

Post-Menarchal Adolescent Girls Demonstrate Multi-Level Reproductive Axis Immaturity

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Introduction

Irregular menstrual periods are very common in the first few years after menarche due to reproductive axis immaturity. While acquisition of estradiol positive feedback (E2+FB) has been proposed as the last step in reproductive development, even premenarchal girls have normal, spontaneous mid-cycle surges (MCS). We hypothesized that delayed maturation of other reproductive axis components explain menstrual irregularity in adolescent girls.

Research Protocol

Participants

- 23 adolescent girls, 12.8 – 17.6 years old
- BMI percentile 41st – 99th; 58% overweight/obese
- 0.4 – 3.5 years post-menarchal
- Normal thyroid, prolactin, and androgen levels
- No excessive exercise, eating disorders, or smoking

Measures

- Monitoring during 2 consecutive menstrual cycles
- Reproductive hormone measurements, each method 2-5x/wk:
 - serum: LH, FSH, E2, progesterone [P], inhibin B [INHB]
 - dried blood spots (DBS): LH, FSH
 - dried urine strips: E2, pregnanediol [Pd]
- Pelvic ultrasounds to document follicle growth and ovulation

Statistical Methods

Standardization of Hormone Measurements

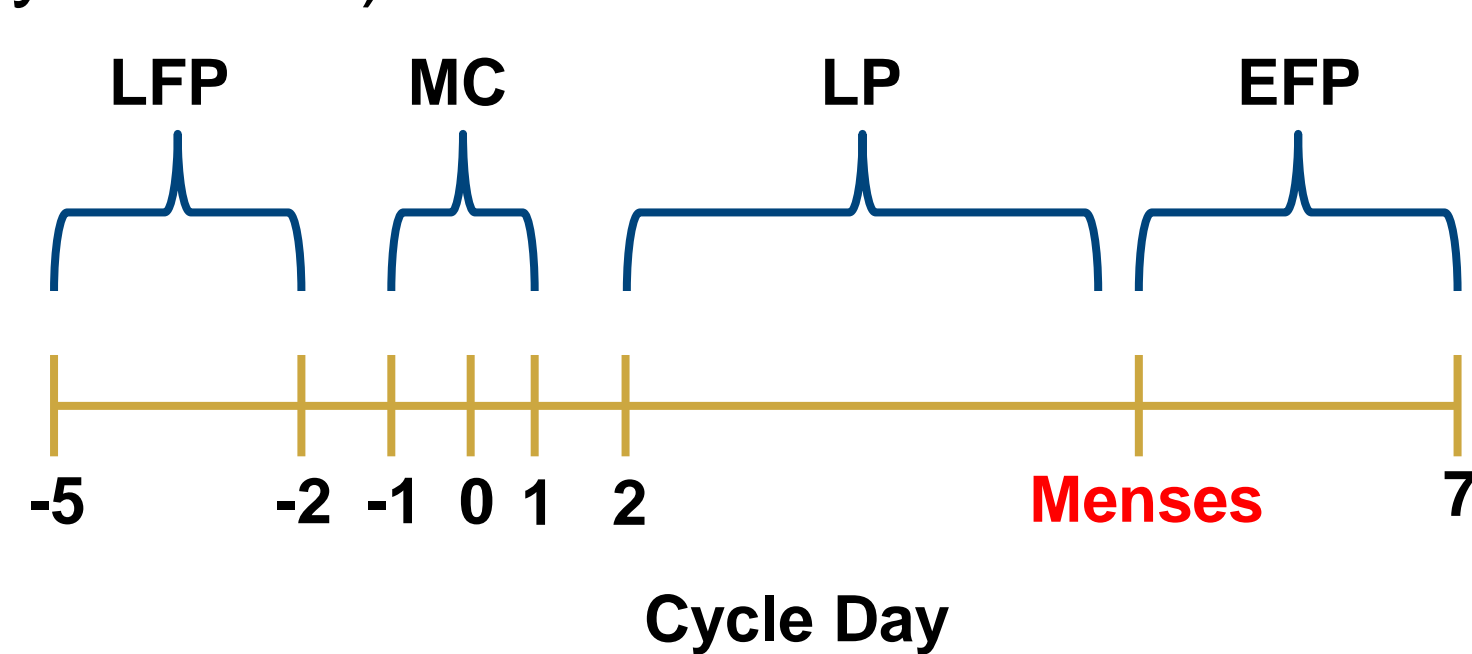
- Passing-Bablok regression to determine conversion from DBS (LH, FSH) and urine (E2) to serum

Menstrual Cycle Classification

- Short OV: ovulatory with short (<10d) luteal phase
- Normal OV: ovulatory with normal luteal phase length
- ANOV: anovulatory
 - ANOV cycles with luteinization (P ≥ 1 ng/ml) and without luteinization combined for analyses

Hormone Dynamics by Cycle Phase

- Cycle 1
- Late Follicular Phase (LFP)
 - Mid-cycle (MC) where midcycle surge = day 0
 - Luteal Phase (LP)
- Cycle 2
- Early Follicular Phase (EFP)
- Hormones compared between each adolescent subgroup and 65 ovulatory historic adult controls¹ using mixed models to account for repeated measures
 - The mid-cycle LH surge adjusted for pre-ovulatory (days -3 to 0) E2 taken as index of E2+FB



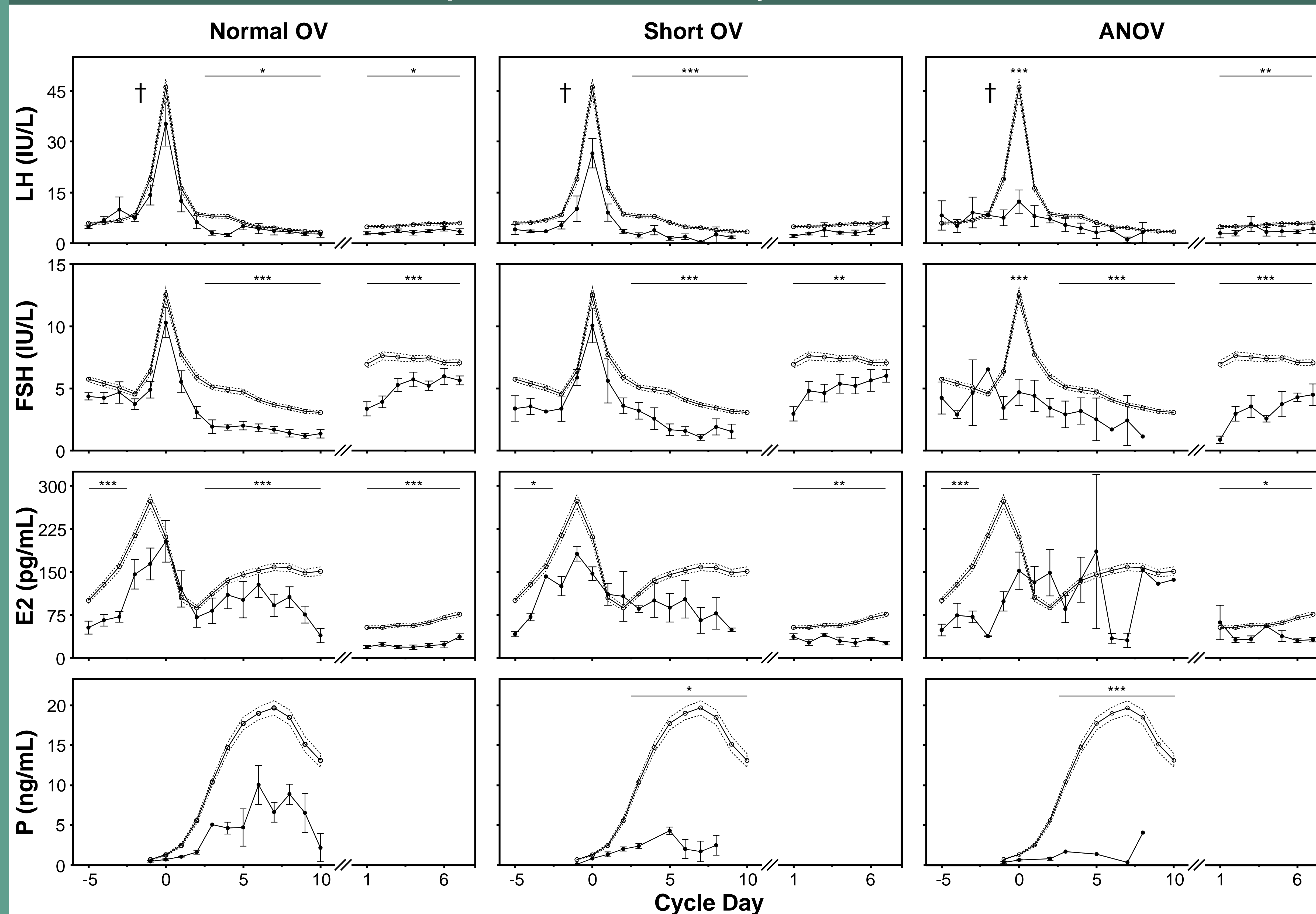
Characteristics of Adolescent Groups

	Normal OV	Short OV	ANOV (luteinization)	ANOV (no luteinization)	Difference among groups, p-value*
n	11	5	5	2	
BMI percentile	79.8 ± 9.3	78.9 ± 5.7	88.7 ± 9.7	69.8 ± 28.8	0.91
Chronologic age (yrs)	14.8 ± 0.8	14.0 ± 0.3	14.1 ± 0.4	13.7 ± 0.1	0.48
Age at menarche (yrs)	12.6 ± 0.2	12.9 ± 0.3	12.3 ± 0.3	12.8 ± 0.1	0.58
Gynecologic age (yrs)	1.9 ± 0.3	1.9 ± 0.5	1.8 ± 0.5	0.8 ± 0.04	0.68
Cycle length (days)	39.4 ± 3.9	25.2 ± 1.1	38.8 ± 5.8	28.5 ± 8.5	0.10
Follicular phase length (days)	27.8 ± 4.0	17.4 ± 1.2	—	—	0.11
Luteal phase length (days)	11.6 ± 0.4	7.8 ± 0.8	—	—	—†
Peak serum progesterone (ng/mL)	7.1 ± 1.3	3.4 ± 0.4	1.8 ± 0.5	0.4 ± 0.2	—†
Peak urine pregnanediol (mcg/g Cr)	1276.7 ± 153.9	588.0 ± 89.0	377.0 ± 81.5	165.0 ± 35.0	—†

All values presented as mean ± SE.

*ANOV girls with and without luteinization combined; †Used in definition of adolescent groups.

Adolescents Demonstrate Diminished LH and FSH Secretion and Luteal Insufficiency Compared with 65 Ovulatory Adult Women

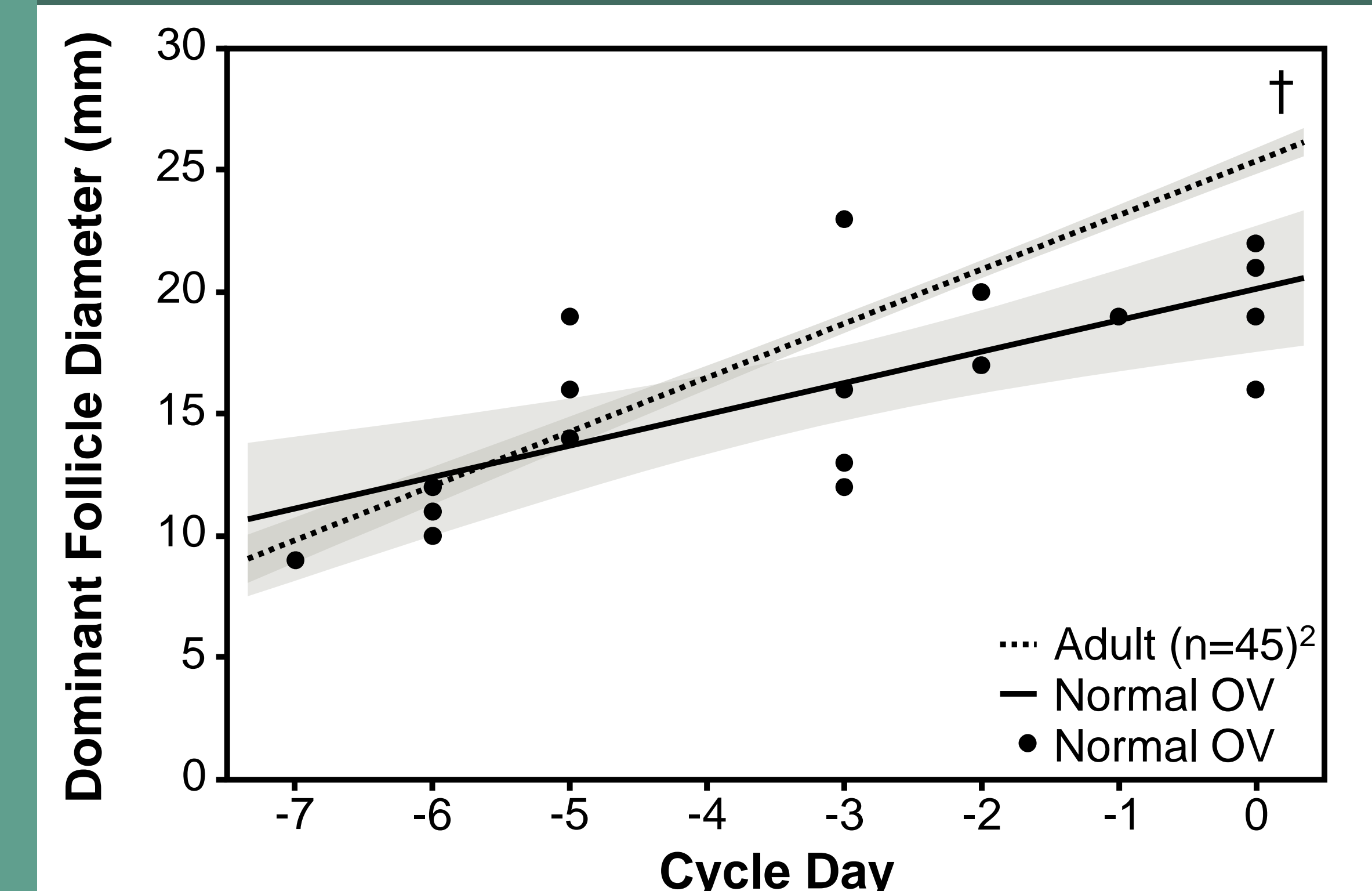


(O) Adults, (●) Adolescents. Dashed lines (adults) and error bars (adolescents) represent ± SE.

†Mid-cycle LH adjusted for pre-ovulatory E2 was similar to adults in normal OV (p=0.3) but lower than adults in ANOV (p<0.01) with a similar trend in short OV (p<0.09).

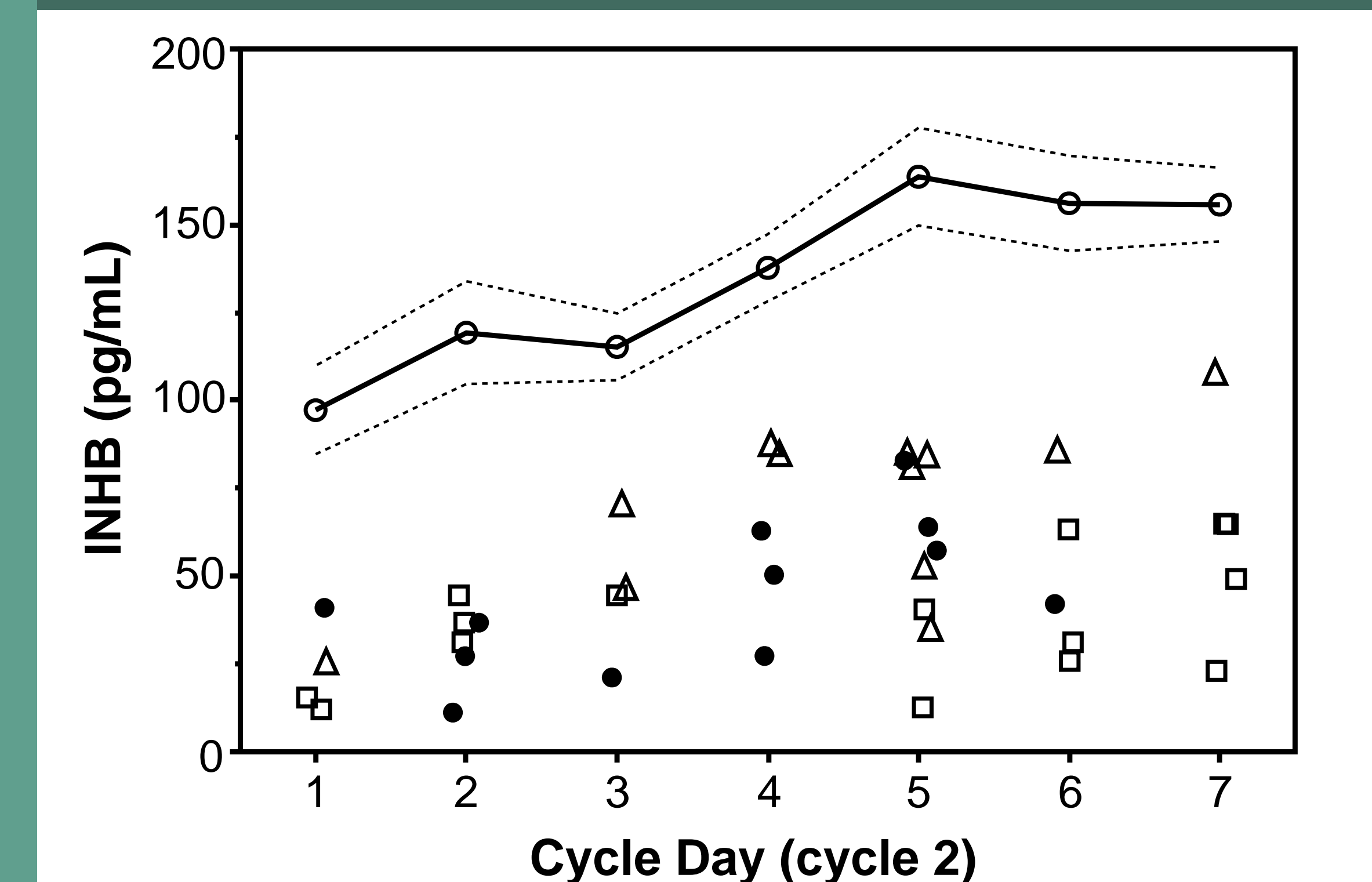
* p<0.05, ** p<0.01, *** p<0.001 for cycle phase (i.e. LFP, MC, LP, EFP) from mixed model analysis.

Normal OV Adolescents Have Slower Follicular Growth Rates than Adults



Regression lines and 95% confidence bands were estimated from a linear mixed model. †Difference between regression lines, p<0.001. (●) individual data points for normal OV adolescents.

Early Follicular Phase INHB Levels are Lower in Adolescents than in Adults



Adult means (O) ± SE (dashed lines) from a subset (n = 11).³ Adolescent individual data points, normal OV (●), short OV (Δ), or ANOV (□). P<0.05 for all comparisons with adults after adjusting for FSH.

Conclusions

- E2+FB is intact in normal OV but remains impaired in short OV and ANOV girls
- Normal OV girls have immature FSH dynamics and follicle growth; they also show luteal insufficiency and decreased ovarian responsiveness to FSH
- These findings suggest the final stage of reproductive axis maturity entails coordinated development of brain and ovary

1. Taylor AE, Whitney H, Hall JE, Martin K, Crowley WF, Jr. *JCEM* 1995; 80:1541-1547.

2. Adams JM, Taylor AE, Crowley WF, Jr., Hall JE. *JCEM* 2004; 89:4343-4350.

3. Welt CK, McNicholl DJ, Taylor AE, Hall JE. *JCEM* 1999; 84:105-111.

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