Primary Amenorrhea Definition

- Absence of menses by age 15.
- Evaluate 5 years after thelarche if no menses (approx. 12-13).
- Evaluate earlier if cyclic pain c/w outflow tract obstruction.

Primary Amenorrhea Etiology

- Gonadal Dysgenesis (ovarian failure) 50%
- Hypoth-Pituitary 25%
- Mullerian Agenesis 15%
- Androgen Insensitivity 5%
- T-Septum or Imperforate hymen 5%
Evaluation

Compartmentalize:

I. Hypoth-Pituitary

II. Ovarian

III. Outflow Tract (uterus and vagina)

Compartment I. Hypoth-Pituitary

• Functional Hypoth Amenorrhea
• Constitutional delay
• GnRH deficiency – Kallmann’s 1:125,000 women, 1:30,000 men
• Hyperprolactinemia
• Infiltrative lesions/tumors

Compartment I. Hypoth-Pituitary

A. Functional Hypoth Amenorrhea – GnRH secretion is not matured. You see low to normal LH and FSH serum levels but overall increased FSH to LH frequency and lack of LH surge. This is a prepubertal anovulation pattern. May be secondary to eating disorder, stress and weight loss.
Compartment I. Hypoth-Pituitary

B. Constitutional Delay (CD) of puberty – rare in girls, common in boys. Delayed adrenarche (axillary hair growth) and gonadarche. CD patients will go on to have normal puberty.

Compartment I. Hypoth-Pituitary


D. Hyperprolactinemia – rare primary amenorrhea cause. Two fasting AM PRL levels. MRI if PRL persistently elevated.

Compartment I. Hypoth-Pituitary

E. Other lesions – Infiltrative disease i.e., sarcoidosis, Langerhans cell histiocytosis, tumors i.e., craniopharyngiomas and germinomas. MRI for diagnosis.
Compartment II. Ovarian

- **Gonadal Dysgenesis (GD)** – The most common cause of primary amenorrhea. 45X (Turners), 46XX (pure GD), 46XY (Swyers Syndrome)
- **Polycystic Ovary Disease (PCO)** – Chronic anovulation with hyperandrogenism. PCO patients may have delayed menarche presenting as primary amenorrhea.

Ovarian/Compartment 2

46 XY Complete Gonadal Dysgenesis (Swyer Syndrome) – early GD. Phenotypic infantile female with uterus and vagina because there was no mullerian inhibiting factor or androgens. Remove testes – 30% risk gonadoblastoma or dysgerminoma. Raised as female on estrogen

Gonadal Dysgenesis

SRY inactivating gene – SRY on the short arm of Y chromosome. You see infantile female genitalia with uterus Swyer syndrome variant. Diagnose with Y DNA hybridization study.
Ovarian/Compartment 2 Enzyme Defects.

17A hydroxylase (CYP17) deficiency. Rare disorder. CYP17 abnormality affects 17A hydroxylase and 17,20 lyse. CYP17 deficiency blocks cortisol and sex steroid production. Increased ACTH drives increase in progesterone, DOC and aldosterone. This leads to Na retention and hypertension.

Steroid Pathway

Cholesterol

\[\text{Pregnenolone} \rightarrow \text{Progesterone} \xrightarrow{17\text{H block}} 17\text{OHP} \rightarrow 17\text{BOHD} \xrightarrow{\text{Aromatase}} \text{Estrone} \rightarrow \text{Estradiol}\]

\[\xrightarrow{21\text{H}} \text{DOC} \xrightarrow{11\text{H}} \text{Aldosterone}\]

\[\xrightarrow{21\text{H}} \text{Deoxy Cortisol} \xrightarrow{11\text{H}} \text{Cortisol}\]

CYP17 Deficiency continued

- 46XX deficient patient has infantile genitalia, normal uterus and vagina, hypertensive.
- 46XY patient will have infantile female genitalia, blind-end vagina, absent uterus and hypertension. Testes may be in the inguinal canal.
III. Outflow Tract

- Congenital abnormalities of outflow tract represent 20% of primary amenorrhea. Pelvic pain is a common complaint with obstruction of outflow tract.

- Imperforate hymen
- Transverse septum
- Mullerian Agenesis
- Androgen Insensitivity
- 5A reductase deficiency
- 17A hydroxylase deficiency

III. Outflow Tract

B. Transverse Septum – Can occur any level from hymenal ring to cervix. No bulging with Valsalva. Diagnose US and MRI.
III. Outflow Tract

C. Mullerian Agenesis – Absent uterus and upper 2/3 rd vagina. In 7-10% you see a rudimentary uterine horn. 1:5,000 incidence but 10% of primary amenorrhea cases. Normal breast and pubic hair.

III. Outflow Tract

D. Androgen Insensitivity (AI) – Complete AI is X-linked recessive. 46XY males appear as females with blind-end vagina and absent pubic hair. High serum testosterone, 46XY karyotype. Testes need to be excised due to 22% risk of testicular cancer generally after age 20. Remove testes after full breast development.

Compartment III.

5A reductase deficiency – 46XY. Genitalia appearance range from infantile female to ambiguous.

T increases at puberty causing virilization i.e., pubic hair growth and penile/clitoral enlargement.

Etiology is inability to convert T to dihydrotestosterone (DHT) Autosomal recessive.
Diagnostic Evaluation

Simplify based on 1. presence of breast development (estrogen production present therefore positive ovarian function) 2. uterine presence or absence and 3. Serum FSH level (differentiates ovarian failure from Hypoth-Pituitary disorders).

History

- Pubertal development including breast hair and growth spurt.
- Family history of puberty delay.
- Childhood illness.
- Stress/weight loss.
- Medications, especially narcotics and antipsychotic’s.
- Galactorrhea
- CNS symptoms i.e., headache, blurred vision.

Exam

- Tanner staging.
- Inguinal masses are testes indicating Y presence.
- Tanners Stigmata – Low hairline, web neck, shield chest etc.
Uterus Absent

- T, Karyotype

<table>
<thead>
<tr>
<th>AI</th>
<th>5A Reductase Deficiency</th>
<th>Mullerian Agenesis</th>
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<tbody>
<tr>
<td>46XY</td>
<td>Male, normal T</td>
<td>46XX, female</td>
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<tr>
<td>Male T</td>
<td>Ambiguous Genitalia</td>
<td>low T</td>
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<td>Virilization at puberty</td>
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Uterus Present

- Breasts, Negative hCG
- Imperforate hymen or septum
- Constitutional delay (rare)
- Hydrid. Dysfunction
- PCOS
- Late onset CAH
- FSH, LH, T, 17OHP
- PRL

- Breasts
- Delayed Puberty
- High FSH
- NL to low
- Ovarian failure
- HP disease
- SRY mutation
- MRI
- Check karyotype

Treatment of Primary Amenorrhea

- Directed to underlying problem.
- Address future fertility.
- Address psychological issues particularly in mullerian agenesis or when 46XY.
Treatment

- Mullerian Agenesis – Vaginal Frank dilators (95% success) or surgical neovaginal procedure i.e., MacIndoe procedure. Give gestational carrier info.
- Imperforate hymen and septum’s – resect.
- AI – Vaginal dilators. Gonadectomy after puberty.

Treatment

- Congenital GnRH deficiency – hormone replacement, FSH, LH stimulate or pulsatile GnRH to induce ovulation for fertility.