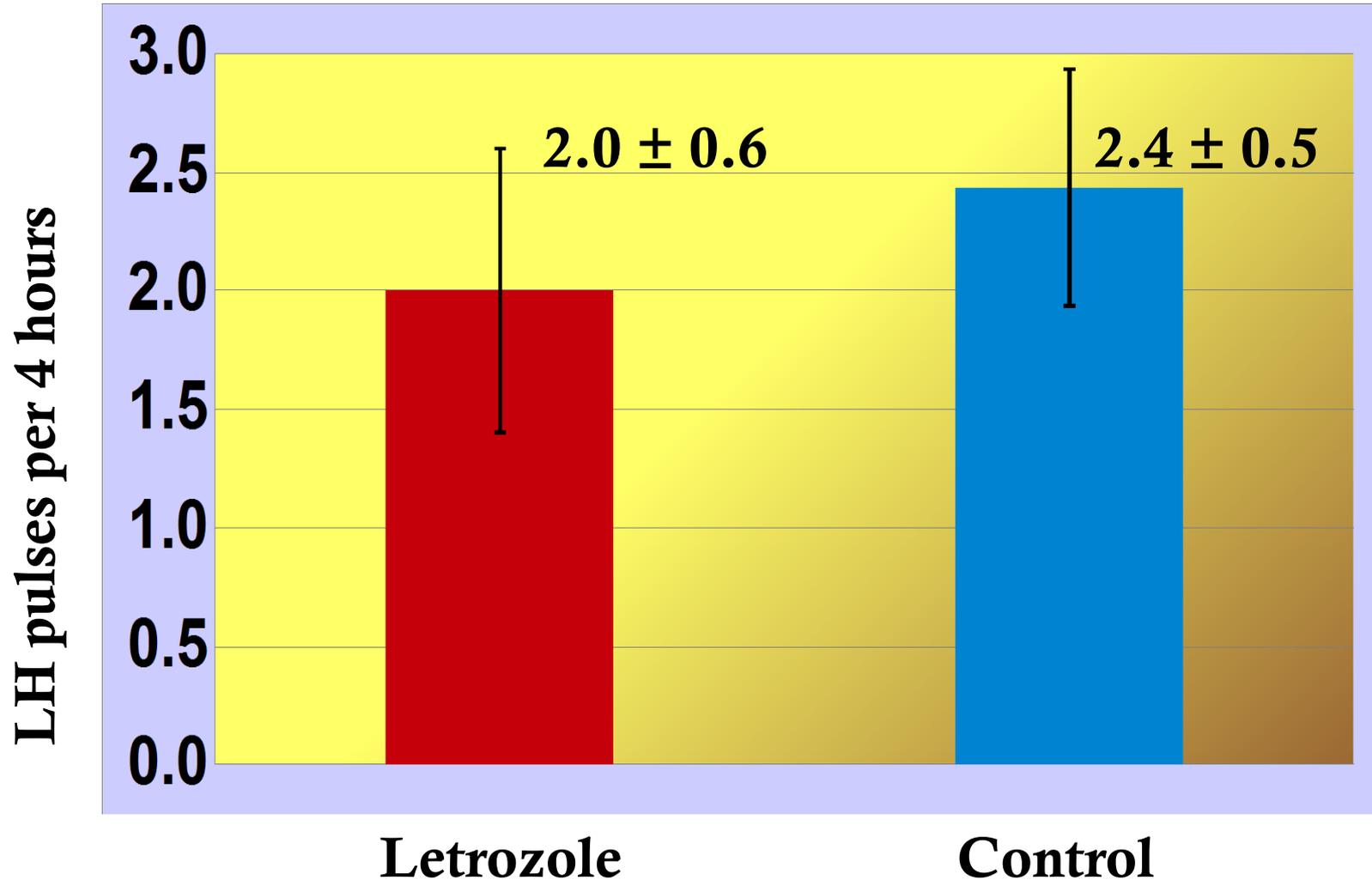
- Local estradiol may be responsible for blunting of LH pulsatility in obesity
- If so, then aromatase inhibition may be an ideal way to 'query' the system

Participants

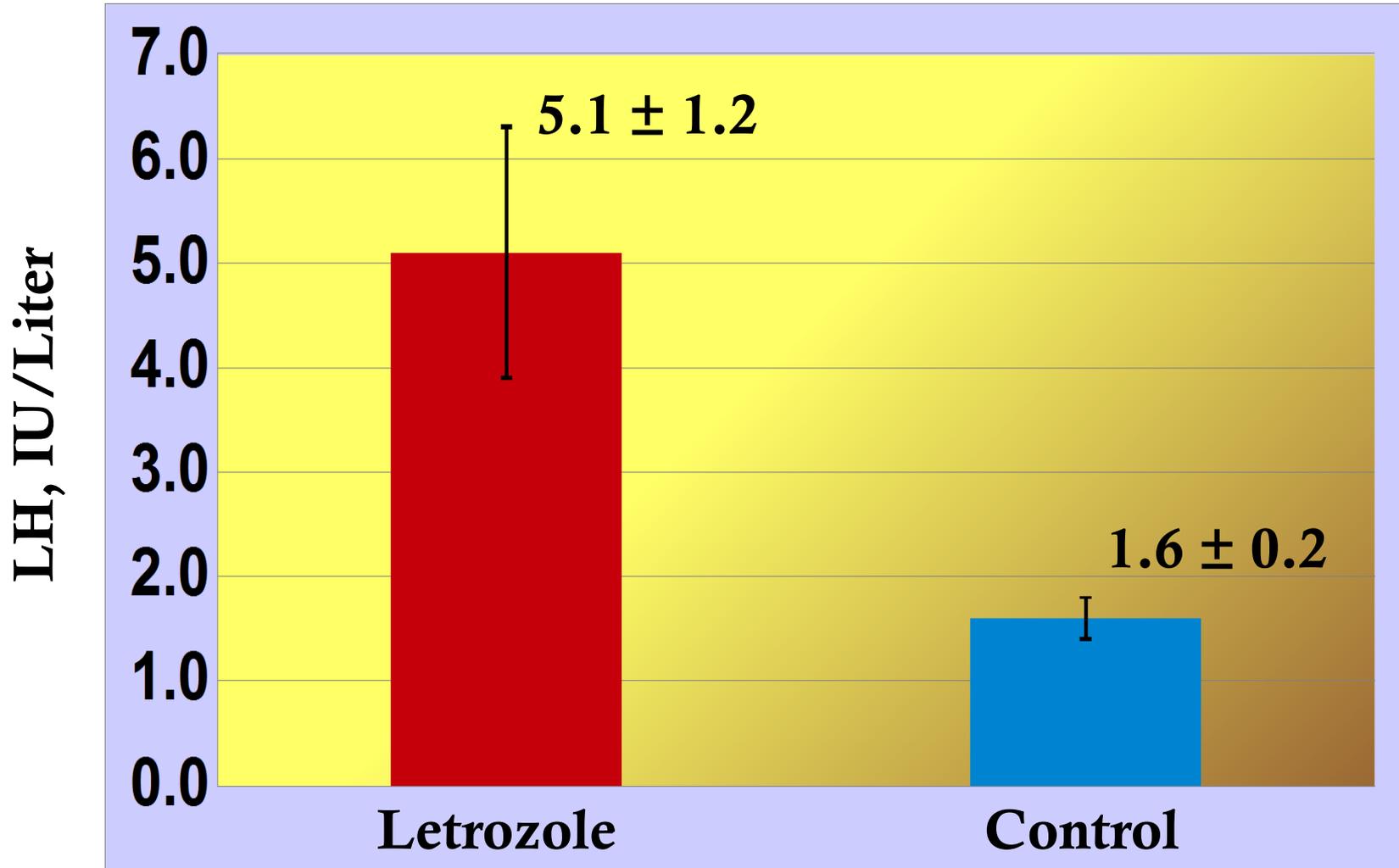
	Letrozole n=5	Control n=12	P
Age, years	32.3 ± 5.7	24.9 ± 4.8	0.07
BMI, kg/m²	20.6 ± 0.6	20.8 ± 1.7	0.82
Menstrual Cycle Length	29.5 ± 3.1	n/a	

LH Pulse Frequency

p = 0.4

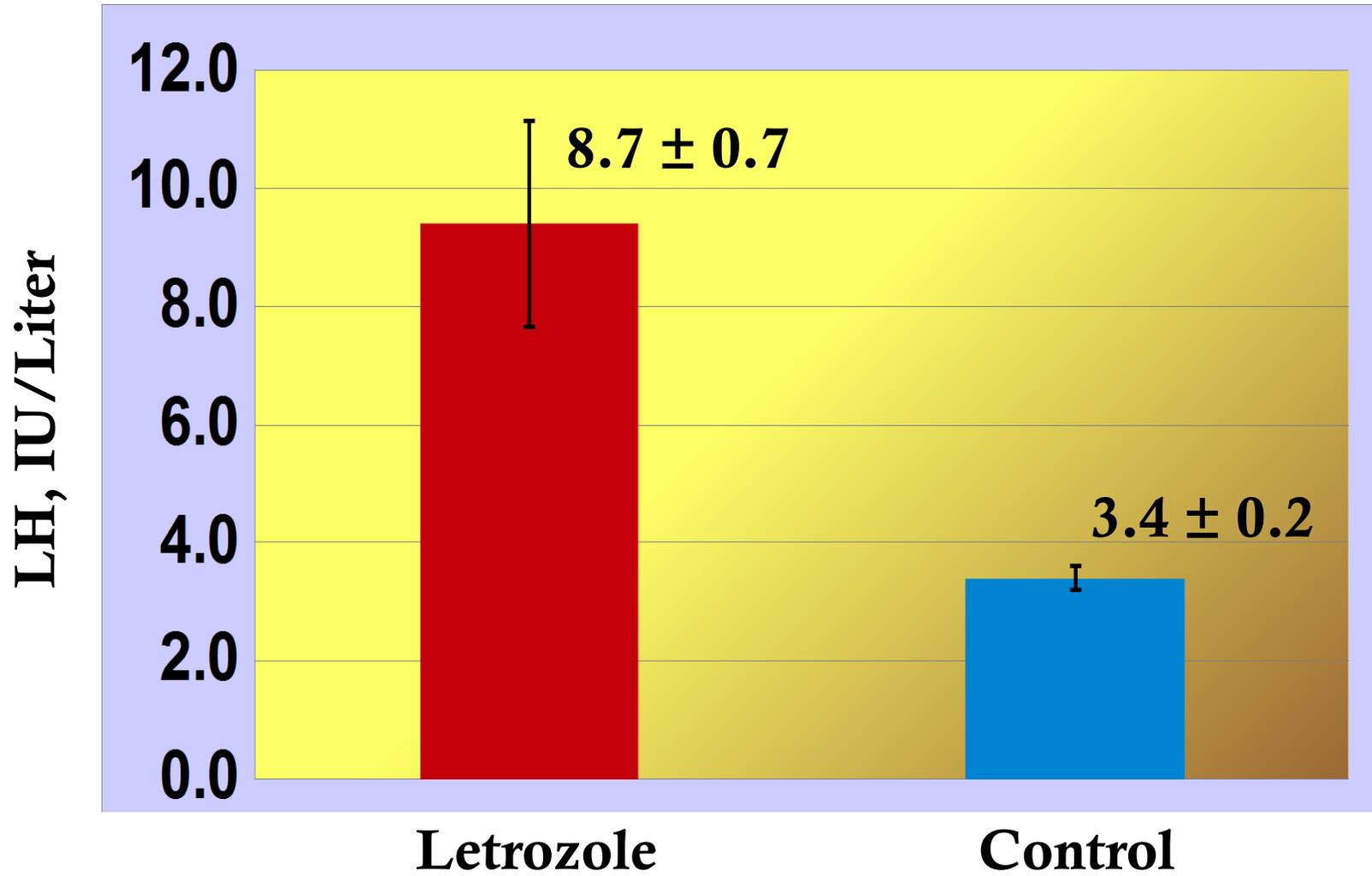


LH Pulse Amplitude *p* < 0.01



Mean Serum LH

p < 0.01



New Challenges/ New Opportunities

- Clinical Research
 - Regulatory burden
 - Role of CTSA
 - Need to collaborate
- Funding Situation
 - Will get worse before it gets better
 - Need to find alternative ways to support research
 - Need to distinguish 'physiologic' research from 'epidemiologic' research