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
<table>
<thead>
<tr>
<th>FSH &amp; LH IU/L</th>
<th>Estradiol pg/mL</th>
<th>Progesterone 17-OHP ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>500</td>
<td>10</td>
</tr>
<tr>
<td>18</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>400</td>
<td>8</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>300</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>200</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Graph showing levels of LH, Estradiol, and 17-OH Progesterone over the menstrual cycle.

- LH peaks at around day 14 and drops post-ovulation.
- Estradiol increases before ovulation and peaks at ovulation.
- 17-OH Progesterone increases after ovulation.

- Menses: Day 1-5
- Ovulation: Day 14
• The **H-P-O Axis** must function normally in order to have a regular menstrual cycle

• **Follicular Phase**
  – Development of a mature ovarian follicle
  – Proliferation of endometrium

• **Luteal Phase**
  - Corpus luteum provides hormonal support for potential pregnancy
• 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

- 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 $\rightarrow$ LH surge
Ultrasound images of ovarian & uterine development

Early follicular phase
- Small follicle
- Thin endometrium

Late follicular phase
- Big (2cm) follicle
- Thick, trilaminar 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
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
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?
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)
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
• 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

<table>
<thead>
<tr>
<th>Treatment (months)</th>
<th>Target E2 (pg/ml)$^b$</th>
<th>E2 dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3–4</td>
<td>0.1 µg/kg</td>
<td>Consider initiation of puberty at age 11–12 yr if there is no breast development. 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.$^c$</td>
</tr>
<tr>
<td>6</td>
<td>3–4</td>
<td>0.1 µg/kg</td>
<td>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.</td>
</tr>
<tr>
<td>12</td>
<td>6–8</td>
<td>0.2 µg/kg</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>~12</td>
<td>12.5 µg</td>
<td>E2 levels below this are believed to accelerate growth more than bone maturation.</td>
</tr>
<tr>
<td>24</td>
<td>~25</td>
<td>25 µg</td>
<td>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.</td>
</tr>
<tr>
<td>30</td>
<td>~37</td>
<td>37.5 µg</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>~50</td>
<td>50 µg</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>~75</td>
<td>75 µg</td>
<td>Typical adult dose; may not be high enough to protect liver, arteries, etc.</td>
</tr>
<tr>
<td>48</td>
<td>50–150</td>
<td>100 µg</td>
<td></td>
</tr>
</tbody>
</table>
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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