AMENORRHEA

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Presenter Disclosure

• Dr. Wood has no Conflict of Interest to disclose

• Dr. Wood has no Financial or Scientific disclosures

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Learning Objectives

• Describe the classification of amenorrhea and list the major causes of primary and secondary amenorrhea.

• Elicit a pertinent history to evaluate amenorrhea and list the essential elements of a focused physical exam to evaluate amenorrhea.

• Select and interpret diagnostic tests to evaluate amenorrhea and describe medical and surgical treatment of amenorrhea.

• Describe the long term follow-up for a patient with amenorrhea focusing particularly on the risks for endometrial hyperplasia and hypoestrogenism.
“FSH, TSH, Prolactin” Work-Up
Definitions

• **Primary Amenorrhea**
  - Absence of menses by age 15 years
  - Absence of breast development or menses by age 13 years

• **Secondary Amenorrhea**
  - If established menses have ceased for longer than 6 months without any physiological reasons.

ALL WOMEN WITH AMENORRHEA SHOULD HAVE A THOROUGH EVALUATION THAT BEGINS WITH A PREGNANCY TEST!
Understanding the Menstrual Cycle

ESTROGEN

PROGESTERONE
Hormonal Regulation

- GnRH pulses
- 120 Minutes FSH
- 60-90 Minutes LH
Hormonal Regulation of the Uterine Cycle
Amenorrhea – Sx of Chronic Disease

• Malnutrition and cirrhosis associated with alcoholism
• AIDS, HIV disease, or other types of immune-deficiency states may induce systemic infection, lipodystrophy, or other chronic health complications
• Occult malignancy with progressive weight loss and a catabolic state may lead to loss of menstrual regularity
• Sickle cell disease and thalassemia
• Type 1 and type 2 diabetes may both be associated with disordered menses
• Epilepsy, as well as antiepileptic medications, are associated with reproductive dysfunction in women.
  • **Polycystic ovarian syndrome (PCOS)**
  • Hypothalamic amenorrhea
  • Hyperprolactinemia
• Chronic kidney disease requiring hemodialysis
  • Associated with loss of menstrual cyclicity
  • Vitamin D deficiency
  • High risk of bone mineral density loss.
Amenorrhea – Long Term Consequences

• ENDOMETRIAL CANCER!

• Germ Cell Tumors

Gonadoblastoma and dysgerminoma in gonadal dysgenesis
Amenorrhea – Long Term Consequences

- **OSTEOPOROSIS**!

- Cardiovascular disease
Amenorrhea – Long Term Consequences

• INFERTILITY!
Classification of Amenorrhea

- Physiological
- Pathological

Physiological:
- Pre-puberty
- Pregnancy related
- Menopause

Pathological:
- Primary
- Secondary
Etiology of Amenorrhea

Hypothalamic-hypogonadism

Weight related amenorrhea (anorexia nervosa)

Hypothalamic-hypogonadism

Pituitary adenoma
Sheehan’s syndrome

PITUITARY

Endocrine

Hypothyroidism
Hyperprolactinemia

OVARIAN

Gonadal dysgenesis
Gonadal failure
PCOS

Congenital absence of uterus and vagina
Vaginal atresia
Imperforate hymen
Asherman’s syndrome

OUTFLOW TRACT AXIS
Primary Amenorrhea

ETIOLOGY

CHROMOSOME MUTATIONS
- Androgen Insensitivity (AIS) (testicular feminization)
- Turner’s syndrome
- Gonadal dysgenesis

HYPOTHALAMUS-PITUITARY

Hypothalamic failure (Kallmann’s syndrome)

OVARIAN

Mullerian Agenesis
- Absent uterus
- Absent of vagina
- Imperforate hymen

OUTFLOW TRACT
Primary Amenorrhea

ETIOLOGY

OUT FLOW TRACT DISORDERS (Imperforate hymen)

Imperforate hymen represents one form of failure of complete canalization of the vagina.

Most frequent obstructive anomaly of the female genital tract. Incidence: 1/1000-10,000

Presentation: primary amenorrhea associated with cyclical abdomen pain – abdominal swelling and urinary retention.

Signs: Bluish bulging membrane at the introitus
Primary Amenorrhea

ETIOLOGY

GONADAL DYSGENESIS (Turner’s Syndrome)

Turner syndrome – clinical features
Chromosomal disorder in females in approximately 1:200 to 1:5000 live births. Complete or partial absence of the second sex chromosome (45,X karyotype).

Characteristic facial features:
- Pocks
- Hypotelorism
- Retrognathic face
- Micropthalmia
- Ear malformations

Cardiovascular system:
- Aortic coarctation
- Bicuspid aortic valve
- Conduction abnormalities

Genitourinary system:
- Ovarian failure
- Renal malformation

Short stature:
- Average adult stature 20 cm (8 inches) shorter than target height

Other manifestations:
- Melanocytic nevi
- Hypertension
- Hypothyroidism
- Steatosis
- Hyperopia
- Hearing loss
- Webbed neck
- Thyroiditis
- Wide-spaced nipples/poor breast development
- Tooth anomalies
Primary Amenorrhea

ETIOLOGY

ANDROGEN INSENSITIVITY (AIS) (Testicular feminization)

A syndrome found in patient with XY chromosome but resistant to androgens (androgen insensitivity)
Has male karyotype (46XY) with female appearance.
Male levels of testosterone

Presentation:
Female appearance with normal breast development and external genitalia, but no pubic/axillary hair
Primary amenorrhea, absent uterus
Gonad - testes
Karyotype Abnormalities and POI

- **Y Chromosome component**
  - Gonadoblastoma Risk
    - 30% dysgerminoma
    - 10% of malignant tumors

- **Turner’s Syndrome (45,X and mosaicism)**
  - Cardiovascular evaluation
    - Risk of cardiac anomalies – coarctation, bicuspid aortic valve, aortic dilation
    - Risk of maternal mortality approximately 2% from aortic aneurysm or rupture
    - Offspring from a spontaneous pregnancy at risk for genetic abnormalities
    - Evaluate for glucose intolerance and thyroid dysfunction

- TS is a relative contraindication for pregnancy; identified cardiac abnormalities are absolute contraindication
Primary Amenorrhea

ETIOLOGY

MULLERIAN AGENESIS
(Mayer-Rokitansky-Kuster-Hauser Syndrome)

• Usually clinically diagnosed if pubic hair present

• Normal breast development

• Pelvic ultrasound shows absent uterus and normal ovaries and/or serum testosterone in normal female range

• Vaginal dilator or vaginoplasty when sexual activity is desired
Primary Amenorrhea

Etiology

HYPOTHALAMIC FAILURE (Kallmann’s Syndrome)

Incidence is 1/50,000 females
More common in males - 1/4000-1/10,000

Congenital disorder (CHH) characterized by:

1) Hypogonadotropic hypogonadism
2) Eunuchoidal features
3) Anosmia or hyposmia
4) Primary amenorrhea

Failure of the hypothalamus to release GnRH at the appropriate time as a result of the GnRH releasing neurones not migrating into the correct location during embryonic development.
Secondary Amenorrhea
Physiological

The most common cause of secondary amenorrhea in reproductive age women is pregnancy and this should always be excluded by physical exam and laboratory testing for the pregnancy hormone - HCG.
Secondary Amenorrhea

ETIOLOGY

ENDOCRINE

Hypothyroidism
Cushing's
Adrenal tumor
Ovarian tumor
(androgen)

Primary ovarian Insufficiency (POI)
PCOS
Surgical removal

OVARIAN

HYPOTHALAMUS-PITUITARY

OUTFLOW TRACT

Pituitary tumor
Sheehan’s syndrome
Hypothalamic dysfunction

Asherman’s syndrome
Hysterectomy
Secondary Amenorrhea

ETIOLOGY

POLYCYSTIC OVARIAN SYNDROME (PCOS)

PCOS accounts for 90% of cases of oligoamenorrhea

Also known as Stein-Leventhal syndrome

The etiology is probably related to insulin resistance, with a failure of normal follicular development and ovulation

The classical picture – AMENORRHEA, OBESE, SUBINFERTILITY and HIRSUITISM
Criteria for PCOS

• Revised 2003 Rotterdam Criteria for Diagnosis of PCOS, affirmed by the Endocrine Society in 2013
  1) Oligo- or anovulation
  2) Clinical and/or biochemical signs of hyperadrogenism
  3) Polycystic ovaries
And exclusion of other etiologies (CAH, androgen secreting tumors, Cushing syndrome)
Hypothalamic dysfunction is a common cause (30%-35%).

It is more often seen as a result of stress, intense exercise, weight loss and eating disorders.

NEED minimum of 18% body fat to bleed.

Infiltrative disease (Craniopharyngioma, sarcoidosis, histiocytosis).
Pituitary failure - It is usually the acquired type as the result of trauma, treatment of pituitary tumor or infarction after massive blood loss (Sheehan’s syndrome).

Pituitary tumor → Hyperprolactinemia which cause secondary amenorrhea.
TSH-induced Hyperprolactinemia

• Primary hypothyroidism
  • Modest (10%) increase in prolactin
  • May have appearance of tumor on MRI

• Mechanism: Increased TRH stimulating lactotropes
Hyperprolactinaemia accounts for 20% of cases of amenorrhea.

Prolactin inhibits GnRH release from the hypothalamus

Drugs that may cause hyperprolactinaemia:
1). Phenothiazines
2). Methyldopa
3). Cimetidine
4). Butyrophenones
5). Antihistamines
Secondary Amenorrhea

ETIOLOGY

ENDOCRINE CAUSES

**Thyroid disorder** and **Cushing’s disease** interfere with the normal functioning of the hypothalamic-pituitary-ovarian axis → present with amenorrhea.

High level of thyroxine inhibit FSH release.

**Androgen – secreting tumors of the ovaries** → cause secondary amenorrhea.
Late Onset Congenital Adrenal Hyperplasia

• Mutation
  • 21-hydroxylase
    • At least half of patients are compound heterozygotes
      • One of them coding for several alleles

• 17-OHP
  • >200 ng/dL
    • 100% negative predictive value
    • 90% sensitive
  • >1500ng/dL after ACTH stimulation confirms diagnosis

• Management
  • Genetic counseling
  • OCPs vs Glucocorticoids to suppress adrenal androgen production
Cushing Syndrome

- Hypertension
- Central Obesity
- Glucose Intolerance
- Easy bruisability
- Straie

• Evaluation
  - 24-hour urinary cortisol
  - Dexamethasone suppression test
Secondary Amenorrhea

ETIOLOGY

ANATOMICAL CAUSES

Usually due to previous surgery.

Commonest example:

1) Hysterectomy
2) Endometrial ablation
3) Asherman’s syndrome (damage to the endometrium with adhesion formation)
4) Stenosis of the cervix following cone biopsy/LEEP
5) Vaginal agglutination (radiation therapy)
Asherman’s Syndrome

• Risks
  • Dilation and curettage
    • Highest risk if peripartum curettage
  • Surgery
    • Myomectomy
  • Infection
    • Tuberculosis in undeveloped countries
POI is an elevated FSH < 40 y/o
1/100 at age 40, 1/250 < 35 y/o

POI may be due to:
1) Smoking, chemotherapy and radiation
2) Following surgery: oophorectomy, cystectomy, ablation of endometriosis
3) Autoimmune etiology
4) Genetic
Fragile X testing in POI

- Fragile X (FMR1) pre-mutation (carrier 1/300)
- Prevalence with POI
  - 2-3% sporadic
  - 14% familial
- Important test because
  - Siblings
    - Risk for POI, children with mental retardation
    - Family
    - Tremor – Ataxia syndrome (FXTAS) risk
    - Cognitive or behavioral deficits
- Other genes associated with POI: FSHR, GALT, FOXL2, AIRE
- Sequential testing: karyotype first then - Fragile X
Autoimmune Causes of POI

- Etiology in 20% of women with POI
  - Anti-thyroid antibodies in 15-20% OF ALL WOMEN
  - No good marker for anti-ovarian antibodies
  - Anti-adrenal antibody testing may be beneficial
  - 10-20% of women with adrenal autoimmune disease develop ovarian failure

- Evaluation for Autoimmune Polyglandular Syndrome (APS)
- History of APS disease against 2 or more organs
  - Mucocutaneous candidiasis - Lupus, rheumatoid arthritis
  - Hypoparathyroidism - Vitiligo
  - Celiac disease - Autoimmune primary adrenal insuff
  - DM type I - Auto immune hypothyroidism
  - Myasthenia gravis
Evaluation of Adrenal Insufficiency and Thyroid Dysfunction in POI

• Adrenal antibodies
• Adrenal 21-hydroxylase antibodies
  • Sensitivity: 100%
  • Specificity: 98%
  • PPV-67%
    • 20-50% risks 5-10 years
• ACTH Stimulation test

• Thyroid stimulating hormone (TSH)
• Antithyroid peroxidase antibodies
• Antithyroglobulin antibodies
A good history can reveal the etiologic diagnosis in up to 85% of cases of amenorrhea.

Then combined with a physical exam are suggestive of a certain etiology.

The workup can sometimes be more directed.
Pubertal/Menstrual History

- Pregnancy?
- Age of thelarche, pubarche and menarche
- Patterns of bleeding
- Documentation of ovulation
  - History
  - P4 levels
  - Urinary LH kit
  - BBT
Evaluation: History and ROS

- Possibility of pregnancy
- Medical history
- Medications
- Prior surgeries
- Dietary history
- Adolescent / pubertal history

- Headaches
- Blurry vision
- Sx of Diabetes Insipidus
- Breast discharge
- Constipation
- Diarrhea
- Hot flashes
- Vaginal dryness
- Insomnia
- Sexual dysfunction
- Excess hair growth
- Acne
- Change in weight
Physical Exam/Anatomic Evaluation

- Breast present or absent
- Uterus present or absent
- Secondary sexual characteristics
- Body habitus
- Hirsutism
- Acanthosis Nigricans
- Enlarged thyroid
- Galactorrhea
- Vaginal atrophy vs estrogenized vagina, cervical mucus
Investigating Primary Amenorrhea

- BLOOD TESTS
- ULTRASOUND
- CT scan of pituitary
- KAROTYPING
- LAPAROSCOPY
## Investigating Primary Amenorrhea

<table>
<thead>
<tr>
<th>SITE OF DISORDER</th>
<th>DIAGNOSIS</th>
<th>INVESTIGATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPOTHALAMUS</td>
<td>Hypothalamic-hypogonadism</td>
<td>FSH, LH and estradiol - Low</td>
</tr>
<tr>
<td>PITUITARY</td>
<td>Pituitary adenoma</td>
<td>Prolactin – High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FSH, LH and estradiol - Low</td>
</tr>
<tr>
<td>OVARY</td>
<td>Gonadal dygenesis (Turner’s syndrome)</td>
<td>FSH and LH – High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Estradiol – Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Karyotype – 45 XO</td>
</tr>
<tr>
<td>MULLERIAN TRACT</td>
<td>Absent uterus</td>
<td>Karyotyping – 46 XY = AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46 XX = Mullerian Agenesis</td>
</tr>
<tr>
<td>GENITAL TRACT</td>
<td>Imperforate hymen</td>
<td>FSH, LH, estradiol – normal</td>
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<tr>
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<td></td>
<td>Examination – imperforate hymen</td>
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</tbody>
</table>
Primary amenorrhea

vagina

no

Pubic hair

yes

congenital uterovaginal agenesis
imperforate hymen
complete transverse vaginal septum

no

Progesterone challenge

esters have developed

no

yes

+ ↓

FSH Level

low

- ↓

abnormal hormonal stimulation of normal ovaries (Hypothalamic-hypogonadism)

high

Estrogenized

abnormal ovaries

+ ↓

Chromosome Analysis

Chromosome Analysis

abnormal hormomal stimulation of normal ovaries (Hypothalamic-hypogonadism)
Investigating Secondary Amenorrhea

Once pregnancy has been excluded

- TSH (thyroid stimulating hormone)
- Progesterone challenge test
- FSH, LH, Estradiol
- Prolactin level
NEGATIVE PREGNANCY TEST

FSH, LH and Thyroid function test
Progesterone challenge test

WITHDRAWAL BLEEDING

HYPOESTROGENIC
Positive E-P challenge test
Very high FSH
Ovarian Failure

NO WITHDRAWAL BLEEDING

HYPOESTROGENIC

COMPRIMISED OUTFLOW TRACT
Negative E-P challenge test
Normal FSH
Asherman’s syndrome (HSG or hysteroscopy)

ANOVULATION
FSH normal + high LH → PCOS
High prolactin → pituitary tumor

Hypothalamic-pituitary failure
Normal or Low FSH
## Investigating Secondary Amenorrhea

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<tr>
<td>HYPOTHALAMUS</td>
<td>Hypothalamic – failure</td>
<td>FSH, LH and estradiol - Low</td>
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<tr>
<td></td>
<td>Weight-related amenorrhea</td>
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<td>PITUITARY</td>
<td>Pituitary adenoma</td>
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<td>FSH, LH and estradiol – Low</td>
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<tr>
<td></td>
<td>Sheehan syndrome</td>
<td>FSH, LH and estrogen - Low</td>
</tr>
<tr>
<td>ENDOCRINE</td>
<td>Hypothyroidism</td>
<td>TSH – raised ; T4 – low or N</td>
</tr>
<tr>
<td>OVARY</td>
<td>Primary ovarian insufficiency (POI)</td>
<td>FSH, LH – high ; E₂ – low</td>
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<td></td>
<td>PCOS</td>
<td>FSH – Normal ; LH - High</td>
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<td>MULLERIAN TRACT</td>
<td>Asherman’s syndrome</td>
<td>HSG / Hysteroscopy</td>
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Treatment of Amenorrhea

Address the underlying causes!

PITUITARY TUMOR → Cabergoline/Bromocriptine/Surgery

ANDROGEN producing tumor of ovary → Surgery

ANDROGEN INSENSITIVITY → removed gonads + HRT

TURNER’S syndrome → HRT/possibly egg donation

IMPERFORATE HYMEN → surgical incision
Treatment of Amenorrhea

THYROID disease – appropriate medical treatment

POI – HRT/egg donation

EATING DISORDERS → referred to psychiatrist

EXCESSIVE EXERCISE – counseling/stress management/HRT

PCOS → appropriate treatment- fertility rx/ovarian drilling/BCPS/Monthly P4 withdrawal/weight reduction/lifestyle

ASHERMAN’s syndrome → breaking down adhesion + insert IUD/uterine stent + estrogen
Treatment of Amenorrhea

**WANT REGULAR PERIOD**

The use of
1) COMBINED ORAL CONTRACEPTIVE
2) HRT
3) Monthly P4 withdrawal

**DESIRE FERTILITY**

Refer to Reproductive Endocrinologist
THANK YOU