Gynecological Problems: 
Case Study Approach 

Joyce King, CNM, Ph.D. 

Disclosure Statement 
I have no real or perceived vested interests that relate to this presentation nor do I have any relationship with pharmaceutical companies, biomedical device manufacturers, and/or other corporations whose products or services are related to pertinent therapeutic areas.

Learning Objectives 
- Review the basic principles of normal menstrual function. 
- Discuss the etiology, evaluation, and management of abnormal uterine bleeding. 
- Discuss the etiology, evaluation and management of polycystic ovary syndrome. 
- Discuss the differential diagnosis of the pelvic mass. 
- Discuss the etiology and work-up of a patient with amenorrhea.
Principles of Normal Menstruation

- Normal menstruation requires an intact hypothalamic/pituitary/ovarian axis and involves the following hormones:
  - GnRH
  - FSH
  - LH
  - Estradiol
  - Progesterone
  - Activin
  - Inhibin

Both estrogen and progesterone are key in the control of the normal menstrual cycle.

Menstrual Cycle Overview

- Average age of menarche - 12.8 years
- Average age of menopause - 52 years
- Average menstrual cycle - 28-30 days
- Average duration of menstruation - 4-6 days
- Average blood loss – 35 mL

Blood loss greater than 60 to 80 mL per cycle is associated with anemia.
Normal Menstrual Flow

- On average, most normal menstruating women use 5 to 6 pads or tampons daily and do not complain of leakage.

Normal Controls of Menstrual Bleeding

- $\text{PGE}_2$ - vasodilation
- $\text{PGF}_{2\alpha}$ - vasoconstriction
- Thromboxane - promotes platelet aggregation
- Prostacyclin - inhibits platelet aggregation
- Normally, both $\text{PGE}_2$ and $\text{PGF}_{2\alpha}$ increase, but $\text{PGF}_{2\alpha}/\text{PGE}_2$ ratio increases near menses.

Causes of Abnormal Uterine/Vaginal Bleeding

### Pregnancy-related bleeding
- Threatened, missed, or incomplete miscarriage
- Ectopic pregnancy
- Molar pregnancy

### Dysfunctional uterine bleeding
- Anovulatory
- Ovulatory

### Pharmacologic agents
- Hormonal contraception
- Hormone therapy
- Tamoxifen
- Glucocorticoids
- Anticoagulants

### Benign uterine neoplasia
- Cervical and endometrial polyps
- Myomas
- Adenomyosis
- Endometrial hyperplasia
Causes of Abnormal Uterine/Vaginal Bleeding

**Inflammatory processes**
- Endometritis
- Cervicitis
- Infectious or atrophic vaginitis

**Pelvic malignancies**
- Endometrial carcinoma
- Cervical carcinoma

**Systemic disease**
- Thyroid disorders
- Coagulation disorders
  - Von Willebrand
  - Platelet function disorders
- Renal failure
- Hepatic failure

Dysfunctional Uterine Bleeding

Dysfunctional Uterine Bleeding (DUB)

Abnormal, unpredictable bleeding of endometrial origin not resulting from an organic cause.
Dysfunctional Uterine Bleeding

- Incidence:
  - 20% puberty
  - 50% > 45 years of age
  - 30% during reproductive years

Diagnosis

- History
- Physical examination
- Appropriate laboratory tests
- Other diagnostic testing

History

- Keep in mind the categories of the causes of abnormal uterine bleeding
- Consider the patient’s:
  - Age
  - Severity of symptoms
  - Fertility plans
  - Weight
  - Previous menstrual patterns
History

- Note:
  - Predictable cyclic menses, even though heavy is generally associated with ovulation.
  - Anovulatory bleeding is usually irregular and unpredictable and most often observed in:
    - Adolescents
    - Perimenopausal women
    - Obese women
    - Women with polycystic ovary syndrome

- Note:
  - Regular cycles that are increasing in amount and/or duration or if there is chronic intermenstrual bleeding superimposed on regular cycling is often associated with uterine structural lesions (i.e. polyps, myomas)
  - The most common cause of a sudden departure from regular cycling is a complication of pregnancy.

History

- Suspect a coagulation disorder:
  - Menorrhagia from menarche
  - Frequent epistaxis
  - Bleeding gums with brushing of teeth
  - Past episodes of excessive bleeding from trauma or surgery
Case #1

24 y.o. complains of heavy periods associated with severe cramping. Her menses typically occur every 28-29 days and last 5 days. Over the past few months they have increased to lasting 8-9 days per cycle with increased pain. She is not on any medication and has no history of a chronic illness. She is sexually active and uses condoms for contraception.

Physical Examination

- Vital signs and weight
- Establish that the bleeding is uterine
- Pelvic exam
  - Uterus
    - Irregular shape – myomas
  - Tender - PID
  - Cervix
  - Vagina
- Bruising and petechiae

On physical examination, the uterus is at the upper end of normal in size. She has no abnormal discharge or bleeding. The adnexa are nonpalpable and no masses are noted on bimanual examination. The remainder of the physical examination is unremarkable.
Diagnostic Testing

- Pregnancy test
- CBC
- BBT
- Serum progesterone levels
- TSH
- Pap smear and STD testing
- TVU/MRI

Diagnostic Testing

- Saline infusion sonography
  - The risk of endometrial hyperplasia and endometrial cancer is remote if the endometrial thickness is less than 4-5 mm
- Adolescents with heavy bleeding since menarche
  - Screen for von Willebrand’s disease (e.g., Rostocetin cofactor assay)
Diagnostic Testing

- Aspiration biopsy of the endometrium
  - Women > 40 years of age with AUB
  - Any age group with a history of 2-3 years of untreated anovulatory bleeding, especially if obesity is present
  - Any bleeding after 12 months of amenorrhea
- Hysteroscopy

Hysteroscopy

Case #1

Diagnostic Testing:
- Pregnancy test – neg
- CBC – Hgb, 9.8; MCV – 70
- Platelet count – normal
- WBC – normal
- U/S – 6 cm fibroid
Note: The diagnosis of DUB is generally a diagnosis of exclusion.

Differential Diagnosis of AUB

- 14-25 years of age
  - Pregnancy
  - Hormonal contraception
  - Cervicitis
  - Anovulation
  - Cervical polyps
  - Endometriosis

- 26-35 years of age
  - Pregnancy
  - Hormonal contraception
  - Cervicitis
  - Cervical polyps
  - Anovulation
  - Myomas
  - Endometriosis
  - Endometrial hyperplasia
Differential Diagnosis of AUB

- 36-45 years of age
  - Pregnancy
  - Anovulation
  - Endometrial hyperplasia
  - Myomas
  - Endometriosis
  - Hormonal contraception
  - Endometrial carcinoma

- > 45 years of age
  - Estrogen therapy
  - Endometrial hyperplasia
  - Myomas
  - Endometrial carcinoma
  - Coital injuries

Other less common causes of DUB

- Abnormal thyroid function
- Coagulation defects
- Severe organ disease
- Foreign object
Successful Strategy in the Management of DUB

- Making the correct diagnosis
- Individualized evaluation
- Attending to the health in general
- Hormone therapy when indicated
- Adequate follow-up

Treatment Goals

- Control bleeding
- Prevent recurrence
- Preserve fertility

Treatment

- Determined by pattern of bleeding, severity of blood loss, and degree of expressed concern.
- Watchful observation
- Stress reduction
Treatment

- Medical Therapy
  - Combined oral contraceptives 1 tablet twice daily x 5-7 days
  - To prevent heavy withdrawal bleeding on discontinuation of this regimen, the patient can continue to take one pill daily until the package of pills is complete.
  - May remain on OCPs or switch to Provera 10 mg daily for days 13-25 every month
  - Continuous OC’s (monophasic formulations)

- NSAIDs Dose and Schedule
  - Commonly used NSAIDs and doses
    - Ibuprofen 800 mg 3 x daily
    - Naproxen sodium 550 mg 3 x daily
    - Mefenamic acid 500 mg 3 x daily
    - Meclofenamate sodium 100 mg 3 x daily
  - Recommended schedule
    - Initiate therapy immediately prior to or on first day of menses, maintain recommended dose for 3 to 5 days
Treatment

- Surgical therapy
  - Operative hysteroscopy
  - Endometrial ablation
    - Laser, roller ball or thermal ablation
  - Myomectomy
  - Uterine artery embolization
  - Hysterectomy

Case #1

What are the options for treating menorrhagia? How would you treat this patient?

Causes of Anovulation

- Central defects
  - Suppression of GnRH is associated with:
    - Immature hypothalamus
    - Stress and anxiety
    - Anorexia nervosa
    - Acute weight loss
    - Hyperprolactinemia
Causes of Anovulation

- Abnormal Feedback signals
  - Elevated estradiol levels:
    - Pregnancy
    - Ovarian or adrenal tumors
    - Thyroid or hepatic disease
    - Extraglandular estrogen production
  - Low levels of estrogen
    - Absence of LH surge → anovulation

Causes of Anovulation

- Local Ovarian Conditions
  - Factors that control follicular growth and development
  - Elevated local androgen concentrations

Causes of Anovulation

- Alterations in ovarian function may arise from:
  - Infections
  - Endometriosis
  - Changes in hormone receptors
  - Abnormal gonadotropins
Effect of Body Weight on Ovulatory function

- ↑ adiposity → ↑ peripheral aromatization of androgens to estrogens
- ↓ sex hormone binding globulin → ↑ free estradiol and testosterone
- ↑ insulin levels → ↑ ovarian androgen production

Polycystic Ovary Syndrome

Amelia 16 year old

- 16 year old presents with mom concerned about infrequent menses.
- Menarche age 11; between 2-3 menstrual cycles a year
- Last menstrual cycle was 2 months ago and lasted 10 days
- Amelia is more concerned about her acne, hirsutism, and obesity
Definition

➢ Lack of consensus
➢ Practical and useful clinical definition (any 2 of the following 3 disorders):
  • Oligo- or anovulation
  • Evidence of androgen excess for which there is no other cause.
  • Polycystic ovaries on U/S examination
➢ Insulin resistance and hyperinsulinemia

2009 Androgen Excess and PCOS Society task force report.

Epidemiology

➢ Occurs in 6% to 8% of reproductive age women
➢ 30% of women with amenorrhea
➢ 75% with oligomenorrhea
➢ 87% with hirsutism

Prevalence Study Reported in 1998

Unselected sample of white and African-American women between the ages of 18 and 45 who presented for a University employment physical in Alabama:
  • 277 consented to evaluation for PCOS
    • 4.7% - white women
    • 3.4% - African American women

This prevalence implies that ~3 million reproductive-aged women in the U.S. have PCOS
Other Reproductive Morbidities

- Infertility
- Abnormal uterine bleeding
- Increased pregnancy loss

Clinical Importance

- Increased prevalence of diabetes
- Increased risk for coronary heart disease
- Increased risk of endometrial cancer

Pathophysiology

- Fundamental pathophysiologic defect in PCOS is unknown
- Interrelated characteristics
  - Insulin resistance
  - Hyperandrogenism
  - Altered gonadotropin dynamics
- Genetics
PCOS is associated with insulin resistance
- Elevated oral glucose testing
- Frequently associated with obesity
- May have acanthosis nigricans
- More pronounced with chronic anovulation
- Pathogenesis remains unclear
Acanthosis Nigricans

- In young women who do not have an adenocarcinoma, acanthosis nigricans strongly suggests insulin resistance.

Key Feature - Hyperandrogenism

- What is the relationship between insulin resistance and hyperandrogenism?
  - Administration of diazoxide, which specifically reduces insulin concentrations, results in a reduction in circulating androgen concentrations.
  - Weight loss and insulin sensitizers, which also lead to a reduction in insulin, similarly are associated with a reduction in androgens.

Key Feature - Hyperandrogenism

- May or may not have elevated serum androgen levels
  - Serum testosterone level is the best marker for ovarian hyperandrogenism

- Biological expression of hyperandrogenism
  - Acne
  - Hirsutism
  - Alopecia
Hirsutism

Alopecia

Key Feature - Anovulation
- Usually chronic
- Presents as oligomenorrhea or amenorrhea of perimenarchal onset
  - Insufficient FSH
  - Decreased estradiol production
  - No LH surge
  - No ovulation
Key Feature - Polycystic Ovaries

- Generally enlarged
- Vaginal scans are more sensitive than abdominal scans

Note: Not all women with PCOS have polycystic-appearing ovaries.

Impaired Glucose Tolerance and Diabetes

- 31% of obese, reproductive-age women with PCOS had impaired glucose tolerance.
- 7.5% had overt diabetes.
- 10.3% of nonobese women with PCOS had impaired glucose tolerance and 1.5% had diabetes.
- Rate almost 3-fold that of the general population.
- Risk is similar in different populations and ethnic groups.

Altered Serum Lipid Profiles

- Elevated cholesterol, triglyceride, and LDL cholesterol
- Low levels of HDL cholesterol – most common lipid alteration
- Findings may vary dependant on:
  - Body weight
  - Diet
  - Ethnicity
Obesity

- Forty percent to 50% of women with PCOS are obese
- Abdominal obesity – increased waist-to-hip ratios
- Obesity worsens insulin resistance
- Obesity associated with a decrease in SHBG → Increase in free testosterone
- Also increases risk for diabetes and CVD

Central Obesity

Waist size > 35

Diagnostic Approach

- The clinician can avoid over-diagnosis or making the wrong diagnosis by using the working definition of polycystic ovarian syndrome as the basis for evaluation:
  - Chronic anovulation
  - Androgen excess
  - Polycystic ovaries
Diagnostic Approach

- History
  - Infrequent menstrual cycles since menarche
  - Hirsutism is the most common manifestation of the androgen component of PCOS
    - Gradual
    - Progressive
  - Acne and oily skin
  - Infertility

*A medication history is also important, since many drugs may cause hirsutism.*

Medications that May Cause Hirsutism

- Antileptics
  - Phenytoin (Dilantin)
  - Valproate (Depakote)
  - Valproic acid (Depakene)
- Corticosteroids
  - Betamethasone (Celestone)
  - Cortisone (Cortone)
  - Dexamethasone (Decadron)
  - Fludrocortisone (Florinef)
  - Hydrocortisone (Cortef)
  - Prednisone (Deltasone)
- Anabolic agents
  - Danazole (Danocone, Cyclomen)
  - Testosterone (Andro 100, Androderm, Testoderm)
  - Minoxidil (Loniten, Rogaine)
- Metoclopramide (Reglan)
- Methyldopa (Aldomet)
- Reserpine (Serpasil)
- Phenothiazines

Diagnostic Approach

- Physical Examination
  - Body mass index (BMI = kg/m²)
  - Abdominal circumference
  - Blood pressure
  - Amount and distribution of excess hair
  - Signs of virilization
  - Skin changes
    - Acne
    - Acanthosis nigricans
    - Striae
  - Abdominal and pelvic exam to exclude any masses
  - Evaluate for galactorrhea
Signs of Virilization
- Clitoromegaly
- Deepening of the voice
- Increased muscle mass
- Loss of breast tissue
- Malodorous perspiration
- Temporal hair recession and balding

Differential Diagnosis for PCOS
- Nonclassical congenital adrenal hyperplasia due to deficiency of 21-hydroxylase
- Cushing’s syndrome
- Androgen-producing adrenal or ovarian neoplasms
- Hyperprolactinemia
- Thyroid disorder
- Premature ovarian failure

Diagnostic Studies
- Differing opinions regarding what laboratory studies should be ordered
- PCOS is primarily a clinical diagnosis
- Given a history of chronic anovulation and androgen excess, the major condition that needs to be excluded to secure the diagnosis of PCOS is congenital adrenal hyperplasia, which is very uncommon.
  - 17-hydroxyprogesterone
Diagnostic Studies

- Total testosterone - >60 ng/dL is considered elevated
- Free testosterone
- SHBG (decreased)

17-hydroxyprogesterone concentrations to rule out 21-hydroxylase-deficient nonclassical adrenal hyperplasia
- To maximize sensitivity
  - Obtain sample in the follicular phase
  - Between 7:00 and 9:00 a.m.
- Results less than 2 ng/mL nonclassical adrenal hyperplasia is safely excluded
- Results greater than 2 ng/mL refer to a reproductive endocrinologist for further evaluation.

Tests for ovulatory function:
- Basal body temperature
- Serum progesterone concentrations
- Endometrial biopsy

If virilization is present
- DHEA-S. If elevated, a CT scan with contrast is recommended to evaluate for an adrenal tumor
Initial Diagnostic Evaluation of PCOS

Oligomenorrhea

Prior history of cyclic bleeding

Since menarche

Hirsutism

No hirsutism

Prolactin, TSH, further evaluation

Testosterone, 17OHP, CAH

NC

PCOS

Diagnostic Studies

➢ Other laboratory tests often advocated:
  - LH/FSH ratios
  - Vaginal probe ultrasound

Diagnostic Studies

➢ Other tests that are indicated to evaluate for comorbid conditions include:
  - Lipid panel
    - Total cholesterol
    - HDL and LDL
    - Triglycerides
  - 2-hour oral glucose tolerance test that measures both fasting and postprandial glucose
  - Fasting serum insulin levels

Adapted from Guzick, Obstet Gynecol 2004
Ameilia

- BMI – 34.5
- Physical Exam
  - Central obesity
  - Facial hair
  - Acne on face, chest, and back
  - No clitoromegaly
- Lab studies WNL
- Ultrasound – multiple cysts within ovaries

Goals of Management

- Decrease androgen levels
- Control symptoms
- Protect endometrium
- Prevent long-term sequelae
- ? Pregnancy

Management

- If patient is overweight or obese (BMI ≥ 25)
  - Life style modification
    - Diet – moderate calorie restriction
    - Exercise
  - Study: Moderate calorie restriction that resulted in 2.5% weight loss:
    - 21% decline in free testosterone
    - 9 of 18 women with irregular cycles resumed regular ovulation
    - 2 women became pregnant
Management

- **Hirsutism**
  - Local measures
    - Shaving
    - Bleaching
    - Depilatories
    - Electrolysis
    - Laser therapy
  - Pharmacologic therapy
    - Blocking androgen action at hair follicles
      - Vaniqua topical cream bid at least 8 hours apart
    - Suppression of androgen production
      - Aldactone 50-200 mg/day
      - Eulexin 250 mg bid or tid
      - Oral contraceptives (i.e. Yasmin)
    - Insulin-sensitizing agents
      - Glucophage
      - Actos

Management

- **Menstrual Irregularity**
  - Oral contraceptives
  - Cyclic progestin
  - Insulin sensitizing agents
OC Recommendation - Yasmin

- Monophasic pill
  - 30 µg ethinyl estradiol
  - 3 mg drospirenone (analogue of spironolactone)
    - Antiandrogenic – suppression of ovarian and adrenal androgen production
    - Antimineralocorticoid – stimulation of Na+/K+-decreased average diastolic blood pressure by 1-4 mm Hg (although, 8.5% have increased diastolic blood pressure)

Benefits of Oral Contraceptives

- Regular withdrawal bleeding
- Reduction in the risk of endometrial hyperplasia or cancer
- Reduction in LH secretion and consequent reduction of ovarian androgens
- Increased sex hormone binding globulin production and consequent reduction in free testosterone
- Improvement in hirsutism and acne

Management

- Infertility
  - Weight loss through diet and exercise in obese women
  - Pharmacotherapy
    - Clomiphene citrate 50 mg – 150 mg daily
    - Clomiphene citrate plus metformin
  - Laparoscopic ovarian drilling (LOD)
  - Injectable gonadotropins
  - In vitro fertilization
Management

- Long-term Health Risks:
  - Life-style modification to improve insulin sensitivity:
    - Low glycemic diet
    - Dietary fiber
    - Fish oil
    - D-chiro-inositol
    - Chromium
  - Exercise
  - Metformin

Treatment Algorithm

PCOS
Chronic anovulation and androgen excess

Irregular bleeding
Hirsutism
Infertility
General Health Risks

If overweight, behavioral weight reduction

Oral Contraceptives
Oral Contraceptives and spironolactone
Medical ovoidation induction
Metformin

Pharmacologic Therapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Examples</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal contraception</td>
<td>Increases SHBG, suppresses LH and FSH, anti androgen</td>
<td>OC, Patch, Nuvaring</td>
<td>Androgen symptoms, Menstrual irregularity</td>
</tr>
<tr>
<td>Antiandrogen</td>
<td>Inhibits androgen from binding to the receptors</td>
<td>Cyproterone acetate, Spironolactone, Flutamide</td>
<td>Androgen symptoms</td>
</tr>
<tr>
<td>GnRH agonist</td>
<td>Down regulation of GnRH secretion</td>
<td>Leuprolide, Nafarelin</td>
<td>Androgen symptoms</td>
</tr>
<tr>
<td>5-alpha reductase inhibitors</td>
<td>Inhibits the production of 5-alpha reductase</td>
<td>Finasteride</td>
<td>Androgen symptoms</td>
</tr>
</tbody>
</table>
### Pharmacologic Therapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Examples</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Reduces hepatic glucose production; lowering insulin levels; May have effect on early carcinogenesis</td>
<td>Metformin</td>
<td>Androgen symptoms; Menstrual irregularity; Ovulation induction; Insulin resistance</td>
</tr>
<tr>
<td>Thiazolidine</td>
<td>Enhances insulin action at target tissue level</td>
<td>Pioglitazone (Actos) Rosiglitazone (Avandia)</td>
<td>Androgen symptoms; Menstrual irregularity; Ovulation induction; Insulin resistance</td>
</tr>
<tr>
<td>D-chiro-inositol</td>
<td>Enhanced insulin action</td>
<td>N/A</td>
<td>Menstrual irregularity; Ovulation induction; Insulin resistance</td>
</tr>
</tbody>
</table>

### Pharmacologic Therapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Examples</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Suppress ACTH and thus adrenal androgen production</td>
<td>Prednisone Dexamethasone</td>
<td>Androgen symptoms; Menstrual problems; Ovulation induction</td>
</tr>
<tr>
<td>Ornithine decarboxylase inhibitor</td>
<td>Inhibition of ornithine decarboxylase</td>
<td>Varilisa</td>
<td>Androgen symptoms; Especially hair growth</td>
</tr>
<tr>
<td>Clomiphene citrate</td>
<td>Antiandrogen; acts to induce rise in FSH and LH</td>
<td>Clomid</td>
<td>Ovulation induction</td>
</tr>
<tr>
<td>Human recombinant FSH + hCG</td>
<td>Follicular recruitment and maturation</td>
<td>Puregon Follistim</td>
<td>Ovulation induction</td>
</tr>
</tbody>
</table>

### Follow-up

- For women who are not interested in pregnancy, follow-up at 6-month intervals.
- Monitor:
  - Weight
  - Blood pressure
  - Glucose
  - Lipids
- Evaluate patient’s symptoms:
  - Menstrual cycles
  - Hirsutism
Ameilia

- Started on oral contraceptives and metformin
- Nutritionist and fitness specialist

Case Study

24 y.o. presents with irregular menses since menarche occurring every 3-6 months. She also complains of increasing facial hair and a 30-pound weight gain over the past 5 years despite numerous diets. Her family history reveals that both her father and paternal grandmother have type 2 DM.

Case Study

Physical Examination:
- Weight – 184
- Height 5’ 6”
- BMI – 29.7
- Increased hair on upper lip, chin, and chest
- Acanthosis nigricans on the dorsal surface of her neck
Case Study

Diagnostic tests:
- Total testosterone (ng/dL) – 71 (<62)
- 17-hydroxyprogesterone (ng/dL) – 143 (<200)
- TSH (mcU/mL) – 2 (0.2-7.0)
- Prolactin (ng/mL) – 11 (0-20)
- Fasting glucose (mg/dL) – 87 (<110)

Case Study

How would you manage this patient?

Resources

- The Hormone Foundation  http://www.hormone.org
AMENORRHEA

- Absence or retardation of secondary sexual characteristics with failure to menstruate by age 14; or presence of normal growth and development of secondary sexual characteristics without menstruation by age 16.

Note: Oligomenorrhea involving less than nine cycles per year requires further investigation.
PHYSIOLOGIC AMENORRHEA

- Delayed puberty
- Pregnancy
- Lactational amenorrhea
- Menopause
- Hormonal contraception

AMENORRHEA - Etiology

- Compartment I - Disorders of the outflow tract or uterus
- Compartment II - Disorders of the ovary
- Compartment III - Disorders of the anterior pituitary
- Compartment IV - Disorders of the CNS (hypothalamus)

AMENORRHEA - Evaluation

- History
  - Exercise patterns
  - History of growth and/or development disorders
  - Emotional stress
  - Family history of genetic anomalies
  - Nutritional status (eating habits)
    - Changes in body weight
  - Other symptoms (nipple discharge, hirsutism, hot flashes, vaginal dryness, or infertility)
AMENORRHEA - Physical Examination

- Temporal balding
- Thyroid enlargement
- Skin changes
- Acne
- Hirsutism
- Breast development
- Galactorrhea
- Body fat distribution
- Clitoromegaly
- Vaginal patency
- Cervical stenosis
- Presence or absence of internal genitalia
- Bilaterally enlarged ovaries
- Pelvic or rectal mass
- Atrophy of genital organs

AMENORRHEA - Diagnostic Evaluation

Step I
- Exclude pregnancy
- TSH, Serum prolactin
- Progestational challenge (Provera 10 mg daily x 5 days)

Goal: Assess level of endogenous estrogens and competence of outflow tract.

AMENORRHEA - Diagnostic Evaluation

Results of Step I:
- Elevated TSH → Hypothyroidism
- Elevated serum prolactin → Compartment III disorder
- + Withdrawal bleed with normal prolactin and TSH → Anovulation → Compartment IV disorder
AMENORRHEA - Diagnostic Evaluation

- Results of Step I:
  - Withdrawal bleed, either the target organ outflow tract is not working or preliminary estrogen proliferation of the endometrium has not occurred.

- Step II
  - Cycle with estrogen (i.e. 1.25 mg conjugated estrogens daily x 21 days) and progesterone (i.e. medrosyprogesterone acetate 10 mg daily for the last 5 days of the estrogen). **If no withdrawal bleed occurs, repeat estrogen/progestin cycle.**

  **Goal:** Assess competence of outflow tract.

- Results of Step II:
  - Withdrawal bleed → defect in Compartment I systems.

  **Abnormalities in Compartment I are rare; in the absence of a reason to suspect a problem, Step 2 can be omitted.**
AMENORRHEA - Diagnostic Evaluation

Step 3 -
- Assay the level of FSH and LH (gonadotropins)

Goal: Ascertain whether the problem is pituitary or ovarian dysfunction.

<table>
<thead>
<tr>
<th></th>
<th>FSH</th>
<th>LH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Adult</td>
<td>5-30 IUL (Ovulatory peak = 2 x base)</td>
<td>5-20 IUL (Ovulatory peak = 3 x base)</td>
</tr>
<tr>
<td>Hypogondotropic</td>
<td>&lt;5 IUL</td>
<td>&lt;5 IUL</td>
</tr>
<tr>
<td>Hypergondotropic</td>
<td>&gt;20 IUL</td>
<td>&gt;40 IUL</td>
</tr>
</tbody>
</table>

Results of step 3: High Gonadotropins
- Menopause
- Premature ovarian failure
- Tumor that produces gonadotropins
AMENORRHEA - Diagnostic Evaluation

- All patients under the age of 30 diagnosed with ovarian dysfunction on the basis of elevated gonadotropins must be further evaluated with a karyotype. The presence of Y chromosome requires removal of the gonads due to a significant increase in the risk of malignancy.

AMENORRHEA - Diagnostic Evaluation

- Results of Step 3: Normal or Low Gonadotropins:
  - Image the pituitary with MRI
  - Normal MRI → Hypothalamic amenorrhea (suppression of pulsatile GnRH)

  Normal or low levels of FSH and LH levels suggest a pituitary or hypothalamic abnormality.

Compartment I Disorders

- Asherman’s Syndrome
- Müllerian anomalies
- Müllerian agenesis
Compartment I Disorders

- Androgen insensitivity
  - Testicular feminization
  - Individual has testes and an XY karyotype
  - Male pseudohermaphrodite
  - Normal testosterone levels
  - Normal testosterone metabolism

Compartment I Disorders

- Androgen insensitivity
  - Sexual differentiation which requires androgens does not take place.
  - Antimüllerian hormone is present, therefore, development of the müllerian system is inhibited.

Compartment II Disorders

- Gonadal dysgenesis
- Turner syndrome
- Mosaicism
- Gonadal agenesis
Compartment II Disorders
- Premature ovarian failure
  - Hypothyroidism
  - Autoimmune process
    - Addison’s disease
    - Diabetes mellitus
  - Destruction of follicles due to infections
  - Physical insult such as irradiation or chemotherapy

Compartment III Disorders
- Pituitary adenoma
- Sheehan’s Syndrome

Compartment IV Disorders
- Hypothalamic amenorrhea
  - Low or normal gonadotropins
  - Normal prolactin levels
  - Normal MRI evaluation of the pituitary
  - No withdrawal bleeding
- Most common causes are due to stress, eating disorders, or weight loss
Compartment IV Disorders

- Weight loss, anorexia, bulimia
  - Food deprivation → Increased Neuropeptide Y → Suppression of GnRH pulses → Amenorrhea
- Exercise
  - Critical level of body fat
  - Effect of stress and energy expenditure

Amenorrhea - Treatment

- Directed at the underlying cause
- Infertility
  - Ovulation induction
- PCOS
  - Establish regular menstrual cycles
  - Treat androgenic signs and symptoms
  - Treat insulin resistance
- Obesity – weight reduction strategies
- Premature ovarian failure – Hormone therapy

Case #3

18 y.o. college freshman presents for her college PE. Her past indicates that she had an appendectomy at age 15 and a stress fracture of her right tibia last year. She is on the track team and has been running competitively for 5 years. Menarche was at age 13 and her periods were regular for the next year.
Case #3

She states that since she started running her periods have been irregular with her last period occurring about 6 months ago. She weighs herself daily, and if her weight goes up by a pound she cuts back on food intake.

Case #3

Physical Examination:
- VS – normal
- Weight – 105 pounds
- Height – 5’ 6”
- BMI – 16.9
- Teeth – slightly worn enamel
- Rest of exam - WNL

Case #3

- What further questions do you need to ask this patient?
- What diagnostic test would you perform?
- How would you manage this patient?