**Secondary Amenorrhea**

Clinical Update & Case Presentations

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**Definitions**

- **Amenorrhea**: absence of menses
  - **Primary**: absence of menarche by age 16
  - **Secondary**: absence of menses in women who previously had menses. Absence must be for:
    - $>3$ cycle intervals according to certain sources
    - $>6$ months according to most sources

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**Events of Puberty**

- **Thelarche** (breast development)
  - Requires estrogen
- **Pubarche/adrenarche** (pubic hair development)
  - Requires androgens
- **Menarche**
  - Requires:
    - GABA from the hypothalamus
    - FSH and LH from the pituitary
    - Estrogen and progesterone from the ovaries
    - Normal outflow tract

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**AMENORRHEA**

**COMPARTMENTS:**

1. CNS—HYPOTHALMUS
2. ANTERIOR PITUITARY
3. OVARY
4. OUTFLOW TRACT (uterine target organ)

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**Etiologies**

- Don’t forget PREGNANCY!
  - Most common cause of secondary amenorrhea
  - Rule out with a urine or serum Hcg before proceeding
- Consider each level of the control of the menstrual cycle:
  - Hypothalamus
  - Pituitary
  - Ovary
  - Uterus
  - Cervix
  - Vagina
  - Involved structurally in the outflow of menstrual blood

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**Secondary Amenorrhea**

- Most common cause is?
- The incidence in women of reproductive age is?
**Most Common Etiologies of Secondary Amenorrhea***

- Pregnancy, Pregnancy, Pregnancy
- Ovarian disease (40%)
- Hypothalamic dysfunction (35%)
- Pituitary disease (19%)
- Uterine disease (5%)
- Other (1%)
  - Systemic disorders
    - Renal failure, liver disorders, DM
  - Medications
    - Psychotropic, metoclopamid...

*1-3% of women of reproductive age

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**Dysfunction of the H-P-O Axis**

- Hypothalamic dysfunction
  - Functional hypothalamic amenorrhea
  - In GnRH secretion
    - Weight loss, eating disorders (Anorexia nervosa)
    - Frequent/vigorous exercise
    - Stress
    - Severe/prolonged illness (i.e. severe burns, systemic illness)
  - Congenital GnRH deficiency (presents as primary amenorrhea)
  - Inflammatory or infiltrative diseases (lymphoma, Langerhans cell histiocytosis, sarcoidosis)
  - Brain tumors (i.e. craniopharyngioma)
  - Cranial irradiation
  - Pituitary stalk dissection or compression
  - Syndromes
    - Prader-Willi
    - Laurence-Moon-Biedl

Adapted from "Etiology, diagnosis and treatment of secondary amenorrhea", UpToDate 2010.

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**Dysfunction of the H-P-O Axis**

- Pituitary dysfunction
  - Hyperprolactinemia
    - Prolactinomas account for 20% of secondary amenorrhea
    - Account for 90% of secondary amenorrhea due to pituitary problems
  - Medications
    - Pituitary tumors
      - Acromegaly
      - Corticotroph adenomas (i.e. Cushing’s disease)
      - Meningioma (of the sella), germinoma, glioma
  - Empty sella syndrome
  - Pituitary infarct/pituitary apoplexy
    - Sheehan’s syndrome (Hyproprolactinemia)

Adapted from "Etiology, diagnosis and treatment of secondary amenorrhea", UpToDate 2010.

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**Polycystic Ovary Syndrome (PCOS)**

- Accounts for 20% of cases of amenorrhea
- Manifestations include:
  - Hirsutism
  - Acne
  - Menstrual irregularities
  - Obesity
  - Acanthosis nigricans
  - Premature pubarche, and/or precocious puberty
- To diagnose, any 2 of 3:
  - Oligomenorrhea/amenorrhea
  - Signs of androgen excess
  - Presence of polycystic ovaries on ultrasound (12 follicles)

Adapted from "Etiology, diagnosis and treatment of secondary amenorrhea", UpToDate 2010.

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**The Hypothalamic-Pituitary-Ovarian Axis**


Adapted from "Clinical features and diagnosis of polycystic ovary syndrome in adolescents", UpToDate 2010.
Other Endocrine Etiologies of Amenorrhea

- **Hyperthyroidism/Hypothyroidism**
  - Mediated by derangements in sex hormone-binding globulin (SHBG):
    - ↑ in hyperthyroid, ↓ in hypothyroid
    - Example: ↑ SHBG → ↑ estradiol concentrations, low-normal serum free estradiol concentrations
    - ↑ LH concentration, ↑ mid-cycle LH surge → amenorrhea or oligomenorrhea, anovulatory infertility
- **Diabetes Mellitus**
- **Exogenous androgen use**

Structural Etiologies of Amenorrhea

- Mullerian anomalies and congenital defects of the urogenital sinus
  - Examples: MRKH, vaginal agenesis, imperforate hymen
  - Typically present with primary, not secondary, amenorrhea
- Potential **structural etiologies** of secondary amenorrhea
  - Acquired scarring of the endometrium due to instrumentation
    - **Asherman's Syndrome**
    - **Endometrial ablation**
  - Scarring of the endometrium due to infection
    - Tuberculosis
    - Cervical stenosis, often due to instrumentation
      - LEEP or Cold knife conization (rare complication)

Asherman's Syndrome

- Results from acquired scarring of endometrial lining
  - Secondary to postpartum hemorrhage or endometrial infection, followed by instrumentation (i.e. D & C)
  - Diagnosis suggested by absence of normal uterine stripe on pelvic ultrasound
  - Can confirm diagnosis by
    - Absence of withdrawal bleeding after administration of estrogen, then progesterin for several weeks
    - Hysteroscopic evaluation of the endometrium

Drug induced amenorrhea

- **Hormonal contraceptives**
- **GnRH analogues**
- **Psychotrophic medications**
**DIAGNOSIS**

- **A GOOD HISTORY**
  - CAN REVEAL THE ETIOLOGIC DIAGNOSIS IN A LARGE PERCENTAGE OF CASES.
- **PHYSICAL EXAM**
- **DIAGNOSTIC TESTS**

**DIAGNOSIS**

? FEATURES OF ANDROGEN EXCESS

- **YES**
- **NO**

**DIAGNOSIS**

- **Exclude Pregnancy**
- **History:**
  - Recent stress, weight change, new diet or exercise habits, illness?
  - New acne, hirsutism, voice deepening?
  - New medications?
    - Recent initiation or discontinuation of OCPs
    - Danazol/androgenic drugs
    - High-dose progestins
    - Metoclopramide and antipsychotics
      - Can increase serum prolactin → amenorrhea

**DIAGNOSIS**

- **History:**
  - Symptoms of hypothalamic-pituitary disease?
    - Headaches
    - Galactorrhea
    - Visual field defects
    - Fatigue
    - Polyuria, polydipsia
    - A large amount of weight loss or weight gain
    - Anorexia nervosa
    - Hypothyroidism
    - Medications
  - Symptoms of estrogen deficiency?
    - Hot flashes
    - Vaginal dryness
    - Poor sleep
    - Decreased libido
    - Breast atrophy
  - History of obstetrical catastrophe, severe bleeding? (Possible Sheehan’s Syndrome)
  - History of D&C (particularly multiple or after infection), endometritis? (Possible Asherman’s Syndrome)

**DIAGNOSIS**

- **Physical Exam**
  - BMI (Ideal: 20-25)
    - BMI > 30 kg/m² seen in 50% of women with PCOS
    - BMI < 18.5 kg/m² may have functional hypothalamic amenorrhea
  - Signs of systemic illness/cachexia
  - Evaluate genital tissue for signs of estrogen deficiency
  - Palpate breasts/attempt to express galactorrhea
  - Neuro exam for visual field defects
  - Skin exam, evaluating for
    - Stigmata of PCOS: Hirsutism, acne, acanthosis nigricans
    - Stigmata of thyroid disorders: thin/dry skin, skin thickening
    - Stigmata of Cushing’s disease: striae

**No features of androgen excess present**

- **Physiological**, e.g. pregnancy, lactation, menopause
- **Iatrogenic**, e.g. depot medroxyprogesterone acetate contraceptive injection, radiotherapy, chemotherapy
- **Systemic disease**, e.g. chronic illness, hypo- or hyperthyroidism
- **Uterine causes**, e.g. cervical stenosis, Asherman’s syndrome (intra-uterine adhesions)
- **Ovarian causes**, e.g. premature ovarian failure, resistant ovary syndrome
- **Hypothalamic causes**, e.g. weight loss, exercise, psychological distress, chronic illness, idiopathic
- **Pituitary causes**, e.g. hyperprolactinemia, hypopituitarism, Sheehan’s syndrome
- **Causes of hypothalamic/pituitary damage**, e.g. tumours, cranial irradiation, head injuries, sarcoidosis, tuberculosis
Premature Ovarian failure (premature menopause)

- chromosomal anomalies
- autoimmune disease

If the woman is under 30, a karyotype should be performed to rule out any mosaicism involving a Y chromosome.

If a Y chromosome is found the gonads should be surgically excised.

Laboratory evidence of autoimmune phenomenon is much more prevalent than clinically significant disease.

Features of androgen excess present

CONSIDER:
- Polycystic ovary syndrome
- Cushing’s syndrome
- Late-onset congenital adrenal hyperplasia
- Adrenal or ovarian androgen-producing tumour

Diagnosis

- **Laboratory Testing**
  - Serum prolactin, TSH, FSH (high in primary ovarian failure)
    - Serum prolactin can be increased by stress, intercourse, nipple stimulation, or eating (fasting AM prolactin best)
    - If FSH is high, consider a karyotype
  - If signs of hyperandrogenism: DHEA-S and testosterone (serum free and total testosterone)
  - If relevant, assess estrogen status
    - Serum estradiol (highly variable in early ovarian failure or recovering hypothalamic amenorrhea)
    - Progestin withdrawal test with Provera 10 mg x 10 days

Treatment

- **For functional hypothalamic amenorrhea (excludes pathologic disease)**
  - Explain need for increased caloric intake and/or reduced exercise
  - Cognitive Behavioral Therapy demonstrated to be effective in helping women resume ovulatory cycles in one small study
- **For hyperprolactinemia**
  - Dopamine agonist therapy
- **Primary ovarian insufficiency or POF**
  - Hormone therapy for prevention of bone loss

Treatment

- **Hyperandrogenism/PCOS**
  - Treatment directed toward symptoms/goals of patient
    - relief of hirsutism
    - fertility
    - prevention of obesity and metabolic defects
  - Endometrial protection via resumption of menses, and if necessary, cyclic or continuous OCPS/hormonal therapy
- **Asherman’s Syndrome**
  - Hysteroscopic lysis of adhesions
  - Long-term estrogen administration to stimulate regrowth of endometrial tissue
## Treatment for Women with PCOS

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Treatment Options</th>
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<tbody>
<tr>
<td>Infertility</td>
<td>Metformin; clomiphene; letrozole; gonadotropins; ovarian cautery</td>
</tr>
<tr>
<td>Skin manifestations</td>
<td>Oral contraceptive + antiandrogen (spironolactone, flutamide, finestride); GnRH agonists</td>
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<tr>
<td>Dysfunctional bleeding</td>
<td>Cyclic progestogen; oral contraceptives</td>
</tr>
<tr>
<td>Weight/metabolic concerns</td>
<td>Diet/lifestyle management; metformin</td>
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</tbody>
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## Secondary Amenorrhea

CASE PRESENTATIONS & MANAGEMENT DISCUSSION & Q&A

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## SECONDARY AMENORRHEA

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- Electronic Version available by request