MEDICINE
TEXAS A&M UNIVERSITY

Endocrine-Reproduction Block

CSIE: ACE –Amenorrhea

Overview of the ACE live session and instructions to Facilitators

Introductions (Start at 8:30 am: 5-10 minutes)

- Start the live session by introducing yourself
- Meet the students and let them introduce themselves
- If you are familiar with the students, take a few minutes to check in on them and how they are doing
- Let the pre-designated AV student/students connect the computer/laptop to the AV system to log on and bring up the google doc forms to be used in the session
- All students should be at the session by 8:30 am. If a student is late, please mark their time of arrival on your evaluation.

Clinical Approach Questions (Start no later than 8:45 am: 10-15 minutes)

- Start with the **Clinical Approach Questions** document on the screen:
    - Ask each clinical approach question and elicit a response from the students (as a large group)
    - If students are not volunteering or speaking up, go around the room and call on them or use the student roster provided in your folder
    - If students are not giving the expected/correct answers, guide them further
    - Ensure that you fill in gaps, if students are missing important points, or necessary information relating to the learning objectives

ACE Table (Start no later than 9:00 am: 45-50 minutes)

- Next direct the students to bring up the **ACE Table** document on the screen*:*
    - *Students have already been assigned into small subgroups of 2-3 students. Each subgroup will have already completed the table, prior to the live session, as an assignment.*
    - *Call on each group one-by-one to present their row(s).*

- *Every student in the groups should be presenting and speaking. Individuals who have clearly not completed or contributed to the completion of the row will lose participation points.*
- Discuss or challenge them if you see gaps in the information provided or if there are erroneous information.
- Once completed, the students are allowed to keep this table for their educational purposes

Practice Clinical Cases (Start no later than 9:50 am: 15-20 minutes)

- Next, direct the students to the **Practice Clinical Cases** document on the screen:
  - As a large group, work to discuss the practice clinical cases
  - Rotate through the students to elicit responses to the questions in each practice clinical case and direct the discussion as needed
  - Reveal the "working diagnosis" for each clinical case after all the questions have been answered
  - *Alternatively* if you have ample time, divide your large group into smaller subgroups and give each subgroup a clinical case to work on (10 minutes) and let each subgroup present (15-20 minutes)

Quiz and feedback (Start no later than 10:10 am: 10-15 minutes)

- Ensure that all students log into Canvas and access the Quiz under the course/CSIE ACE folder/Quiz
- Access the **brown envelope in your maroon folder** and **read out loud the quiz password**
- If a student experiences technical issues, access the brown folder for a backup copy
- The quiz will take *10 minutes* to complete
  - During the quiz, please access the one page **student evaluation form** (in the brown envelope) and evaluate each student using the given grading rubric
  - Students can leave once done with their quiz
- Conclude the session and release the students by 10:20 am
- Leave the completed student evaluation form in the brown envelope within the maroon folder
- Return the folder and envelop to the coordinator during the debriefing session

PLEASE ENSURE THAT ALL FILLED-IN STUDENT EVALUATIONS ARE IN THE BROWN ENVELOPE BEFORE YOU LEAVE THE ROOM

Quick Overview of Student Expectations and Assessment:

Student Expectations

- Students are expected to arrive on time, in professional dress, white coat and badge.
- Students are expected to actively participate, show professional behavior such as appropriate listening skills and refraining from disrupting the session (please see the **student evaluation** rubric for more details).
- Students are expected to have prepared for the live session by reading the **preparation guide** and **assigned reading material** to prepare them for the live session.

ACE Assessment

- This CSIE ACE comprises of 3% of the overall block grade in the following way:
  - 1.5% for the individual quiz given at the end of the session

- 1.5% for the student evaluation form (provided by you as the facilitator)

ACE Amenorrhea Learning Objectives:

1. Define primary and secondary amenorrhea.
2. Name the organ systems commonly associated with amenorrhea.
3. Develop a clinical approach to the chief complaint of amenorrhea.
4. Develop a differential diagnosis for amenorrhea based on history, physical exam findings (e.g. estrogenization and breast development), and diagnostic tests.
5. Differentiate between different causes of amenorrhea (e.g. Turner syndrome, polycystic ovarian syndrome, hypothalamic amenorrhea, Asherman syndrome, etc.) given key clinical features.
6. Assess for and exclude pregnancy in patients presenting with amenorrhea.
7. Identify appropriate diagnostic testing in the evaluation of amenorrhea.
8. Identify the common laboratory or radiographic abnormalities associated with causes of amenorrhea.

CC: Amenorrhea

Clinical Approach & Questions:

Approach to the Patient with Amenorrhea

Useful Terms and Definitions:

Normal Menstrual Cycle – typically occurs every 21 to 35 days and bleeding normally lasts from 3-7 days.

Definition of Primary Amenorrhea – failure to menstruate by age 15 in the presence of normal growth and secondary sexual characteristics, or by age 13 if there is a complete absence of secondary sexual characteristics.

Definition of Secondary Amenorrhea – failure to menstruate after having previously normal menstruation. Absence of menses for more than 3 months in girls or women who previously had regular menstrual cycles or 6 months in girls or women who had irregular cycles.

Definition of Oligomenorrhea – fewer than 9 menstrual cycles per year or cycle length greater than 35 days.

Definition of Menopause – permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause.

Approach Questions:

1. What organ systems or categories are most frequently involved in a case of amenorrhea?

Endocrine, gynecological, genetic

2. Within these systems, what is your differential diagnosis for each?

- Endocrine
  - Pregnancy, polycystic ovary syndrome (PCOS), functional hypothalamic amenorrhea (stress, excessive exercise, eating disorders), physiological delay of puberty, natural menopause, congenital GnRH deficiency, androgen-secreting tumor, sellar mass, congenital adrenal hyperplasia, androgen insensitivity syndrome
- Gynecological
  - Mullerian agenesis, transverse vaginal septum, Asherman syndrome, imperforate hymen
- Genetic
  - Turner syndrome

3. What are *common* conditions that cause amenorrhea?

- Secondary amenorrhea - pregnancy, functional hypothalamic amenorrhea (stress, excessive exercise, eating disorders), polycystic ovarian syndrome, natural menopause, medications
- Primary amenorrhea – physiological delay of puberty (constitutional delay of puberty, chronic systemic disease, acute illness) and other causes would include gonadal dysgenesis (Turner syndrome), Mullerian agenesis (absence of vagina with at times absence of uterus), isolated GnRH deficiency, transverse vaginal septum and all conditions that can cause secondary amenorrhea.

4. What are some conditions that can cause amenorrhea in children versus adults?

While it is always important to differentiate causes by age, the differential diagnosis for amenorrhea is very similar in children and adults.

5. What are *life-threatening* causes of amenorrhea?

Generally the causes of amenorrhea are not acutely life-threatening but:

- Patient with PCOS can develop endometrial cancer.
- Turner syndrome with Y-chromosome mosaicism is at high risk of gonadoblastoma.

Further information for the ACE table and discussion

What HPI questions would you ask the patient? (Pain, Onset, Duration, Timing, Location, Quality, Severity, Modifiers, Associated symptoms, Context)

History

- In primary amenorrhea, evaluate the adolescent for **estrogenization,** which includes a growth spurt, axillary and pubic hair, apocrine sweat glands, and **breast development**.
- Lack of estrogenization can be due to hypothalamic or pituitary disorder, ovarian failure, and/or chromosomal abnormality. *Breast development specifically is helpful in determining ovarian function.*
- Associated symptoms
    - *Hirsutism*, *acne*, and a history of *irregular menses* can be suggestive of hyperandrogenism from either **PCOS**, an **androgen-secreting tumor**, or **5-alpha-reductase deficiency**. Biologically active tumors will have an acute onset of virilization.
    - *Headaches, visual field defects*, fatigue, or *polyuria* and *polydipsia* can be presenting symptoms of a **sellar mass**.
    - Ask about smell – *anosmia* seen with **Kallmann syndrome** as cause of amenorrhea.
    - *Galactorrhea* can be a symptom of hyperprolactinemia from a **pituitary mass**.
    - Has there been stress, change in weight, diet, or exercise habits? Is there an *eating disorder or illness*? These can be symptoms associated with **functional hypothalamic amenorrhea.**
    - *Hot flashes, vaginal dryness, poor sleep or decreased libido* are symptoms of estrogen deficiency found in **primary ovarian insufficiency**.
    - *Fatigue, cold intolerance, weight gain, dry skin* can suggest **hypothyroidism**.
    - *Tremor, palpitations, heat intolerance, weight loss* with an increased appetite may point towards **hyperthyroidism**.
    - Ask about *polyuria, polydipsia, and polyphagia* since **type I diabetes** can cause hypothalamic amenorrhea.
    - Symptoms of *diabetes, arthropathy, bronze skin*, with symptoms of *heart failure* and amenorrhea, may be associated with **hemochromatosis**. Hemochromatosis can cause hypothalamic amenorrhea.
    - Chronic or recurrent *diarrhea, malabsorption, weight loss*, and *abdominal distension* or *bloating* can be symptoms of **celiac disease**, which can also cause hypothalamic amenorrhea.
    - *Cyclical pelvic pain* with primary amenorrhea can be a symptom found in **outlet obstruction.**
    - Associated *anosmia* with primary amenorrhea might be **isolated GnRH deficiency**.

Another approach to the history (courtesy Dr. Marcela Jimenez):

Regarding the chief complain (amenorrhea):

- Start with differentiating primary vs secondary. Previous menstrual cycles, regular/irregular

If primary amenorrhea:

- Ask about **estrogenization** which includes a growth spurt, axillary and pubic hair, apocrine sweat glands, and **breast development**.

- Ask about pelvic pain. *Cyclical pelvic pain* with primary amenorrhea can be a symptom found in **outlet obstruction (imperforate hymen or transverse vaginal septum).**

If secondary amenorrhea:

- Ask about **galactorrhea**: *Galactorrhea* can be a symptom of hyperprolactinemia from a **pituitary mass**.
- Ask about **headache/visual changes/vomiting**: *Headaches, visual field defects*, fatigue, or *polyuria* and *polydipsia* can be presenting symptoms of a **sellar mass**.
- Ask about **smell:** *anosmia* seen with **Kallmann syndrome** as cause of amenorrhea. Also *anosmia* with primary amenorrhea might be **isolated GnRH deficiency**.
- Ask about **fatigue, cold intolerance, weight gain, dry skin**: associated with hypothyroidism.
- Ask about **excessive hair and acne**: *Hirsutism*, *acne*, and a history of *irregular menses* can be suggestive of hyperandrogenism from either **PCOS**, an **androgen-secreting tumor**, or **5-alpha-reductase deficiency**. Biologically active tumors will have an acute onset of virilization.
- Ask about ***tremor, palpitations, heat intolerance, weight loss*** with an increased appetite. They might point towards **hyperthyroidism**.
- Ask about ***polyuria, polydipsia, and polyphagia*** since **type I diabetes** can cause hypothalamic amenorrhea
- Ask about ***polyuria, polydipsia, and polyphagia + arthropathy, bronze skin.*** Symptoms of *diabetes, arthropathy, bronze skin*, with symptoms of *heart failure* and amenorrhea may be associated with **hemochromatosis**. Hemochromatosis can cause hypothalamic amenorrhea.
- Ask about **bowel habits (diarrhea).** Focus on type of diarrhea. Chronic or recurrent *diarrhea, malabsorption, weight loss*, and *abdominal distension* or *bloating* can be symptoms of **celiac disease**, which can also cause hypothalamic amenorrhea.
- Ask about **stress, change in weight, diet, or exercise habits**. Is there an *eating disorder or illness*? These can be symptoms associated with **functional hypothalamic amenorrhea.**
- *Hot flashes, vaginal dryness, poor sleep or decreased libido* are symptoms of estrogen deficiency found in **primary ovarian insufficiency**.

What other pertinent element of the patient's history would you focus on?

Past Medical History

- A history of *neonatal crisis* suggests **congenital adrenal hyperplasia**.
- A history of multiple chronic diseases may affect the hypothalamic-pituitary axis.
- *Hearing loss, congestive heart failure, and hypertension* are common with **Turner syndrome**.
- *Obstetrical catastrophe, severe bleeding, **dilation and curettage**, or endometritis* can cause scarring of the endometrial lining (**Asherman syndrome**).
- A history of *heart failure and liver disease* can occur with **hemochromatosis.**

- A history of *brain cancer requiring cranial radiation* that later resulted in amenorrhea may suggest **primary ovarian insufficiency**.

Family history

- Is there a history of delayed or absent puberty?
- Is there a family history of celiac disease or hemochromatosis?
- Are there first-order relatives with thyroid disease, diabetes, PCOS, and infertility?

Social history

- Sexual history - pregnancy is the most common cause of secondary amenorrhea
- Social stressors – may contribute to amenorrhea
- Drug abuse - heroin can cause a decrease in GnRH

Medications

- Newly initiated or discontinued oral contraceptives can be associated with several months of amenorrhea (e.g., danazol or high-dose progestin)
- Metoclopramide and antipsychotic drugs can increase prolactin
- Opiates – heroin/methadone can cause a decrease in GnRH

What pertinent exam findings would you look for? (Vitals, General, HEENT, Lungs, Cardiac, Abdomen, Musculoskeletal, Neuro-Psych)

Physical exam

- Vitals and Growth Parameters
    - *Short stature* may suggest **Turner syndrome** or **growth hormone deficiency due to hypothalamic-pituitary disease.** Short stature on growth curve may also suggest celiac disease. Growth failure can be a sign of hypothyroidism.
    - *High blood pressure* in a patient *with Turner features* can reveal an associated **coarctation of the aorta.** Blood pressure should be evaluated in both arms.
    - *BMI > 30* is found in more than 50% of women with **PCOS**.
    - *BMI < 18.5* may have functional **hypothalamic amenorrhea** due to an eating disorder, strenuous exercise, or systemic illness due to weight loss.

- General Appearance

- Dysmorphic features such as a low hairline, webbed neck, shield chest, and widely spaced nipples, and shortening of the 4th or 5th metacarpals can suggest Turner syndrome.

- HEENT
  - Peripheral visual fields should be checked by confrontation and fundi examined as seen with intracranial tumors
  - Test for smell – Kallmann syndrome
  - Parotid gland swelling and/or erosion of dental enamel can suggest an eating disorder (e.g., bulimia nervosa).
  - Palpate thyroid for enlargement

- Abdominal and genital exam
  - Palpate abdomen for any masses
  - Assess Tanner stage of patient
  - Breast exam: evaluate for breast development and galactorrhea
  - A pelvic exam: may reveal an intact hymen, transverse vaginal septum, or vaginal and/or uterine agenesis (mullerian agenesis, androgen insensitivity syndrome), which all can cause primary amenorrhea
  - Look for vaginal atrophy and dryness, which are signs of estrogen deficiency
  - Clitoromegaly can be seen with causes of androgen excess

- Skin
  - Hirsutism, acne, and acanthosis nigricans can be seen in PCOS.
  - Vitiligo in association with hyperpigmentation can be a sign of Addison disease.
  - Striae and easy bruisability can point towards Cushing's syndrome.
  - Bronze skin may be a sign of hemochromatosis.

What laboratory values and/or studies would you order to narrow your differential diagnosis? (depending on the clinical data, not all will be ordered on each patient)

Initial labs (both primary and secondary amenorrhea)

- First **rule out pregnancy** (urine or serum hCG)
- **FSH and LH, prolactin, TSH** to test for premature ovarian insufficiency (POI), hyperprolactinemia, and thyroid disease, respectively
- If there is clinical evidence of hyperandrogenism (hirsutism, acne, scalp hair loss [alopecia]), order the above labs and add the following:
  - Total testosterone
  - Dehydroepiandrosterone sulfate (DHEAS)

- 7AM 17-hydroxyprogesterone to rule out non-classic 21-hydroxylase deficiency. ACTH stimulation test can be used to confirm diagnosis.

Imaging

- If a normal vagina or uterus is not obvious on exam, then a **pelvic ultrasound** should be done to **confirm the presence of ovaries, uterus, and cervix**. Ultrasound can also help identify an outlet obstruction.
- **MRI of head** or sella – if concern for **intracranial tumor** (e.g. microadenomas)
- **Bone age** – delayed in **constitutional delay of puberty**

Follow up labs for primary amenorrhea

Further lab evaluation begins with the **presence or absence of a uterus** followed by studies evaluating the hypothalamus and ovary. The hypothalamus is evaluated by FSH and ovarian function can be assessed by the presence or absence of breast development.

- Uterus present (primary amenorrhea will typically be a chromosomal abnormality causing gonadal dysgenesis)
  - High FSH
    - Indicative of primary ovarian insufficiency
    - **Karyotype** is needed to show complete or partial deletion of the X chromosome **(Turner syndrome)**
    - The presence of Y chromosome material (SRY) is associated with a higher risk of gonadal tumor and would benefit from a gonadectomy
    - If patient has hypertension as well as minimal body hair and absent secondary sexual characteristics, then CYP17 deficiency should be evaluated. These patients will have elevations of progesterone and deoxycorticosterone with low values of 17-alpha-hydroxyprogesterone.
  - Low or normal FSH (first focus on breast development to determine ovarian function)
    - Adequate breast development with low/normal FSH. Start thinking about secondary causes of amenorrhea.
      - May have an anatomic abnormality (primary amenorrhea), PCOS, hyperprolactinemia, or thyroid disease (last three can also cause secondary amenorrhea)
      - Pelvic ultrasound is helpful in determining an anatomic abnormality
      - Consider pituitary causes such as a pituitary mass. Consistently high prolactin should be confirmed and an evaluation of TSH should be done prior to ordering an MRI of the pituitary.
      - If physical exam findings show hyperandrogenism, serum testosterone and DHEA should be measured to help diagnose PCOS or androgen-secreting tumors.
    - No breast development (suggesting low estrogen state) with low/normal FSH. Low estrogen + inappropriate FSH response = central hypothalamic-pituitary disorder). Measure LH with FSH. Degree of LH and FSH suppression may help point towards a diagnosis.

- LH and FSH are both very low
    - Congenital GnRH deficiency, constitutional delay of puberty (rare in girls), or other disorders of the hypothalamic-pituitary (HP) axis should be considered.
    - A low TSH with a low free T4 (central hypothyroidism) also confirms HP disorder.
- LH is low and FSH is low/normal
    - Functional hypothalamic amenorrhea (FHA) is likely.
    - A history of an eating disorder, excessive exercise, stress, or a systemic illness is helpful in diagnosing FHA.
    - Systemic illness such as celiac disease, type I diabetes, and inflammatory bowel disease can cause FHA.
    - In the absence of a clear explanation for amenorrhea, an MRI of the pituitary should be performed.

- Uterus is absent
    - Evaluate with a karyotype and measurement of serum total testosterone.
    - Mullerian agenesis will have a normal 46, XX karyotype, female phenotype, and a testosterone level in the female range.
    - Androgen insensitivity syndrome (AIS) will have a 46, XY karyotype, normal female phenotype, sparse axillary and pubic hair, and a testosterone level in the male range.
    - 5-alpha-reductase deficiency will have a 46, XY karyotype, male testosterone levels, but in contrast to androgen insensitivity, which has a female phenotype, will undergo striking virilization at the time of puberty

Follow up testing for secondary amenorrhea

- Assess estrogen status (Progesterone Challenge or Estrogen & Progesterone Challenge)
    - Endogenous estrogen will prime the endometrium to ?secrete? progesterone in a normal physiological situation.
    - Providing the patient with exogenous progesterone via the progesterone withdrawal test is an indirect measure of endogenous estrogen over time. This is in contrast to a one-moment-in-time, random serum estrogen measurement, which is very variable.
        - Withdrawal bleeding confirms that patient has normal levels of endogenous estrogen.
        - Absence of bleeding may indicate either hypoestrogenism or an outflow tract disorder.
        - Endometrial thickness on pelvic ultrasound serves the same purpose as the progesterone withdrawal test but is more cumbersome to perform.

- Normal or low FHS concentration
    - If all the above mentioned labs are normal, then the patient likely has hypothalamic-pituitary disorder or PCOS.

- A low or "normal" level of FSH in the setting of a low estrogen relatively speaking is considered an inappropriate FSH response and should prompt a consideration of hypogonadotropic hypogonadism.
- How to distinguish between functional hypothalamic amenorrhea and PCOS.
  - The history will differ (e.g., PCOS will have clinical hyperandrogenism while FHA may have a history of low BMI and excessive exercise).
  - When there is a mixture of clinical presentation (e.g., hirsutism with low BMI) then LH may be helpful to differentiate the two.
  - FSH > LH in FHA; FSH < LH in PCOS.
  - Also, women with FHA are hypoestrogenic while women with PCOS are typically well-estrogenized.
- When hypothalamic amenorrhea is suspected, consider screening for celiac disease, type I diabetes, and hemochromatosis with fasting glucose/A1C, tissue transglutaminase antibody, and iron studies.

- <u>High serum prolactin</u>
  - Since psychological stress can increase prolactin, it is recommended to repeat prolactin levels, particularly when it is less than 50 ng/ml.
  - Test also for hypothyroidism since this can also cause high prolactin. TRH will stimulate both TSH and PRL secretion.
  - If first sample is >50 ng/ml or second sample is still high, then consider ordering an MRI of the pituitary if there are no other clear explanations for high prolactin (e.g., untreated hypothyroidism or antipsychotic drug use).
- <u>High FSH levels</u>
  - Obvious causes of POI include gonadotoxic chemotherapy or radiotherapy
  - If a history of cancer treatment does not exist, consider performing a karyotype to look for Turner syndrome.
  - In women with 46XX and spontaneous POI, it is recommended to also test for anti-adrenal antibodies and for fragile X premutation (FMR1 gene premutation).
- <u>Normal labs with a history of uterine instrumentation</u>
  - Evaluate for intrauterine adhesions (Asherman syndrome) with a progestin challenge. If withdrawal occurs, then an outflow tract disorder can be ruled out.
  - If patient fails to withdraw, then an estrogen and progesterone cycle can be administered and if patient continues to fail to have a withdrawal bleeding then a hysterosalpingogram or hysteroscope can be used to confirm diagnosis.
- <u>High serum androgen concentration</u>
  - Typically in this situation the patient will have PCOS, but if levels are very high then consider androgen-secreting tumors of the ovary or adrenal gland.
  - If testosterone is greater than 150-200 or if DHEAS is greater than 700 then consider androgen-secreting tumor.

- Abnormal TSH
    - Hyper- and hypothyroidism can cause oligo- and amenorrhea.
    - Check both TSH and free T4
    - A suppressed TSH and free T4 may be either central hypothyroidism or severe eating disorder

Other labs to consider:

- CBC - unexplained anemia may be celiac disease or from chronic disease
- Erythrocyte Sedimentation Rate (ESR) – marker for inflammation seen with chronic disease such as inflammatory bowel disease
- Iron panel (Fe, TIBC, Ferritin, transferrin saturation) - unexplained iron deficiency may suggest celiac disease. Elevated transferrin saturation and elevated serum ferritin can suggest hemochromatosis.
- AST, and ALT - may be elevated in hemochromatosis.
- 8 AM cortisol level followed by a dexamethasone suppression test can be used if there is a concern for Cushing's syndrome.

ACE Table

Chief Complaint – Amenorrhea (there are 8 entities to be filled by students- see yellow highlights)

Diagnosis/Entity	System	History	Physical Exam Finding	Labs	Radiology/Procedure
Imperforate Hymen	Gynecologic – Outflow tract, Congenital	Primary amenorrhea associated with normal development of breast and pubic hair, cyclic pelvic pain due to menstrual blood not having an egress is most common reason for acute presentation	Bulging blue mass at the introitus (hematocolpos), may also be palpated as a perirectal mass	-None usually needed if PE is able to identify -Pregnancy test, TSH, FSH, LH, Prolactin - normal, if done	Pelvic US – to confirm hematocolpos during presentations with pain
1. Mullerian Agenesis	**Gynecologic – Outflow tract, Congenital**	Primary amenorrhea with otherwise normal pubertal development	Vaginal opening ends with a blind pouch	-Pregnancy test, TSH, FSH, LH Prolactin – normal, if done -Karyotype is 46 XX	Pelvic US – uterus absent, variable normal ovaries

				-Testosterone: expected female range	Abdominal US or MRI – renal and skeletal abnormalities
Androgen insensitivity syndrome	Gynecologic – Outflow tract, Congenital	Primary amenorrhea with normal breast development, sparse or absent pubic and axillary hair	Vaginal opening end with a blind pouch	-Pregnancy test, TSH, FSH, LH, Prolactin – normal if done -Karyotype is 46 XY -Testosterone: male range	Pelvic US confirms absent uterus, testes may be intra-abdominal or in inguinal canal (risk of malignancy so remove after puberty)
2. Asherman Syndrome	**Gynecologic – Outflow tract, Acquired**	Secondary amenorrhea, ask about prior gynecologic procedures (ex. endometrial curettage, ablation, C-section with adhesion) or prior infections (endometritis or TB)	Normal exam, may have surgical scars	-Pregnancy test, TSH, FSH, LH, Prolactin – normal if done Estrogen/progestin withdrawal test – does not result in expected bleeding	Confirm with hysterosalpingogram or hysteroscopy
3. Turner syndrome	**Genetic – primary ovarian insufficiency**	Primary or secondary amenorrhea Short stature is the most consistent finding, dysmorphic features, cardiac and renal abnormalities, hypothyroidism, may be subtle, failure to start or complete breast development	Look for characteristic dysmorphic features – shield chest with widely spaced nipples, short and webbed neck, cubitus valgus, neonates with lymphedema of hands and feet	-Elevated FSH and LH levels -Karyotype 45, X - hypothyroidism common in these patients so may have abnormal TFT (also monitor for celiac, IBD, metabolic syndrome and DM)	Renal and cardiac US to look for other abnormalities associated with this condition
Radiation, chemotherapy	Endocrine – acquired ovarian insufficiency	May be primary or secondary amenorrhea, history of chemotherapy (often multiple drug regimens) or radiation	Non-specific for amenorrhea	Elevated FSH and LH consistent with ovarian failure	Pelvic US - may be done as part of work up for secondary amenorrhea

		(often more damaging than chemo)			
4. Prolactinoma	**Endocrine - pituitary**	Amenorrhea or oligomenorrhea, galactorrhea, headaches, bitemporal visual field deficit	Breast exam for galactorrhea and visual field testing	Elevated prolactin levels (50% of women with hyperprolactinemia will have a prolactinoma, if >200 ng/ml nearly 100% will have prolactinoma)	MRI of brain – most sensitive for diagnosis of pituitary masses and empty sella syndrome
5. Constitutional pubertal delay	**Endocrine – hypothalamic**	Constitutional delay less common in girls than boys but it can occur (considered a diagnosis of exclusion), often family history of late bloomer	Delayed growth, adrenarche, and gonadarche	-CBC, ESR, TSH, T4, Prolactin –normal -FSH, LH – consistent with bone age	**Delayed bone age**
6. Functional hypothalamic amenorrhea	**Endocrine – hypothalamic**	Identify stress, excessive exercise, eating disorder (ED), pubertal development may be normal or delay depending on age of onset	May be underweight, bradycardia common with excessive exercise and anorexia, look for evidence of ED	Usually clinical diagnosis but also diagnosis of exclusion so CBC, ESR, Pregnancy test, TSH and Free T4, LH and FSH (normal to low), Prolactin, (also consider screening for celiac disease or IBD)	None usually needed
Chronic disease	Endocrine – hypothalamic	Thorough review of symptoms to identify signs of systemic disease if not known, pubertal developmental may be normal or delayed depending on age of onset	Thorough PE to identify signs of occult disease if not known, cachexia may be present	CBC, CMP, ESR, Pregnancy test, TSH, Prolactin, FSH or LH (may be normal or low) (consider celiac screening and work up for IBD)	Depends on suspected condition, consider MRI to rule out CNS lesion

7. Polycystic ovary syndrome	**Endocrine – ovarian**	Oligomenorrhea or amenorrhea with signs of hirsutism and acne (hyperadrogenism), may have premaute pubarche or precocious puberty depending on age of onset	Hirsutism, acne, obesity (Increased BMI), acanthosis nigricans	-Pregnancy test, TSH, Prolactin – normal -Elevated LH:FSH ratio (>3:1) may be seen -serum testosterone (normal or mild elevation) -17-OH progesterone (normal) -DHEA-S (normal or mild elevation) -also work up for metabolic syndrome (Lipid panel, LFTs, Insulin, Fasting glucose)	US – polycystic ovaries (string of pearls sign)
8. Thyroid disease (Hyper/hypothyroidism)	**Endocrine – thyroid**	hyper – palpitations, nervousness, insomnia, fatigue hypo – weight gain, fatigue, constipation	Often normal thyroid exam for goiter or nodule Hand tremor seen with hyperthyroidsim	TSH and Free T4 Hyper – High free T4, low TSH Hypo – High TSH, low free T4	Depends on cause
Congenital adrenal hyperplasia – late onset	Endocrine – adrenal	Oligo or amenorrhea with virilization – deep voice, notable hirsutism, infertility	Clitoromegaly with hirsute features, may have poorly developed vaginal labia	As with PCOS but with elevated 17-OH progesterone levels	May have Pelvic US as part of amenorrhea evaluation - normal
Pregnancy	Endocrine – physiologic	Amenorrhea in a normal developed female who is sexually active, breast changes, non-specific	Normal exam, may note breast and skin changes	Pregnancy test positive (detection of hCG in plasma or urine)	US – confirm an intrauterine pregnancy etc.

		symptoms – fatigue, weight gain, nausea			
Natural Menopause	Endocrine – physiologic	40-55, average age in US is about 51 years, amenorrhea for one year, genetics, smoking, chemo/radiation affect age of onset, may have hot flashes, changes in mood or libido	Scalp hair loss or hirsutism, vaginal atrophy	Elevated FSH and LH	None needed
Contraception	Endocrine - pharmacologic	Question about available forms particularly extended-cycle combined OCPs, injectable medroxyprogesterone acetate (Depo-Provera), implantable etonogestrel (Implanon), and levonorgestrel-releasing intrauterine devices (Mirena)	Normal	None usually needed	None needed
Medications (non-contraceptives)	Endocrine, pharmacologic	Listed medications that can cause amenorrhea - antidepressants, antihypertensives, antihistamines, antipsychotics, and opiates	Normal	Diagnosis of exclusion – screening test – pregnancy, TSH, FSH, LH, prolactin	None needed

ACE- AMENORRHEA PRACTICE CLINICAL CASES (3 cases)

Case 1

CC: "I haven't had my period for 4 months"

A 20-year-old woman presents to the clinic for amenorrhea. The patient underwent menarche at age 12 years and has had normal menstrual cycles. She has not had a menstrual cycle in 4 months. She has no medical history of note. Family history is remarkable only for hypothyroidism. She takes no medications. She is a junior in college and is sexually active and monogamous with her boyfriend. She does not drink alcohol or use drugs. On physical examination, vital signs are

normal. Visual fields, thyroid, and pelvic examination findings are normal.

Questions:

1) Is this primary or secondary amenorrhea?
2) What else would you ask this patient?
3) What is your differential diagnosis? (list at least 4 and put them in order of most likely to least likely)
4) What lab test would you like next?
5) What is the likely diagnosis?

Answers:

1) Secondary
2) Ask about contraception, physical activity, stress etc., signs and symptoms of hypothyroidism (she is on the college track and swim teams; use of condom occasionally; no other signs or symptoms)
3) Pregnancy, hypothalamic, PCOS, hypothyroid
4) Pregnancy test – negative, TSH normal, FSH normal, Prolactin normal
5) Hypothalamic due to exercise

Diagnosis for case 1: Functional hypothalamic amenorrhea

Case 2

CC: "I am 16 and I have never had a period."

A 16-year-old female presents to the clinic for evaluation of amenorrhea. She has not had a menstrual cycle. She is a junior in high school. She participates in choir. She does not get exercise outside of required PE classes. She has recently become sexually active in the last year. She does not drink alcohol, smoke, or use drugs. On physical exam, vital signs are normal. She has normal breast development. Pelvic exam shows a normal vaginal canal without a cervix identified.

Questions:

1) Is this primary or secondary amenorrhea?
2) What else would you ask this patient?
3) What is your differential diagnosis? (list at least 4 and put them in order of most likely to least likely)
4) What lab test would you like next?
5) What is the likely diagnosis?

Answers:

1) Primary
2) Ask about family history, contraception
3) Mullerian agenesis, androgen insensitivity, imperforate hymen, constitutional delay, pregnancy
4) Pregnancy test –negative, Karyotype - 46XX, Testosterone level – normal female range
5) Mullerian agenesis

Diagnosis Case 2: Mullerian agenesis

Case 3

CC: "I am having trouble with my periods"

A 28 year-old female is evaluated for amenorrhea. The patient underwent menarche at age 11. For several years, she had monthly periods. Over the last 6 years, her menstrual cycle has become inconsistent and occurs about every 2-3 months. Her last menstrual period was 4 months ago. She takes a daily multivitamin. She is a secretary for a financial firm. She is married and sexually active. She does not drink alcohol or use drugs. She smokes 1 pack per day. On physical exam, vital signs are normal. Her BMI is 35 kg/m^2. Pelvic examination is normal.

Questions:

1) Is this primary or secondary amenorrhea?
2) What else would you ask?
3) What is your differential diagnosis? (list at least 4 and put them in order of most likely to least likely)
4) What lab test would you like next?
5) What is the likely diagnosis?

Answers:

1) Secondary
2) Ask about contraception, PCOS features, hypothyroid features, etc. (patient states use of condoms occasionally, no other signs or symptoms.)
3) Pregnancy, PCOS, premature ovarian failure, hypothyroidism
4) Pregnancy test - positive
5) Pregnancy

Diagnosis Case 3: Pregnancy

ACE Amenorrhea Quiz Questions:

1. An 18-year-old woman presents to the clinic for evaluation. She is going to college next year and inquires about sexually transmitted infection (STI) prevention. She has never had a period, but expects it "any day", as her mother had menarche at a later age (17 years). She is not currently sexually active. Vital signs are stable. Which of the following **BEST** describes this patient's condition at this time?
   a. Menopausal
   b. Perimenopausal
   c. Primary amenorrhea
   d. Secondary amenorrhea

2. A 21-year-old woman presents to the clinic for annual evaluation. She has no specific complaints. Upon review of systems, she relays that she hasn't had a period in 7 months. Menarche occurred at age 14 years. She is not currently sexually active. Vital signs are stable. Physical examination shows an overweight woman in no acute distress. Breasts appear normally developed with no masses. Abdominal examination is remarkable for increased subcutaneous fat, with a normal-sized uterus. Pelvic examination is unremarkable. Which of the following **BEST** describes this patient's condition at this time?
    a. Menopausal
    b. Perimenopausal
    c. Primary amenorrhea
    d. Secondary amenorrhea

3. Which of the following is useful in the workup of amenorrhea?
    a. Urine hCG
    b. FSH level
    c. TSH level
    d. Prolactin level
    e. History and Physical
    f. All of the above

4. A 14-year-old female presents for evaluation of primary amenorrhea. On exam you notice her height is less than the 5th percentile. Physical exam also shows a webbed neck, widely spaced nipples, low hair line, and a short 4th metacarpal. The best study to confirm your suspected diagnosis is:
    a. LH
    b. Karyotype
    c. TSH
    d. Bone age
    e. Prolactin level

5. A 20-year-old track athlete presents with a three month history of amenorrhea. She typically has regular periods. Her blood pressure is normal and she is at the 50th %ile for her height. Her BMI is 17 (underweight). Her hCG, prolactin, and TSH were all normal. Her labs show that her FSH and LH are low. Which of the following is the most likely cause of her amenorrhea?
    a. Functional hypothalamic amenorrhea
    b. Polycystic ovarian syndrome
    c. Congenital adrenal hyperplasia
    d. Turner syndrome

6. Which of the following should be excluded in all patients presenting with amenorrhea at their initial evaluation?
    a. Polycystic ovarian syndrome

b. Pregnancy
c. Mullerian agenesis
d. Turner Syndrome
e. Prolactinoma

7. Which physical exam finding is suggestive of adequate estrogen levels and ovarian function?
   a. Hirsutism
   b. Acanthosis nigricans
   c. Acne
   d. Breast development

8. All of the following are characteristics of prolactinoma except?
   a. Perirectal mass
   b. Galactorrhea
   c. Headaches
   d. Elevated prolactin level
   e. Visual field deficit

9. A 32-year-old woman presents six months after the birth of her daughter with no menstrual bleeding. She had bleeding for eight weeks after delivery and was found to have retained placental tissue. She underwent a dilation and curettage (D&C) procedure, which stopped the bleeding. She is not breast feeding. She was given estrogen then progesterone by her OB and she still did not bleed. What is the most likely organ system and cause of her amenorrhea?
   a. Endocrine, hypothyroidism
   b. Endocrine, stress
   c. Endocrine, eating disorder
   d. Gynecologic, ovarian tumor
   e. Gynecologic, Asherman syndrome
   f. Gynecologic, Mullerian agenesis

10. True or false. Functional hypothalamic amenorrhea can be caused by stress, weight loss or exercise.
    a. True
    b. False

Answers:
1. C (Objective 1)
2. D (Objective 1)
3. F (Objective 3,6,7)
4. B (Objective 3,4,5)

5. A (Objective 3, 4, 5)
6. B (Objective 3, 6)
7. D (Objective 3, 4)
8. A (Objective 3, 4, 5)
9. E (Objective 2, 3, 4, 5)
10. A (Objective 3, 4, 5)

ACE Amenorrhea Learning Objectives:

1) Define primary and secondary amenorrhea.
2) Name the organ systems commonly associated with amenorrhea.
3) Develop a clinical approach to the chief complaint of amenorrhea.
4) Develop a differential diagnosis for amenorrhea based on history, physical exam findings (e.g. estrogenization and breast development), and diagnostic tests.
5) Differentiate between different causes of amenorrhea (e.g. Turner syndrome, polycystic ovarian syndrome, hypothalamic amenorrhea, Asherman syndrome, etc.) given key clinical features.
6) Assess for and exclude pregnancy in patients presenting with amenorrhea.
7) Identify appropriate diagnostic testing in the evaluation of amenorrhea.
8) Identify the common laboratory or radiographic abnormalities associated with causes of amenorrhea.