Overview of Reproductive Endocrinology

Maria Yialamas, MD

I have no conflicts of interest to report.

Female Hypothalamic-Pituitary-Gonadal Axis

Hypothalamus

LH

GnRH

Pituitary

E2,

FSH

Pregesterone,

Inhibin A & B

Ovary

Hormone Secretion in the Normal Menstrual Cycle

Length 25-35 days
Luteal phase 12-14 days
Follicular phase variable

Days Centered to Ovulation

Welt et al, JCEM 1999

Case #1: History

- 19 year old woman presents to your clinic for evaluation because she has had no menses for 8 months.

- Her menarche was at age 13, and she had regular menses until 8 months ago.

- About one year ago, she increased her aerobic exercise with a 20 lb weight loss.

Case #1: History

- She has not had any headaches, vision changes, hot flushes, or night sweats.

- She has no history of an eating disorder.

- Her thyroid review of systems are negative.
**Case #1: Physical Exam**
- BMI 18  BP 100/60  P60
- Skin with no hirsutism, acne, or alopecia.
- Visual fields full.
- Thyroid size is normal. No nodules.
- No galactorrhea.
- Pelvic exam normal.

What is her diagnosis and what labs would you order?

---

**Amenorrhea**
- Primary Amenorrhea
  - Absence of menses by age 16
- Secondary Amenorrhea
  - Absence of menses for 3 months

Pathophysiologic considerations are the same for both.

Incidence of genetic & anatomic abnormalities higher with primary amenorrhea.

---

**Etiologies**

- Pregnancy
- Uterine or Outflow Tract Disorders
- Ovulatory Disorders

---

**Causes of Primary Amenorrhea**

<table>
<thead>
<tr>
<th>System</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>27%</td>
</tr>
<tr>
<td>Pituitary</td>
<td>2%</td>
</tr>
<tr>
<td>PCOS</td>
<td>7%</td>
</tr>
<tr>
<td>Ovary</td>
<td>43%</td>
</tr>
<tr>
<td>Uterus/Outflow Tract</td>
<td>19%</td>
</tr>
</tbody>
</table>

---

**Causes of Secondary Amenorrhea**

<table>
<thead>
<tr>
<th>System</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>30%</td>
</tr>
<tr>
<td>Pituitary</td>
<td>15%</td>
</tr>
<tr>
<td>PCOS</td>
<td>30%</td>
</tr>
<tr>
<td>Ovary</td>
<td>12%</td>
</tr>
<tr>
<td>Uterus/Outflow Tract</td>
<td>7%</td>
</tr>
</tbody>
</table>

---

**Diagnostic Lab Evaluation**

- βhCG (rule out pregnancy!)
- FSH (best test for ovarian failure)
- Prolactin
- TSH
Case #1: Labs

- FSH 3.2 IU/L
- Prolactin 6.3 ng/mL
- TSH 2.6 μU/mL
- βhCG neg

- Provera challenge was negative for a withdrawal bleed.

What is her diagnosis?

Hypothalamic & Pituitary Etiologies

- Hypothalamic Amenorrhea (HA)
- Hyperprolactinemia
- Tumors and Destructive/Infiltrative Lesions
- Genetic: IHH, Kallmann syndrome
- Cranial Irradiation
- Others: hypo- or hyperthyroidism, excess cortisol
- Pituitary tumor (mass effect)
- Lymphocytic hypophysitis
- Pituitary infarction
- Empty-sella syndrome

Hypothalamic Amenorrhea

- Etiology
  - Energy Output > Energy Input
    - Weight loss
    - Eating Disorders
    - Excessive exercise
  - Stress
    - Psychological
    - Physical

Hypothalamic Amenorrhea

- Leptin
  Peripheral signal indicating sufficient energy stores for reproduction.

Management Questions

- Does this patient need a MRI?
  - Headaches or neurological symptoms
  - Elevated prolactin
  - History unclear
  - Primary amenorrhea
- How about a Bone Mineral Density Scan?
  - amenorrhea >6 months
Hypothalamic Amenorrhea: Recovery

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recovery Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eating Disorder n=15</td>
<td>50%</td>
</tr>
<tr>
<td>Idiopathic n=9</td>
<td>30%</td>
</tr>
<tr>
<td>Stress/Weight Loss n=6</td>
<td>80%</td>
</tr>
</tbody>
</table>

Perkins et al., 2001

Hypothalamic Amenorrhea: Treatment

- Weight gain, decrease exercise
- Oral contraceptives or hormone replacement therapy
- Calcium and Vitamin D

Case #2

- 27 yo with 3 months amenorrhea
- Moderate exercise, no eating disorders
- Insomnia
- No hirsutism, mild acne
- History of hypothyroidism on thyroid hormone replacement

Case #2

- Family history of early menopause
- Physical exam unremarkable
- Labs:
  - FSH 56 IU/L, TSH 3.7 μU/mL, neg βhCG, prl 10.8 ng/mL
- Diagnosis?
- Further workup?

Primary Ovarian Insufficiency

- Elevated FSH, age < 40 yrs
- Repeat testing important: follicular phase
- Causes:
  - Turner’s syndrome
  - X chromosome deletions, translocations
  - Fragile X premutations
  - Autoimmune
  - Chemotherapy or radiation therapy
  - Galactosemia, FSH/LH receptor mutations, blepharophimosis, BMP 15 mutations

FSH, LH high
Estradiol low
Primary Ovarian Insufficiency:

Diagnostic Tests

• **Karyotype**
  – Age <30 yrs, familial cases, ?everyone
  – Turner’s features
• Fragile X Premutation screen
• Anti-thyroid and anti-adrenal antibodies
• Anti-ovarian antibodies poor test
• Ovarian biopsy is not helpful

Primary Ovarian Insufficiency:

Treatment

• Oral contraceptive pills or hormone replacement therapy
• Calcium and vitamin D

Case #3: History

• 28 year old woman presents to your clinic for evaluation of irregular menses
• She describes irregular menses since age of menarche which was at 14 years of age
• She has also had problems with increased hair growth on her upper lip and chin
• She does not have hot flashes, night sweats, galactorrhea, or positive thyroid review of systems
• She is on no meds currently and has a family history of type 2 diabetes.

Case #3: Physical Exam

• BMI of 29
• Skin with hirsutism of the upper lip, chin, and sides of her face. No acanthosis.
• No clitoromegaly.

What labs/studies would you order?

Case #3: Labs

• Laboratory testing reveals normal
  – TSH
  – Prolactin
  – FSH
  – Androgen levels (total testosterone and DHEAS).

What is the diagnosis?
**PCOS: Epidemiology**

- 4.7-6.8% of women have PCOS as defined by the NIH criteria (Knockenhauer et al., JCEM 1998; Diamanti-Kandarakis, JCEM, 1999; Asuncion, JCEM 2001)
- Most common cause of female infertility (50-60%)
- May be the most endocrinopathy in young women

**PCOS: NIH Definition**

- Menstrual dysfunction – < 9 menses per year
- Hyperandrogenism
  - Hirsutism, acne, alopecia and/or
  - Elevated serum androgens
- Exclusion of other diseases (e.g., hyperprolactinemia, androgen secreting tumors, CAH)

(NIH Conference, 1990)

**PCOS: Rotterdam Definition**

- 2 out of 3 of the following must be true:
  - Oligo- or anovulation
  - Clinical and/or biochemical signs of hyperandrogenism
  - Polycystic Ovaries
- Exclusion of other etiologies (e.g., hyperprolactinemia, CAH, androgen secreting tumors)

(ESHRE/ASRM sponsored PCOS Consensus Workshop Group, Fert and Ster, 2004)

**Polycystic Ovarian Syndrome**

- Hypothalamus
- Pituitary
- Adipose Tissue
- Muscle
- Ovary

**Polycystic Ovary (PCO):**

- multiple small (2 – 9 mm) follicles
- peripheral distribution
- increased stromal volume
- ovaries usually enlarged

**Normal ovary:**

- fewer follicles
- random distribution
- no increased stroma

**Polycystic Ovarian Morphology (PCOM)**

- 100% of women with PCOS have PCOM (Taylor et al JCEM 1997)
- 23% of normally cycling women will have PCOM (Polson et al, Lancet, 1988)
- Present in other ovulatory disorders (hyperprolactinemia, late onset CAH, adolescence (Aziz R. JCEM 2006)
Clinical Manifestations

- Oligo- or anovulation
- Hyperandrogenism
- Infertility
- Insulin Resistance

122 obese women with PCOS, by age 40
- 35% had IGT
- 10% had type 2 diabetes

Treatment of PCOS

Hyperandrogenism
- Weight loss
- Cosmetic measures
- Hormonal therapy

Oligo-amenorrhea
- Metformin

Insulin Resistance
- Weight loss
- Exercise
- Metformin
- Monitor BPs, lipids

Infertility
- Weight loss
- Metformin
- Ovulation Induction/IVF
Summary

• Hypothalamic Amenorrhea
  – Diagnosis
  – Management (MRI, BMD)
  – Treatment (weight gain, OCPs)

• Premature Ovarian Failure
  – Definition
  – Diagnostic evaluation (karyotype, Fragile X)
  – Treatment options (OCPs, HRT)

• PCOS
  – Epidemiology
  – Diagnosis (NIH versus Rotterdam criteria)
  – Clinical Manifestations (anovulation, hyperandrogenism, fertility, insulin resistance)
  – Treatment options (weight loss, OCPs, spironolactone, metformin)

Question #1

24 year old woman with a 6 month history of amenorrhea comes in for evaluation. Her thyroid review of systems are negative. She does not have hot flushes, night sweats, or galactorrhea. She is on no medications. Physical exam is unremarkable. hCG negative. FSH and TSH normal. Prolactin is slightly elevated at 30 ng/mL (<18 ng/mL) and confirmed on repeat evaluation.

What is the next best step?
A) Treat with bromocriptine/cabergoline
B) Treat with an oral contraceptive pill
C) Give a progesterone challenge
D) Obtain a pituitary MRI
E) Repeat the prolactin in 3 months. No treatment for now.

Question #2

34 year old woman with a 4 month history of amenorrhea comes to see you for evaluation. Her menses had occurred every 2 months before they stopped. Her exercise routine is unchanged; she runs about 25 miles per week. She has had no hot flushes or night sweats. Her thyroid review of systems are normal. FSH and TSH, and prolactin are normal. hCG negative.
Question #2

What would you do next?

A) Provera challenge
B) Treat with OCPs
C) Treat with metformin
D) MRI of the pituitary gland
E) Pelvic ultrasound

Question #2

What would you do next?

A) Provera challenge
B) Treat with OCPs
C) Treat with metformin
D) MRI of the pituitary gland
E) Pelvic ultrasound

References

• Perkins RB et al. 2001 Aetiology, previous menstrual function and patterns of neuro-endocrine disturbance as prognostic indicators in hypothalamic amenorrhoea. Hum Reprod 16: 2198.