Amenorrhea:
you will never be confused again

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Case #1
21 y.o. thin, G₀ student desires birth control pills. LMP 4 months ago.
Happy about not having periods "like some other girls in her dorm."

Case #2
48 y.o. G₃P₃ with regular heavy menses until four months ago. Now reports hot flushes.

Case #3
28 y.o. on OCPs for 11 months now with no periods for 4 months
Goals

- Understand “menorrhea” (normal cycles)
- Know 8 major causes of secondary amenorrhea
- Know systematic approach
- Know when to refer

The Menstrual Cycle:

- Follicular
  - FSH
  - Developing follicle
  - Estrogen
  - Endometrial proliferation
    - “bricks”
- Luteal
  - LH
  - Corpus luteum
  - Progestin
  - Endometrial stabilization
    - “mortar”

- Regular, monthly menses = ovulation

Normal, ordered endometrial lining: bricks and mortar

Unstable, thick endometrial lining: all bricks, no mortar

As conceptualized by Dr. Robert Nachtigal
Unstable, thin endometrial lining: all mortar, no bricks

Endometrial lining on OCPs (containing estrogen and progestins): Lots of mortar with just a few stabilizing bricks

Definition: amenorrhea

Primary - the absence of menarche by age 16 years
Secondary - the absence of menstruation for 6 or more months in women with past menses

Secondary amenorrhea: differential diagnosis

1. Pregnancy
2. Menopause (‘premature ovarian failure’ if under age 40)
3. Chronic anovulation / polycystic ovarian syndrome (PCOS)
4. Hyperprolactinemia (breastfeeding, prolactinoma)
5. Medications (e.g., neuroleptics, progestins)
6. Hypothalamic anovulation (weight loss / exercise induced)
7. Asherman's syndrome (endometrial scarring)
8. Hypothyroidism
Work-up

- History
- Physical
- Laboratory tests
- Diagnostic in vivo tests

### History

<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pregnancy</td>
<td>Sexually active</td>
</tr>
<tr>
<td>2. Menopause</td>
<td>Hot flashes, night sweats</td>
</tr>
<tr>
<td>3. Chronic anovulation/PCOS</td>
<td>Prior irregular cycles</td>
</tr>
<tr>
<td>4. Hyperprolactinemia</td>
<td>Galactorrhea</td>
</tr>
<tr>
<td>5. Medications</td>
<td>OCPs, progestins, neuroleptics, etc</td>
</tr>
<tr>
<td>6. Hypothalamic</td>
<td>Weight loss, exercise</td>
</tr>
<tr>
<td>7. Asherman's syndrome</td>
<td>Recent uterine surgery (D&amp;C)</td>
</tr>
<tr>
<td>8. Hypothyroidism</td>
<td>Constipation, fatigue</td>
</tr>
</tbody>
</table>

### Physical Examination

<table>
<thead>
<tr>
<th>Condition</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pregnancy</td>
<td>Uterine size</td>
</tr>
<tr>
<td>2. Menopause</td>
<td>Urogenital atrophy</td>
</tr>
<tr>
<td>3. Chronic anovulation/PCOS</td>
<td>Hirsutism</td>
</tr>
<tr>
<td>4. Hyperprolactinemia</td>
<td>Galactorrhea</td>
</tr>
<tr>
<td>5. Medications</td>
<td>-</td>
</tr>
<tr>
<td>6. Hypothalamic</td>
<td>Urogenital atrophy</td>
</tr>
<tr>
<td>7. Asherman's syndrome</td>
<td>-</td>
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<tr>
<td>8. Hypothyroidism</td>
<td>-</td>
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</tbody>
</table>

### Laboratory Examination

<table>
<thead>
<tr>
<th>Condition</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pregnancy</td>
<td>B HCG</td>
</tr>
<tr>
<td>2. Menopause</td>
<td>Follicle stim horm (FSH)</td>
</tr>
<tr>
<td>3. Chronic anovulation/PCOS</td>
<td>-</td>
</tr>
<tr>
<td>4. Hyperprolactinemia</td>
<td>Fasting prolactin</td>
</tr>
<tr>
<td>5. Medications</td>
<td>-</td>
</tr>
<tr>
<td>6. Hypothalamic</td>
<td>FSH, LH</td>
</tr>
<tr>
<td>7. Asherman's syndrome</td>
<td>-</td>
</tr>
<tr>
<td>8. Hypothyroidism</td>
<td>Thyroid stim horm (TSH)</td>
</tr>
</tbody>
</table>
At first visit

- 3/8 diagnoses ruled out (pregnancy, Asherman’s and medications)
- Send patient for prolactin, TSH
- Do progestin challenge test

Progestin challenge test

- Mimics ovulation and the function of the corpus luteum (you are providing progesterone instead of the corpus luteum)
- Can use medroxyprogesterone acetate (Provera®) 10 mg po QD X 10 days
- Return in 2 weeks
- If bleeding occurred, then the patient is not estrogen deficient (she has bricks) and the diagnosis is chronic anovulation.

At second visit (2 weeks later)

- Results of prolactin and TSH known: if normal, 5/8 diagnoses ruled out.
- Results of progestin challenge known: if no bleeding, 6/8 diagnoses ruled out (and the patient has an estrogen deficient state).
- Hypothalamic anovulation and menopause are the 2 remaining diagnoses
- Get an FSH: if low, hypothalmic amenorrhea; if high, menopause

Estrogen status

- Note that 5/8 diagnoses are all estrogen deficient states (hyperthyroidism, hyperprolactinemia, hypothalamic dysfunction, medication-induced amenorrhea and menopause)
Can we be even briefer?

- Perhaps
- First visit: rule out Asherman’s and medications by history; rule out pregnancy by hCG (3/8)
- Order TSH, prolactin and FSH (7/8)
- Assume chronic anovulation and prescribe oral contraceptive pills (if no contraindications)
- Second visit: if prolactin, FSH or TSH abnormal, treat accordingly; if they are normal, make presumptive diagnosis of chronic anovulation and continue oral contraceptive pills

Absolute contraindications to combined oral contraceptive pills

WHO criteria, 2006

- Current breast cancer
- Hypertension (>160/>100)
- Deep venous thrombosis (prior, current, major surgery)
- Breastfeeding and within 6 weeks of delivery
- Stroke, ischemic heart disease
- Migraine with aura
- Liver disease: cancer, active hepatitis

Treatments

Contemporary practice focused on treatment of the primary problem

- Hyperprolactinemia: imaging, bromocriptine
- Hypothyroidism: replacement therapy
- Hypothalamic amenorrhea: oral contraceptive pills, estrogen replacement therapy; gonadotropin injections (if pregnancy desired)
- Medication-induced amenorrhea: if medication is needed, consider oral contraceptive pills, estrogen replacement therapy

Treatments

Chronic anovulation

If pregnancy not desired, can use oral contraceptive pills or cyclic medroxyprogesterone acetate.

If pregnancy desired, ovulation induction (e.g., clomiphene citrate)
**Polycystic Ovarian Syndrome**  
*(ACOG, 2002)*

A state of “unexplained hyperandrogenic chronic anovulation”
Hyperandrogenism can be based solely on clinical criteria (e.g., hirsutism)
Most occurs in 6-10% of women; 65% are hirsute
Recommended screening: glucose intolerance (2-hour glucose level after a 75-g fasting challenge) and dyslipidemia (fasting lipoprotein profile, LDL, HDL and TGs)

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**Case #2**

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Summary

• Most causes of secondary amenorrhea can be solved and treated in the primary care setting (only 8 major diagnoses)
• Chronic anovulation and PCOS are frequent causes
• Using “bricks and mortar” analogy can be useful for patients
• If cases are confusing, refer