THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Reproductive Health and Pituitary Disease

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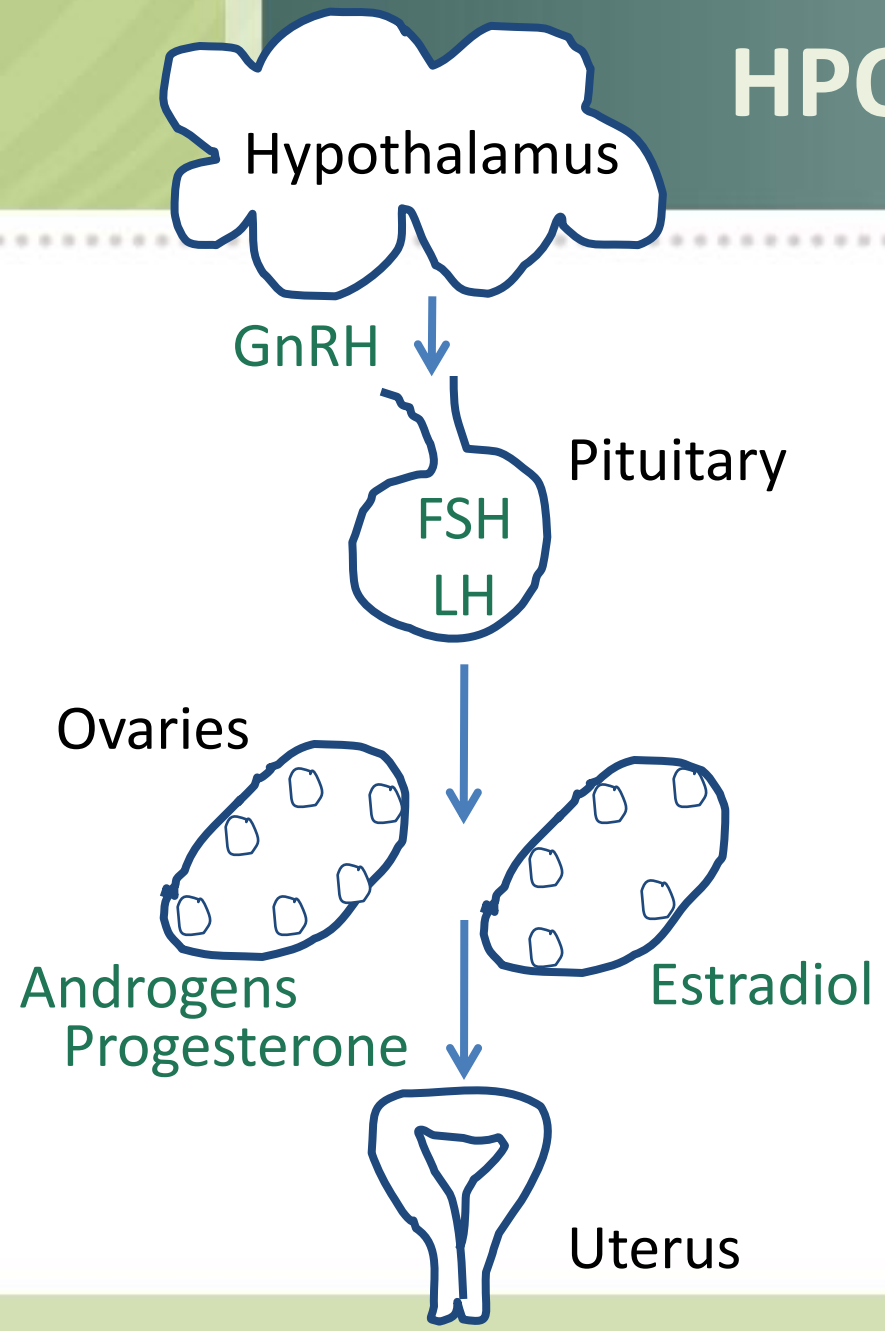
Objectives

- Review the physiology of the hypothalamic-pituitary-ovarian (HPO) axis
- Gain familiarity with management of reproductive-aged women with hyperprolactinemia
- Understand the approach to reproductive-aged women with central hypogonadism
- Review the use of reproductive hormones for induction of puberty in girls with central hypogonadism

Physiology of the Hypothalamic-Pituitary-Ovarian Axis


FSH & LH IU/L
Estradiol pg/mL
Progesterone 17-OHP ng/mL
20
18
16
14
12
10
8
6
4
2
0
500
400
300
200
100
0
10
9
8
7
6
5
4
2
1
0
LH
Progesterone
Estradiol
17-OH Progesterone
2
4
6
8
10
12
14
16
18
20
22
24
26
28
Menses
Ovulation

HPO Axis

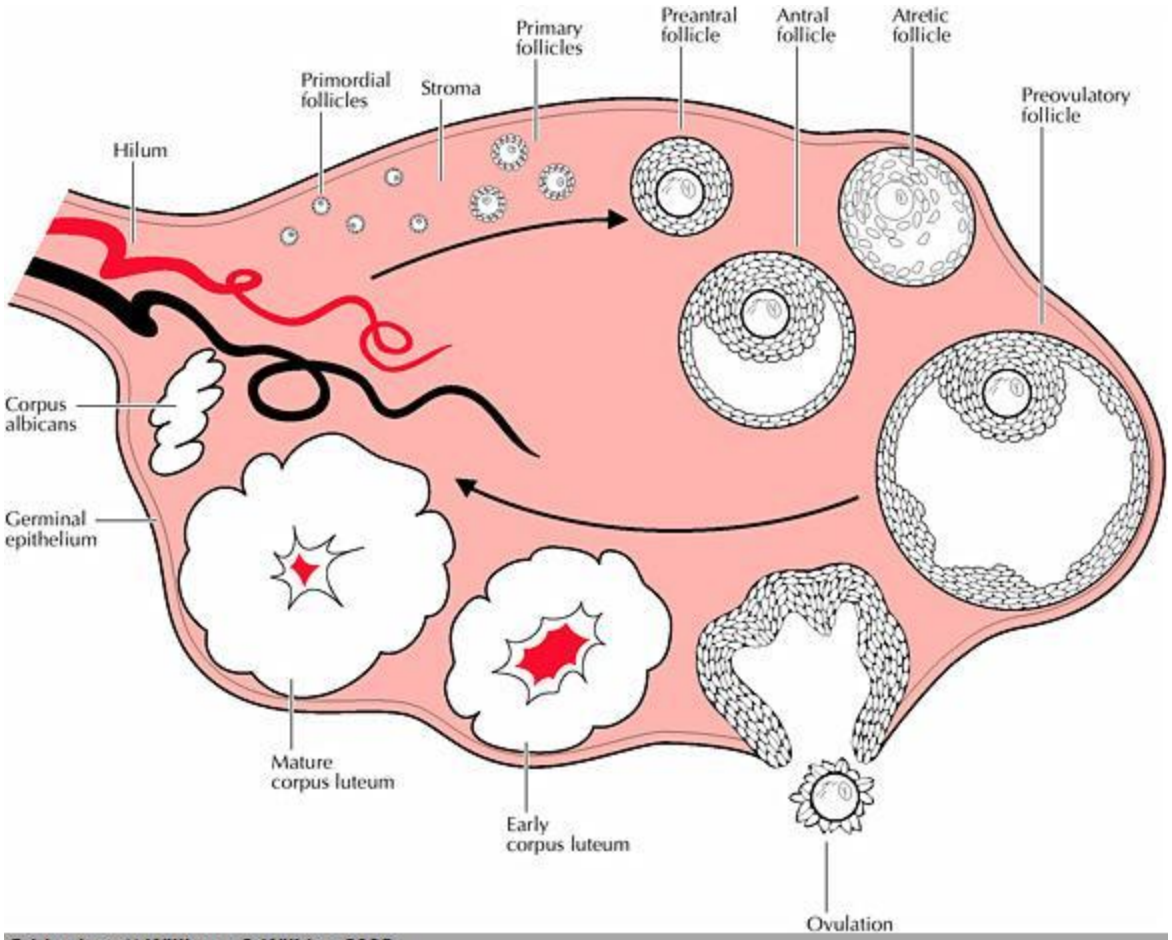


- The **H-P-O Axis** must function normally in order to have a regular menstrual cycle
- <u>Follicular Phase</u>
  - – Development of a mature ovarian follicle
  - – Proliferation of endometrium
- <u>Luteal Phase</u>
  - - Corpus luteum provides hormonal support for potential pregnancy

Anterior Pituitary: FSH & LH

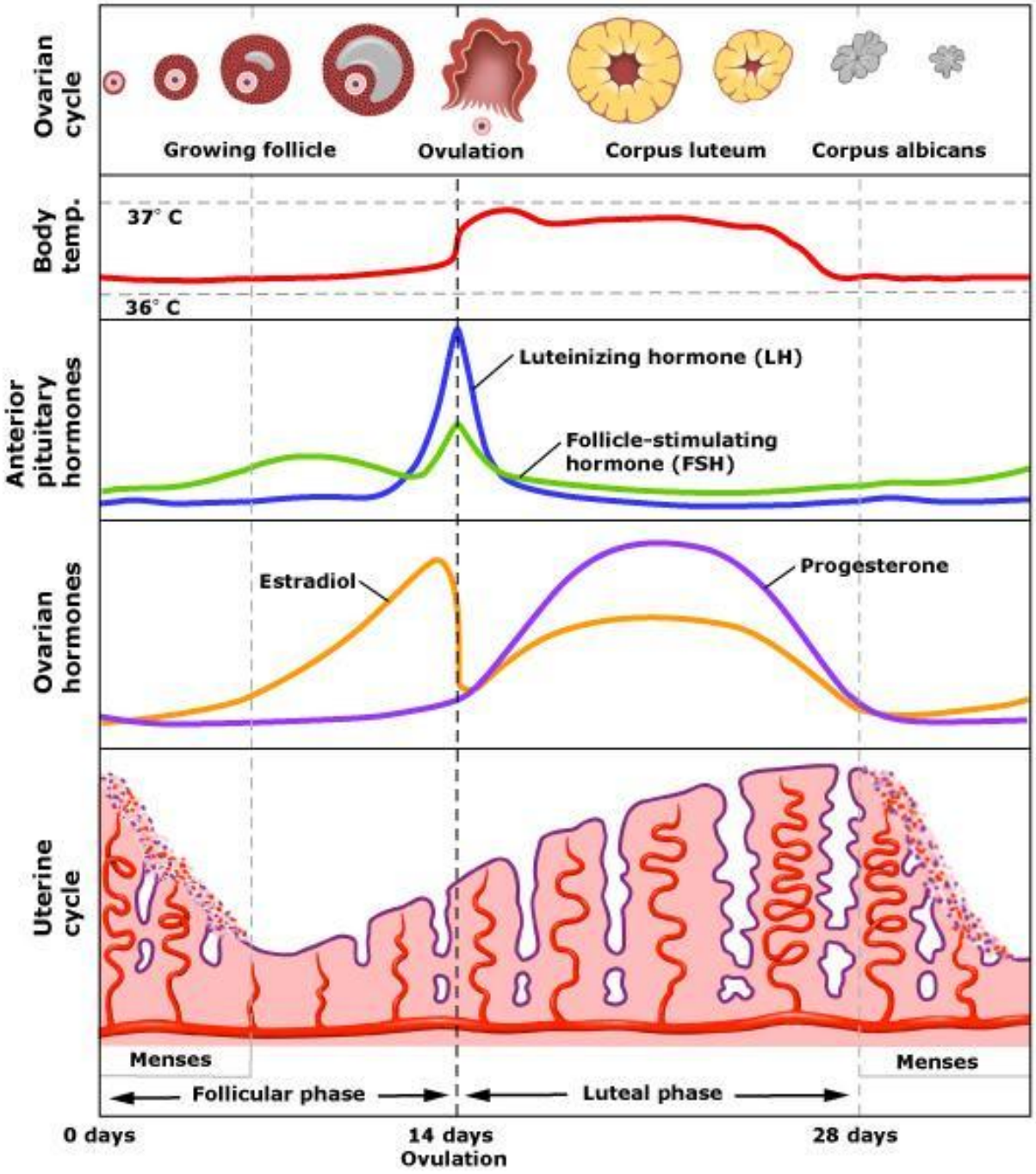
- FSH and LH are glycosylated polypeptides
  - Comprised of alpha and beta subunits
  - alpha subunit identical for TSH, FSH, LH , and hCG
- Gonadotropins are stored in the gonadotroph cells, and release with binding of GnRH to its receptor
- Release of relative amount of FSH versus LH is dependent upon frequency of GnRH release
  - GnRH release pulsatile, neuroendocrine feedback
  - Slower frequency favors FSH release
  - Faster frequency favors LH release

Ovary: Folliculogenesis



Leon Speroff, M.D., Marc Fritz, M.D.; CLINICAL GYNECOLOGIC ENDOCRINOLOGY AND INFERTILITY; 7th; 0781747953; Lippincott Williams & Wilkins ; 01/01/2005; R2 OnLine Library.
http://www.r2library.com/Resource/Title/0781747953

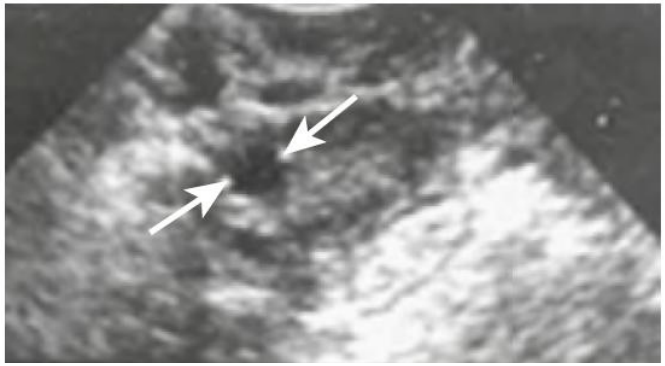
- High levels of FSH in the early follicular phase drive follicular growth
- Estradiol/inhibin produced by the granulosa cells provide negative feedback
- FSH levels drop, resulting in monofollicular growth
- Sustained elevated estradiol → LH surge

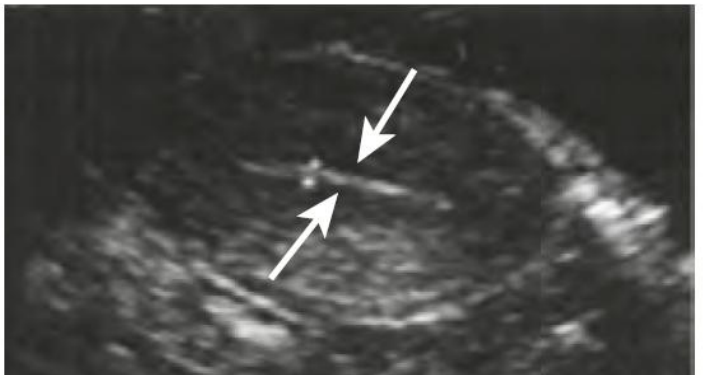

Ovarian cycle
Growing follicle
Ovulation
Corpus luteum
Corpus albicans
Body temp.
37° C
36° C
Anterior pituitary hormones
Luteinizing hormone (LH)
Follicle-stimulating hormone (FSH)
Ovarian hormones
Estradiol
Progesterone
Uterine cycle
Menses
Menses
Follicular phase
Luteal phase
0 days
14 days
Ovulation
28 days

Ultrasound images of ovarian & uterine development

Early follicular phase

- Small follicle
- Thin endometrium





The Menstrual Cycle

- The menstrual cycle provide insight to the functioning of the HPO axis:
  - Cycles typically occur every 28-35 days
  - Regular cycles = ovulatory
- Estradiol produced by the growing follicle and corpus luteum
  - Oligomenorrhea or amenorrhea, depending on the cause, can result in a hypoestrogenic state
  - Prompts evaluation and either correction of menstrual irregularity or hormone replacement

Hyperprolactinemia

Case: Secondary amenorrhea

- 28yo G0 referred for secondary amenorrhea
- Menstrual cycles used to be monthly, then spaced to every 2-3 months and now no bleeding x 6 months
- Not currently sexually active
- Otherwise healthy, no current meds
- Admits to galactorrhea, scant
- Denies hirsutism, acne, headaches
- Labs: FSH 3 mIU/mL, LH 1.2 mIU/mL, estradiol <20, TSH 1.4, **prolactin 64**, total testosterone 22 ng/dL
- Repeat prolactin 59, MRI with 7mm microadenoma

Hyperprolactinemia

- Hyperprolactinemia:
  - Adenomas (prolactin-secreting, or non-functioning)
  - Medications
  - Others (hypothyroidism, chest wall trauma, etc)
- Prolactin acts centrally to alter GnRH secretion
- Degree of hyperprolactinemia → severity:
  - 20-50 ng/mL: luteal phase defect, short menstrual cycles, infertility
  - 50-100 ng/mL: oligomenorrhea/amenorrhea
  - >100 ng/mL: amenorrhea, hot flashes, vaginal dryness

Hyperprolactinemia: management

Desires Fertility

- Dopamine agonist: cabergoline or bromocriptine
- Typical rapid resolution of galactorrhea, and return of regular ovulatory menstrual cycle
- Tolerance of dopamine agonist improved with vaginal route
- Once pregnant:
  - Microadenoma/non-adenoma cause: stop medication with + pregnancy test
  - Macroadenoma: may do ok off medication, may need to be reinitiated or consider surgery

Hyperprolactinemia: management

Non-Fertility Patient

- Goal:
  1) Restore circulating estrogen levels (bone/tissue health)
  2) Provide predictable menstrual bleeding pattern

- 2 Options:
  1) Dopamine agonist: cabergoline or bromocriptine
  2) Combined oral contraceptives

  * Recommend annual prolactin levels on those on combined OCs with adenomas to ensure no growth

Central Hypogonadism

Case: Central Hypogonadism

- 28 yo G0 with history of optic sheath tumor, s/p surgery and radiation
- Panhypopituitarism, on thyroid and glucocorticoid/mineralocorticoid replacement
- Menstrual cycles were regular prior to treatment of her tumor
- Notes dry skin, fragile hair, vaginal dryness
- FSH 1.2 mIU/mL, LH 0.3 mIU/mL, estradiol < 20

What is the appropriate treatment for this patient?

Central Hypogonadism: Management

Non-Fertility Patient

- Goal:
  1) Provide estrogen replacement (bone/tissue health)
  2) Provide endometrial protection & predictable menstrual bleeding pattern

- 2 Options:
  1) Cyclic estrogen + progestin therapy
     - e.g. Estradiol 2mg D1-24, Prometrium 100mg D21-28
  2) Continuous therapy (combined oral contraceptives)

Central Hypogonadism: Management

Desires Fertility

- Oral agents (clomid, letrozole) unlikely to be effective, manipulate HPO axis → not going to work
- Gonadotropin therapy
  - Daily injections (FSH +/- LH) will lead to follicular growth
  - Multiple preparations: purified urinary, recombinant
  - May take a few weeks to initially respond (priming)
  - Monitoring with ultrasound and serum estradiol levels
  - Cost can be prohibitive ($750-1500 per cycle)
  - Luteal support: supplement corpus luteum with estradiol, progesterone in case inadequate

Induction of Puberty

Case: Delayed Puberty

- 13yo with history of craniopharyngioma
- s/p surgical resection x 2 with resultant hypopituitarism
- Managed with thyroid, glucocorticoid, and growth hormone replacement
- Tanner Stage I
- Would like to start pubertal development
- Bone age: 10.5 yrs

Induction of Puberty

Goals

1) Maximize growth
2) Breast development
3) Predictable bleeding pattern

Treatment

- Start with low dose estrogen therapy
- Slowly taper up dose in coordination with use of growth hormone/monitor bone age
- Once bleeding start progestin therapy or switch to combined OC

Induction of Puberty: E2 protocol

TABLE 3. Pubertal induction and maintenance estrogen therapy using TDE: a protocol using low growth-promoting doses for 18–24 months[a]

Treatment (months)	Target E2 (pg/ml)[b]	E2 dose	Notes
			Consider initiation of puberty at age 11–12 yr if there is no breast development.
0	3–4	0.1 μg/kg	Cut and apply a portion of a matrix patch to deliver 0.1 μg/kg E2. Apply in p.m. and remove in a.m.[c]
6	3–4	0.1 μg/kg	Wear a 0.1 μg/kg equivalent portion of the patch continuously. Change patch as directed (once or twice weekly). Check random E2 level to ensure E2 is in target range.
12	6–8	0.2 μg/kg	
18	~12	12.5 μg	E2 levels below this are believed to accelerate growth more than bone maturation.
24	~25	25 μg	
30	~37	37.5 μg	
36	~50	50 μg	Start progestin (earlier, if breakthrough bleeding occurs): 200–300 mg micronized oral progesterone for about 12 d/month qhs (causes drowsiness) or 5 mg oral medroxyprogesterone for about 12 d/month.
42	~75	75 μg	
48	50–150	100 μg	Typical adult dose; may not be high enough to protect liver, arteries, *etc.*

Davenport. JCEM 2010; 95:1487

Summary

- Discussed the normal physiology of the HPO axis and the menstrual cycle
- Reviewed the management of hyperprolactinemia in reproductive-aged women, interested & not interested in fertility
- Reviewed the management of central hypogonadism in reproductive-aged women
- Discussed the use of reproductive hormones for induction of puberty in girls with central hypogonadism

Any Questions?

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