AMENORRHEA
Ahmad Hammoud MD, MPH

DEFINITION
- No period by age 14 in absence of growth or secondary sexual characteristics
- No period by age 16 regardless of growth and secondary sexual characteristics
- Menstruating women: no period for 3 cycles or 6 months.

MENSTRUATION
- Uterus and outflow tract
- Ovaries
- Anterior pituitary
- CNS and Hypothalamus
EVALUATION OF AMENORRHEA:
- History and physical exam
- Look for galactorrhea: significant whether it’s spontaneous or expressed.
  - Secretion form multiple ducts are hormonal as opposed to secretion from one duct that is pathologic.
- Exclude pregnancy
- Rarely elevated TSH: hypothyroidism. Hypothyroidism can cause galactorrhea by the stimulatory effect of TRH on pituitary cells that produce Prolactin

EVALUATION OF AMENORRHEA:
- Amenorrhea
  - TSH
  - Prolactin
  - Progesterone challenge test
- Galactorrhea
  - TSH
  - Prolactin
  - MRI (pituitary) (can be omitted if normal cycles and normal prolactin)

PROGESTERONE CHALLENGE TEST:
- Assess levels of endogenous estrogen
  - Parenteral progesterone in oil 200mg
  - Oral micronized progesterone 300 mg daily at bed time
  - Oral MDA 10mg for 5 days
- Response within 2-7 days
**PROGESTERONE CHALLENGE TEST:**

- If + (bleeding: even if few spots):
  - Anovulation, no further evaluation if no galactorrhea and normal TSH.
  - 5mg MPA first two weeks of month
  - Low dose OCP
  - Screen for endometrial cancer even at young age.

- If negative progesterone challenge test:
  - Estrogen–progesterone challenge test: CE 1.25mg or estradiol 2mg for 21 days then oral MPA 10mg for 5 days.
  - If no bleeding: anomalies in the uterus or outflow tract: uncommon
  - If no history this step can be omitted.

**EVALUATION**

- If no response to progesterone change test (and + response to E-P challenge test): FSH, LH
  - **A. High gonadotropins**: FSH >20 and LH > 40
    (after repeat measurements several months apart):
    - Premature ovarian failure
  - **B. Normal gonadotropins**: consistent with CNS/Hypothalamic etiology
  - **C. Low gonadotropins**:
    - Pituitary or CNS hypothalamic: Imaging
    - MRI better than CT

**COMPARTMENT 1: OUTFLOW TRACT AND UTERUS**

- **Asherman’s syndrome**
  - Overzealous post partum curettage.
  - Intrauterine infection: TB
    - (Diagnosis: culture of endometrial bx, chlamydia.
  - After uterine surgeries: C/S, myomectomy or metroplasty
  - After uterine embolization
  - After Sheehan syndrome

- **Presentation**:
  - Amenorrhea, hypomenorrhea, dysmenorrhea.
  - Recurrent miscarriage
  - Infertility
COMPARTMENT 1: OUTFLOW TRACT AND UTERUS

- Asherman’s syndrome
  - Diagnosis: HSG, hysteroscopy +++
  - Treatment:
    - Hysteroscopic resection
    - Intrauterine pediatric Foley removed after one week
    - CE 2.5mg QD for 2 months with MPA 10 mg last 10 days of month.
    - May need repeated attempts.
  - Pregnancy rate 70-80%: complicated by PTL, accreta, previa and PPH

COMPARTMENT 1: OUTFLOW TRACT AND UTERUS

- Mullerian agenesis (Mayer-Rokitansky-Kuser-Hauser syndrome) 1/5000, 46XX
  - Absence of the uterus and upper part of vagina
  - Differential diagnosis: androgen insensitivity, imperforate hymen, transverse vaginal septum
  - One third has urinary tract abnormality
  - 12% skeletal anomalies (spine, digits)
  - Diagnosis: US, MRI, laparoscopy

COMPARTMENT 1: OUTFLOW TRACT AND UTERUS

- Mullerian agenesis (Mayer-Rokitansky-Kuser-Hauser syndrome) 1/5000, 46XX
  - Treatment: progressive vaginal dilators: begin post direction 2 wk than upward, 20 min daily;
  - Vagina will be created in several months.
  - Tight undergarment or bicycle seat.
  - If failed or patients unwilling: surgical treatment.
COMPARTMENT I: OUTFLOW TRACT AND UTERUS

- **Androgen insensitivity:**
  - 46XY
  - Consider this diagnosis if:
    - Amenorrhea with no uterus
    - Female with inguinal hernia
    - Patient with absent body hair
  - Testosterone in the normal or high range for male
  - Remove gonads at age 16-18

COMPARTMENT II: OVARIES:

- **Gonadal dysgenesis:**
  - 30-40% of primary amenorrhea
  - 50% 45X; Turner
  - 25% mosaics
  - 25% 46XX

- Karyotype

- Premature ovarian failure

COMPARTMENT III: ANT PITUITARY

**Pituitary Prolactin secreting Adenoma:**

- 50% of all pituitary adenoma

- When prolactin increase => galactorrhea =>
  - Defective luteal phase => anovulation
  - Amenorrhea.

- Increased prolactin inhibits GnRH pulsatility via
  - Increased opioid activity.
PITUITARY PROLACTIN SECRETING ADENOMA:

- **Medical**: Dopamine agonist treatment:
  - Bromocriptine:
    - Lysergic acid derivative.
  - **PO**:
    - Half life 3 hours
    - 10% side effects: N-V, headache, faintness. Orthostatic hypotension and neuropsychiatric symptoms.
    - Start 2.5 mg at bed time with glass of milk or snack then after a week add another 2.5 mg at breakfast or lunch. There is a slow release oral form
  - **Vaginal**: less side effects : 2.5 mfg BID

- **In patients attempting pregnancy**: daily treatment until pregnant. Or only in follicular phase of treatment cycles. No documented side effect in pregnancy
- 80% of patients with amenorrhea with galactorrhea with no tumor resume menses in an average of 5.7 weeks. Suppression of galactorrhea is slower.
- Macroadenoma can shrink after bromocriptine up to 10 mg qd.
- Cabergoline: 0.5-3mg weekly, fewer side effects can be taken vaginally as well.

- **Surgery**:
  - Transphenoidal technique via a sub labial incision
  - Return of menses in 30% of macroadenoma and 70% of microadenoma
  - Recurrence 50%
  - Complications: panhypopituitarism, CSF leak, Db insipidus, mortality<1%
  - If after surgery: amenorrhea or oligomenorrhea or increased prolactin; prolactin levels Q6months and imaging q year for 2 years then every few years.
  - Tumor growth after surgery: dopamine agonist
PITUITARY PROLACTIN SECRETING ADENOMA

- **Radiation:**
  - Less satisfactory, slow response
  - Panhypopituitarism can occur after up to 10 years.
  - Usually reserved for post operative growth or persistence that is unresponsive to medical treatment.

COMPARTMENT III: ANT PITUITARY

- **Other non neoplastic pituitary disorders:**
  - Cysts, TB, sarcoidosis, fat deposit.
  - Lymphocytic hypophysitis (pregnancy and 6 months post partum: transphenoidal surgery is diagnostic and therapeutic for this lethal condition).
  - Internal carotid aneurysms, obstruction of aqueduct of Sylvious.
  - Pituitary ischemia (Sheehan): failure of lactation and loss of pubic and axillary hair, very rare.
  - Genetic disorder like the Laurence-Moon-Biedl and Prader-Willi.

COMPARTMENT IV: CNS DISORDERS:

- **Hypothalamic amenorrhea:**
  - Deficiency in GnRH pulsatile secretion
  - CRH increase endogenous endorphin that suppress GnRH pulsatility
  - Several levels of reproductive impairment: inadequate luteal phase, anovulation with menstrual irregularities, severe suppression will cause hypothalamic amenorrhea
  - Causes
    - Stress
    - Underweight
  - Diagnosis of exclusion after CNS imaging
Compartment IV: CNS Disorders

- Inherited genetic defect as a cause of hypothalamic amenorrhea
- Kallman syndrome:
  - Rare in female
  - GnRH deficiency due to lack of migration of olfactory axon and GnRH neuron.
  - Amenorrhea and anosmia
  - X linked (KAL gene, Xp22.3), AR, AD

- Mutation of GnRH receptor
- Adrenal Hypoplasia Congenita: mutation in DAX1

Compartment IV: CNS Disorders

- Treatment:
  - Counseling on relation between weight and menstrual function
  - Weight gain: minimum 2600 calories per day.
  - Psychological and psychiatric help: Cognitive behavioral therapy, antidepressant.
  - Fertility can be achieved through induction of ovulation
  - Disorder can persist during pregnancy: IUGR and PTL. Need expert help.
  - Return to normal of hormonal levels does not result always in reversal of amenorrhea; they may still need hormone replacement to reduce risk of osteoporosis

Compartment IV: CNS Disorders

- Also hormonal therapy without weight gain does not reduce risk of osteoporosis
  - 0.625 CE or 1mg estradiol daily with MPA 5mg or 0.7 mg norethindrone 2 weeks every month. Or a combined treatment if they wish to avoid menstruation (0.625mg CE with 2.5 mg MPA daily)
  - Periodic measurement of bone density
  - If they want to avoid pregnancy: OCP
  - Supplemental calcium 1000-1500mg daily