Amenorrhea Lecture

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Primary Amenorrhea

• Pubertal delay >2.5 SD later than the mean
  – No breast development by age 13
  – Absence of menarche by age 15
  – Abnormally slow pace
    • Mean duration from onset of puberty to onset menarche is 2.4 +/- 1.1 years
Primary Amenorrhea

- Diagnostic Evaluation:
  - Presence/Absence of breast development
  - Presence/Absence of uterus
  - FSH level

- History
  - Pubertal changes, family history, change in weight, exercise, galactorrhea, neurologic symptoms, cyclic pain

- Physical exam
  - Height, weight, tanner staging, pelvic exam/ultrasound

- Labwork
  - hCG
  - FSH, LH, estradiol
  - Prolactin
  - TSH
Primary Amenorrhea

• Classification:
  – Hypergonadotrophic hypogonadism
    • FSH >20 IU/L; LH >40 IU/L
    • Primary gonadal failure
  – Hypogonadotrophic hypogonadism
    • FSH and LH <5 IU/L
    • Primary hypothalamic-pituitary dysfunction
  – Eugonadotrophic
    • FSH and LH of 5 to 20 IU/L
    • Normal HPO axis
    • Anatomic, ovulatory dysfunction
Primary Amenorrhea

- Most common etiologies:
  - Chromosomal abnormalities – 50%
  - Hypothalamic hypogonadism – 20%
  - Mullerian agenesis – 15%
  - Transverse vaginal septum/imperforate hymen – 5%
  - Pituitary disease – 5%
  - Other – 5%
    - Androgen insensitivity
    - CAH
    - PCOS

Primary Amenorrhea: Hypogonadotropin Hypogonadism

- Constitutional delay
  - +family history, short stature, diagnosis of exclusion (30%)
- Isolated gonadotropin deficiency
  - Kallman syndrome
    - 1/50,000 females, anosmia
- Structural lesion/tumor
  - Craniopharyngioma
- Chronic illness
- Functional hypothalamic amenorrhea:
  - Undernutrition
  - Intense exercise
  - Stress
Primary Amenorrhea: Eugonadotropin

- Mullerian agenesis – 15%
- Transverse vaginal septum/imperforate hymen – 5%
- Pituitary disease – 5%
- Other – 5%
  - Androgen Insensitivity Syndrome
  - CAH
  - PCOS
Secondary Amenorrhea

• Oligomenorrhea
  – Less than 8 menstrual cycles per year
  – Cycle length > 45 days
  – Absence of menstruation 6 consecutive months

• History
  – Screen for hypothyroid, PCOS (androgen excess?), change in weight/exercise, galactorrhea,

• Physical exam
  – Height, weight, pelvic exam (we know outflow tract is present)

• Labwork
  • hCG
  • FSH, LH, estradiol
  • Prolactin
  • TSH
## Common Causes of Secondary Amenorrhea

Table 3-2: Common Causes of Secondary Amenorrhea (Excluding Pregnancy) and Relative Frequencies

<table>
<thead>
<tr>
<th>Organ</th>
<th>Cause</th>
<th>Relative Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>Abnormalities of height/weight and nutrition</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Stress</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Infiltrative disease (craniopharyngioma, sarcoidosis, histiocytosis)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pituitary</td>
<td>Prolactin-secreting pituitary tumor</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Empty sella syndrome</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sheehan syndrome</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>ACTH-secreting pituitary tumors (Cushing disease)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Ovary</td>
<td>Premature ovarian failure</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Polycystic ovarian disease</td>
<td>30</td>
</tr>
<tr>
<td>Uterus</td>
<td>Asherman syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>Late-onset adrenal hyperplasia</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism or hyperthyroidism</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>Ovarian tumors</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*ACTH, Adrenocorticotropic hormone.*

**35%**
Clinical Scenario
16 year old presents no menses for last 7 months.

- Pgyn: menarche at 12.5 yrs, “pretty regular.”
- PMH: none
- Meds: none
- PSH: none
- SH: high school junior, president of class, on travel team field hockey. Actively being recruited at collegiate level.

• PE:
  - Height 5’7”
  - Weight 115 #
  - BMI =18
  - Nl pelvic exam
  - labs:
    • hCG negative
    • FSH 5.1, LH 3, e2=19
    • TSH, PRL WNL
  - MRI: no cranial lesion
Functional Hypothalamic Amenorrhea

- Energy Deficit
  - Weight loss
  - Exercise induced
- Suppression GnRH secretion
  - Decreased gonadotropin pulsation
  - Low or normal LH secretions, low estradiol
  - FSH usually in normal range
  - Mimics prepubertal state

Cortisol high
Leptin low
Low/NI FSH
Low LH
Low estradiol
Functional Hypothalamic Amenorrhea

• Common cause amenorrhea
  – Primary 20%
  – Secondary 35%

• Stress
• Exercise
• Weight Loss
  – Anorexia
35 year old presents with hot flashes, amenorrhea for 2 years.

– Pgyn: menarche at 11, regular menses until age 15, some skipped months.
– Seen by OB/Gyn OSH. Told FSH level high. Given pill to allow ovary to rest/recover. Told to gain weight.
– PMH: none
– Meds: none
– PSH: none
– SH: community college freshman. No T/E/D.

• Physical Exam
  – 5’6” 135#, BMI 24.8
  – Nl pelvic exam

• Labwork
  – Old records FSH=51
  – Repeat FSH = 72

• Referred for evaluation and management.
Hypergonadotropin Hypogonadism

- Ovarian dysfunction, always pathologic
  - Loss of negative effect sex steroid feedback on the hypothalamus

No ovarian response
- Low estradiol
- High FSH
Hypergonadotrophic Hypogonadism

- Genetic: CHECK KARYOTYPE
  - Primary amenorrhea: 55% abnormal
  - Secondary amenorrhea: 13.3 %

- Radiation/chemotherapy
- Autoimmune
- Galactosemia
- Idiopathic
Premature Ovarian Failure

• Elevated FSH level < 40 yo
  – 1/100 at age 40, 1/250 < 35 yo
  – 2-10% of pts with amenorrhea
• 90% idiopathic
  – Follicle depletion, dysfunction
• 5-10% lifetime pregnancy rate
  – Varying, unpredictable ovarian function (POI)
• Usually presents secondary amenorrhea
  – 10% cases primary amenorrhea

Rebar, Ann NY Acad Sci, 2008
Evaluation of Premature Ovarian Failure

• Karyotype
  – Assess abnormalities in X chromosome

• Fragile X premutation carrier testing
  – Long arm X chromosome
  – 2% sporadic cases, 14% familial

• Adrenal antibodies
  – 4% of sporadic POF
  – 50% with + antibody develop adrenal insufficiency

• Thyroid testing
  – TSH, thyroid auto-antibodies
  – 14-27% of women
Evaluation of Premature Ovarian Failure

• Fragile X premutation carrier testing
  – X linked, common form of mental retardation
  – Screen family history affected males
  – FMR1 gene
    • Affected subjects > 200 CGG repeats
      – Methylation of gene, lack transcription, absent protein
    • Premutation 55-200 CGG repeats
      – Decreased FMR1 protein
      – Can expand to a full mutation when transmitted by females
        » Implications for sister, donor oocyte
      – 12-28% of premutation carriers will develop POF
Management Premature Ovarian Failure

• Emotional well-being
  – Unexpected infertility, life-altering
    • Increased shyness, social anxiety, impaired self-esteem
  – Schedule return visit
  – Refer to psychologist
  – Support group (http://pofsupport.org)
  – Family planning options
    • Donor egg
Management Premature Ovarian Failure

- Physical well-being
  - Hot flashes
  - Vaginal Dryness
  - Osteoporosis
    - Measure bone mineral density at diagnosis
    - Calcium 1200 mg, Vit D 800 IU, weight bearing exercise
    - Bisphosphonates NOT advised
      - long skeletal half life, fetal effects uncertain
## Major Causes of Primary and Secondary Amenorrhea

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy</strong></td>
<td></td>
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<tr>
<td><strong>Anatomic abnormalities</strong></td>
<td></td>
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<tr>
<td>Congenital abnormality in Mullerian development*</td>
<td>Isolated defect</td>
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<tr>
<td></td>
<td>Testicular feminization syndrome</td>
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<tr>
<td></td>
<td>5-Alpha-reductase deficiency</td>
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<td></td>
<td>Vanishing testes syndrome</td>
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<td></td>
<td>Defect in testis determining factor gene</td>
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<tr>
<td>Congenital defect of urogenital sinus development*</td>
<td>Agenesis of lower vagina</td>
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<tr>
<td></td>
<td>Imperforate hymen</td>
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<tr>
<td>Acquired ablation or scarring of endometrium</td>
<td>Asherman’s syndrome</td>
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<td></td>
<td>Tuberculosis</td>
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<td><strong>Disorders of the hypothalamic-pituitary-ovarian axis†</strong></td>
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<tr>
<td>Hypothalamic dysfunction</td>
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<tr>
<td>Pituitary dysfunction</td>
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<tr>
<td>Ovarian dysfunction</td>
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<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

*Present as primary amenorrhea only
†The multiple causes of hormonal dysfunction are listed on the next table.
<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamic dysfunction</td>
<td>Functional hypothalamic amenorrhea</td>
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<tr>
<td></td>
<td>Weight loss, eating disorders</td>
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<tr>
<td></td>
<td>Exercise</td>
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<td></td>
<td>Stress</td>
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<td></td>
<td>Severe or prolonged illness</td>
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<tr>
<td></td>
<td>Congenital gonadotropin–releasing hormone deficiency</td>
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<td></td>
<td>Inflammatory or infiltrative diseases</td>
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<td></td>
<td>Brain tumors – eg, craniopharyngioma</td>
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<td></td>
<td>Pituitary stalk dissection or compression</td>
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<td>Cranial irradiation</td>
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<td>Brain injury – trauma, hemorrhage, hydrocephalus</td>
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<td></td>
<td>Other syndromes – Prader–Willi, Laurence–Moon–Biedl</td>
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<tr>
<td>Pituitary dysfunction</td>
<td>Hyperprolactinemia</td>
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<tr>
<td></td>
<td>Other pituitary tumors – acromegaly, corticotroph adenomas (Cushing’s disease)</td>
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<tr>
<td></td>
<td>Other tumors – meningioma, germinoma, glioma</td>
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<td></td>
<td>Empty sella syndrome</td>
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<tr>
<td></td>
<td>Pituitary infarct or apoplexy</td>
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<tr>
<td>Ovarian dysfunction</td>
<td>Ovarian failure (menopause)</td>
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<tr>
<td></td>
<td>Spontaneous</td>
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<td></td>
<td>Premature (before age 40 years)</td>
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<td>Surgical</td>
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<tr>
<td>Other</td>
<td>Hyperthyroidism</td>
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<td></td>
<td>Hypothyroidism</td>
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<tr>
<td></td>
<td>Diabetes mellitus</td>
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<td>Exogenous androgen use</td>
</tr>
</tbody>
</table>
Secondary Amenorrhea

Obtain β-hCG

Positive
Pregnancy

Negative
Obtain:
1. Height/Weight
2. Prolactin (PRL)
3. FSH
4. Testosterone (if indicated)
5. Thyroid Function Tests (if indicated)

Abnormal Height/Weight

Elevated PRL
R/O Hypothyroidism
Examine Possible Diet/Excessively Thin
Obese Hypothalamic Nutrition Manipulations

Obese
Excessively Thin
Renal Failure
Dietary/Chlorpropamide

CT Scan of Hypothalamus
and pituitary
Treat with Bromocriptine

Obese
Excessively Thin

Elevated FSH
Repeat FSH Monthly (x3)

If FSH Remains Elevated

Check 17-OH Progesterone

History of D & C Preceding Amenorrhea (NL PRL, NL FSH)

Hyperandrogenism

Normal

Elevated

Ovarian Hyperandrogenism
Estrogen Progesterone Replacement

Adrenal Hyperplasia
Treat With Glucocorticoids

No Withdrawal

Suppress Ovarian Androgen Secretion with Oral Contraceptives

Hysteroscopy and Hysterosalpingogram

Asherman's Syndrome

Trial of Estrogen-Progesterone to Stimulate Withdrawal Bleeding

Ovarian Failure