Basic Science:
A. Embryology and Development/Anatomy
   1. Normal Mullerian Development
      1. Wolffian and Mullerian Ducts co-exist thru 8 weeks
      2. By 3rd month nonfunctioning ducts disappear
      3. Paramesonephric ducts contact in midline to form Y shape →
         primordial uterus, tubes, upper 1/3 vagina
      4. By 10th week: fallopian tubes, uterus, upper vagina
      5. 20th uterine mucosa is differentiated into endometrium
      6. 22nd uterine cavity, cervical canal, vagina
   2. Abnormal Development:
      1. Failure of the midline ducts to fuse, connect to urogenital sinus, create appropriate lumen/resorption of central vaginal cells
         i. Septate (35%)
         ii. Unicornuate (10%)
         iii. Didelphus (8%)
         iv. Bicornuate (26%)
   3. Classes:
      1. Class I-hypoplasia/agenesis
         i. uterine/cervical agenesis or hypoplasia.
         ii. Mayer-Rokitansky-Kuster-Hauser syndrome
            1. often exhibit extragenital anomalies
               a. 25-50 % have urologic anomalies, such as unilateral renal agenesis, pelvic or horseshoe kidneys, or irregularities of the collecting system
               b. 10-15 % have skeletal anomalies involving the spine, ribs, and extremities.
               c. Other less common anomalies include congenital heart lesions, abnormalities of the hand, deafness, cleft palate, and inguinal or femoral hernias
      2. Class II (unicornuate uterus):
         i. unicornuate uterus is the result of complete, or almost complete, arrest of development of 1 müllerian duct
         ii. If incomplete, as in 90% of patients, a rudimentary horn with or without functioning endometrium is present.
         iii. If obstructed, it may come to surgical attention when presenting as an enlarging pelvic mass
         iv. Earlier SAB, ectopics, malpresentation, IUGR, PTL
      3. Class III (didelphys uterus):
REI CREOG REVIEW

i. complete nonfusio of both mullerian ducts
ii. individual horns are fully developed and almost normal in size
iii. Two cervices are inevitably present
iv. longitudinal or transverse vaginal septum may be noted (can be obstructed, ipsilateral kidney)
v. Didelphys uteri have the highest association with transverse vaginal septa, but septa also may be observed in other anomalies.
vi. Consider metroplasty; however, since each horn is almost a fully developed uterus, patients have been known to carry pregnancies to full term

4. Class IV - bicorneate uterus
   i. results from partial nonfusion of the mullerian ducts
   ii. The central myometrium may extend to the level of the internal cervical os (bicorneate unicollis) or external cervical os (bicorneate bicollis).
   iii. demonstrates some degree of fusion between the 2 horns
   iv. horns of the bicorneate uterus are not fully developed; typically, they are smaller than those of didelphys uteri.
   v. Some patients are surgical candidates for metroplasty.

5. Class V-septate uterus
   i. failure of resorption of the septum between the 2 uterine horns.
   ii. histologically, the septum may be composed of myometrium or fibrous tissue.
   iii. fundus is typically convex but may be flat or slightly concave (<1-cm fundal cleft).
   iv. highest incidence of reproductive complications.
   v. Differentiation between a septate and a bicorneate uterus is important
   vi. septate uteri are treated by using transvaginal hysteroscopic resection
   vii. bicorneate uterus, an abdominal approach is required to perform metroplasty.

6. Class VI-arcuate uterus
   i. single uterine cavity with a convex or flat uterine fundus
   ii. considered a normal variant because it is not significantly associated with the increased risks of pregnancy loss and the complications found in other subtypes

7. Class VII-diethylstilbestrol-related anomaly
   i. 15% of women exposed to DES during pregnancy.
ii. Hypoplasia
iii. T-shaped uterine cavity
iv. abnormal transverse ridges, hoods, stenoses of the cervix, and adenosis of the vagina with increased risk of vaginal clear cell carcinoma.

4. Other anomalies:
   1. Transverse/Longitudinal vaginal septum
      i. Treatment:
         1. Longitudinal: Surgery is not required in asymptomatic women but may facilitate vaginal delivery
         2. Transverse: complete removal of the septum, with care to avoid bladder / rectum. The septal tissue is resected and then the normal vaginal mucosas from each vagina are sutured together over the defect created by the resection
         3. excised in total as retained fragments of septum may cause dyspareunia..

B. Endocrine
   1. Hypothalamic-pituitary axis
      ii. Hypothalamic hormones are small peptides generally active only at high concentrations
      iii. Anterior Pituitary: bathed in capillary network of pituitary blood containing hormones released in median eminence
      iv. ACTH, MSH, endorphins, GH, LH, FSH, TSH, PRL
      v. Posterior Pituitary: contains axons and nerve terminals from SON, PVN
Hypothalamic stimulatory hormones

- Corticotropin-releasing hormone - from PVN, SON and arcuate nuclei and limbic system
  - ACTH - basophilic corticotrophs, product of proopiomelanocortin (POMC) gene
  - MSH - alternate product of POMC gene
- GHRH - two forms, 40 and 44 amino acids
  - GH - acidophilic somatotrophs
- GnRH - mostly released from preoptic neurons
  - LH and FSH
- Thyrotropin-releasing hormone - three amino acids; released from anterior hypothalamic area
  - Thyroid-stimulating hormone - thyrotropes represent about five percent of anterior pituitary cells
- Prolactin-releasing factors - include serotonin, acetylcholine, opiates, and estrogens
  - Prolactin - lactotrophs represent 10 to 30 percent of anterior pituitary cells

Hypothalamic inhibitory hormones

- Somatostatin – 14 amino acids
  - Inhibits the release of growth hormone
- Prolactin-inhibiting factors - includes dopamine
  - Major prolactin control is inhibitory

2. Thyroid
   i. Critical Determinants of brain and somatic development in infants
   ii. Critical in metabolic activity in adults
   iii. Major targets include: skeleton, heart, metabolic regulation
   iv. Many drugs alter thyroxine absorption/metabolism: retinoic acid agonists, cigarettes, PCBs, iodine
   v. T3:
      1. T3 modifies gene transcription in virtually all tissues to alter rates of protein synthesis and substrate turnover
      2. 20% from direct thyroid secretion
      3. 80% from conversion from T4
3. Bone Formation/Resorption:
   i. Osteoclasts: bone resorption
      1. Low Ca\(^{2+}\) stim PTH which increases osteoclasts
      2. High Ca\(^{2+}\) decreases PTH decreasing the number and activity of osteoclasts, resulting in less bone resorption
   ii. Osteoblasts: bone formation
   iii. Osteoporosis is characterized by low bone mass with normal mineralization and disrupted architecture.
   iv. The anomalies in the architecture include fewer and thinner bony spicules, and formation of horizontal struts without functional roles.
   v. The decreased bone mass is theorized to derivate from either low peak bone mass, increased bony destruction, or decreased bone formation during remodeling.
   vi. Peak bone mass has relationships with dietary, genetic, and environmental factors.
   vii. Twin studies have revealed genetic determinants account for 40-80% of the differences in peak bone mass.
   viii. Numerous genes have been linked to variations in BMD, including the vitamin D receptor, estrogen receptor-a, Sp-1 cleavage site of the collage gene, BMP-2, LDL LRP-5, TGF-B, Apolipoprotein E, and the phosphodiesterase 4D (PDE4D) gene. Several of these genes have been found to modulate the impact of calcium on BMD, including VDR, collagen 1 alpha 1.

4. Prolactin
i. 198 amino acid polypeptide
ii. Structure similar to growth hormone
iii. Produced by lactotrophs of anterior pituitary
iv. Dopamine inhibits prolactin secretion
v. TRH stimulates release of prolactin via gene transcription
vi. Estrogen stimulates prolactin via gene transcription, lactotroph proliferation, increases TRH receptors, decreases dopaminergic activity
vii. Hyperprolactinemia:
1. Induced hypogonadism
2. Typically causes oligomenorrhea or amenorrhea
3. Galactorrhea
4. Causes:
   a. Pregnancy
   b. Hypothyroid
   c. Renal or Liver Disease
   d. Ectopic Secretion (bronchogenic/renal cell cancers)
   e. Stress
   f. Breast Stimulation
   g. Radiation
   h. Trauma
   i. Infiltration
   j. Tumors
   k. Granulomatous Lesions
   l. Infection
   m. Medication
      i. Estrogen, neuroleptic drugs, reglan, antidepressant drugs, cimetidine, methyldopa, verapamil, risperidone
viii. MRI should be obtained with elevated Prolatin levels
ix. Macroadenoma: >1cm
    1. Treatment essential when causes neurological symptoms
x. Microadenoma: <1cm
   1. 95% do not enlarge during 4-6 years of observation
   2. Treatment when causes hypogonadism
xi. Dopamine agonist
   1. Decrease hyperprolactinemia and size of lactotroph adenomas
   2. Types:
      a. Cabergoline (ergot dopamine agonist)
      b. Bromocriptine (ergot derivative)
      c. Pergolide (ergot derivative)
   3. Decrease in prolactin within 2-3 weeks
      a. Usually precedes the decrease in size (6 weeks)
b. Surgical management should be considered when
   c. Medical treatment unsuccessful

xii. >3 cm giant lactotroph
    1. Usual Transsphenoidal

xiii. Radiation
    1. Slow fall in prolactin (up to 10 years)
5. Adrenal Steroid
6. Steroid hormone biosynthesis

- Cholesterol $\rightarrow$ pregnenolone
  - $P_{450}^{SSC}$
  - $P_{450}^{c17}$
  - $3\beta$-DH
  - $\Delta^5$-isomerase
  - 17-OH progesterone
  - 17,20 desmolase
  - Dehydroepiandrosterone (DHEA)
  - $3\beta$-DH
  - $\Delta^5$-isomerase
  - 4-androstene-3,17-diol
  - 4-androstene-3-17-dione
  - $3\beta$-DH
  - $\Delta^5$-isomerase
  - 17-keto-reductase
  - aromatase
  - estrone
  - estradiol
  - 5α-reductase
  - testosterone
  - dihydrotestosterone

7. Menstrual Cycle
   i. Follicular Phase: onset of menses to LH surge
   ii. Early Follicular Phase
      1. Ovary least active: low E and P
      2. Release from negative feedback results in increase GnRH pulse frequency
      3. Increase in FSH $\rightarrow$ recruitment of next cohort follicles
      4. Follicles secrete inhibin B $\rightarrow$ inhibit FSH
      5. Increase in LH pulse frequency
   iii. Mid-Follicular Phase:
      1. Modest increase in FSH stimulates folliculogenesis and E2 production
      2. Follicles reach antral phase
      3. E2 and inhibin A increase
4. E2 feedback inhibits FSH and LH pulse frequency
5. GnRH pulse generator increases
6. Endometrium proliferates, increase in gland numbers

iv. Late Follicular phase:
   1. Dominant follicle evolving
   2. E2 and inhibin A suppress FSH, LH
   3. FSH induced LH receptors in the ovary and increases ovarian secretion of intrauterine growth factors like IGF-I
   4. Dominant follicle grows 2mm/day until mature size 20-26mm
   5. Rising E2 results in thickened EMS and cervical mucus (spinnbarkeit)

v. Luteal Phase: LH surge to onset menses
   1. Serum E2 increases until one day before ovulation
   2. LH surge occurs due to positive feedback
   3. Small increase in FSH
   4. Oocyte in dominant follicle complete first meiotic division
   5. Granulosa cells around dominant follicle luteinize and produce progesterone which slows the pulse generator
   6. 36 hours later oocyte released
   7. Endometrium changes due to progesterone increase → cessation of mitosis and organization of glands. Loss of triple stripe
   8. Increase in progesterone from corpus luteum
   9. Slowing of LH pulses
   10. Inhibit A produced by corpus luteum
   11. E and P decline if fertilization does not occur
   13. H-P axis is released from neg feedback as E and P decline, next cycle begins
(Average values. Durations and values may differ between different females or different cycles.)
C. Pharmacology:
   1. Ovulation induction
      a. Clomid:
         i. SERM
         ii. Used to induce ovulation in anovulatory/oligoovulatory (normogonadotrophic)
         iii. Ovulatory Rate of 80%
         iv. Pregnancy Rate 30-40%
         v. Start on day 5, 50mg for 5 days
         vi. 12 or more cycles may increase risk ovarian cancer (borderline)
         vii. Twins in 6.9-9%
         viii. Triplets 0.3-0.5%
         ix. Primary site action is hypothalamus (blocks negative feedback of circulating endogenous estrogens)
REI CREOG REVIEW

1. Creates increase in LH pulsatility and amplitude

x. Ovarian:
1. actions are secondary to increase LH and FSH. Estrogen agonist, therefore enhances FSH stimulation of LH receptors on granulosa cells

xi. Uterus/Cervix:
1. acts as ANTIestrogen
2. increase uterine volume/endometrial thickness
3. data on cervical mucus are conflicting

xii. Monitoring:
1. BBT/LH kits/serial TVUS
2. mid luteal progesterone >3ng indicates ovulation

xiii. NEJM study shows clomid superior to metformin in achieving live birth in infertile women with PCOS

2. Osteoporosis
a. Calcium and Vitamin D
   i. Ca: 1200-1500 mg
   ii. Vit D 600-800 IU
   iii. NEJM article found small but significant improvement in hip bone density, with bone density 1.06 percent higher than placebo. Although this lead to a 12% decrease in hip fractures, it was not statistically significant and cause marginal increased the risk of kidney stones

b. Bisphosphonates
   i. alendronate 5mg to10mg qd or 35-70mg q week
      1. Fracture Intervention Trial showed reduced vertebral AND hip fx
      2. Only one studied 10 years
      3. Rx when osteopenic does NOT reduce fracture risk
   ii. risedronate at 5mg daily or 30-35mg weekly
   iii. IV: concerns for jaw osteonecrosis

c. Selective Estrogen Receptor Modulators
   i. SERMs have tissue specific agonist-antagonist activity, acting as pure antagonists when acting thru estrogen receptor b but can function as partial agonists when acting thru receptor a. Concentrations of estrogen receptor B are higher in developing cancellous bone, whereas concentrations of estrogen receptor a are higher in cortical bone
   ii. Raloxifene
      1. +bone, - breast/endometrium
2. MORE study: Decrease vertebral fractures

d. Estrogen
   i. Decrease vertebral and nonvertebral fractures by 34% (WHI)

e. Calcitonin
   i. 200 IU nasal
   ii. PROOF study found decrease in vertebral
   iii. Many side effects

f. Strontium ranelate
   i. Dissociating bone formation and resorption, stimulating calcium uptake and inhibiting resorption
   ii. Two major trials, the SOTI and TROPOS have found decreased rates of both vertebral and nonvertebral fractures at three years when patients were given calcium and strontium ranelate
   iii. Not studied beyond 3 years

g. Parathyroid Hormone- anabolic agent
   i. Increase vertebral and nonvertebral
   ii. No human evidence for osteosarcoma

3. Ovulation Inhibition
   a. Lupron
      i. GnRH agonist
   b. Antagon
   c. OCPs

Pediatric and Adolescent Gynecology

Problems in Pediatric Patients (Birth to Menarche):

Vulvovaginitis: Most common gyn problem for prepubertal girls
Presentation: introital irritation, discharge; may be burning w/ urination; may be bloody
Pathophysiology: primary irritation of the vulva w/ secondary involvement of the lower 1/3 of the vagina. Girls prone to vulvar infection b/c no labial fat pads to protect, unestrogenized vulvar/vaginal epithelium, neutral pH of vaginal epithelium. Vagina lacks glycogen, lactobacilli and sufficient antibodies. Major factor is poor personal hygiene. Another RF is upper respiratory infection and child autoinoculating her vulva.
Micro: 75% of cultures have a nonspecific etiology w/ GI tract flora; 25% of cultures will grow out a specific bug such as Strep, GC, CT, Trich. Group A Strep most common.
Causes: allergy, skin infection, ectopic ureter or sexual abuse.
While an STI is a red flag for sexual abuse, many infants have been infected w/ CT during childbirth and remain colonized for several years. 

**Ddx for persistent or recurrent vulvovaginitis:** includes foreign body, pinworms, primary vulvar skin disease, ectopic ureter and child abuse. 

**Treatment:** treat underlying cause if identified; otherwise, improving perineal hygiene is key. Persistent/recurrent cases can be treated w/ po antibiotics and creams such as A&D. Pinworms is treated w/ mebendazole (treat all family members).

**Normal physiologic discharge:** May be reason for clinic visit, although normal finding. Six to 12 months before menarche, girls often develop a physiologic discharge secondary to increased estrogen levels. Micro only shows sheets of epithelial cells. Tx = reassurance.

**Vulvar diseases:**

_**Lichen sclerosus** – pruritic, white, wrinkly atrophic appearance, classic perianal “figure-of-eight” or “hourglass” rash; **Dx:** cutaneous bx  
 **Tx:** topical steroids

_**Lichen planus** – pruritic, purple polygonal papules, **Dx:** cutaneous bx  
 **Tx:** topical steroids

**Prepubertal vaginal bleeding:** Numerous causes. Causes include trauma, retained foreign bodies, neoplasia, precocious puberty, vulvovaginitis, lichen sclerosis, blood dyscrasia, exposure to exogenous estrogens. Two bacterial infections of vagina often implicated include Shigella and Group A Strep (may present 7-10 days after URI or sore throat).

**Adhesive vulvitis:** denuded epithelium of adjacent labia minora agglutinates and fuses the two labia together; most common in ages 3-6; no treatment needed unless child has trouble voiding; most cases will spontaneously separate but can be treated w/ topical estrogen cream which will result in separation; forceful separation should not be performed; if labial adhesions don’t resolve, refer to REI for evaluation of congenital anomaly.

**Trauma:**

**Straddle injuries:** often presents as a hematoma, place foley catheter upon presentation as area can swell and later make voiding difficult; consider voiding cystourethrogram if hematuria is present to r/o bladder/urethra injury; treat w/ observation/cold compresses for first 6 hrs; if hematoma stable, tx is warm sitz baths for a few days
Accidental penetration: usually ages 2-4, from falling on sharp object such as a pencil; presents w/ hematuria, vaginal d/c, bleeding; if injury is not stable and the injury is above the hymen, may require surgical exploration; work-up includes imaging, anoscopy, sigmoidoscopy

Foreign body in the vagina: commonly ages 2-4; often present w/ bloody or purulent vaginal d/c within wks; persistent vaginal d/c warrants EUA to assess for foreign body; antibiotics to prevent ascending infection

Lacerations: often from forceful abduction from gymnastics, waterskiing, etc.; EUA may be required to assess extent of injury

Clitoral strangulation or ischemia: p/w pain, irritability, sometimes cellulitis; often caused by a hair; outcome depends on degree of ischemia

Sexual abuse: Defn: contact or interaction btwn a child and adult in which the child is being used for sexual stimulation of that adult or another person; can be committed by another minor if substantially older than victim or abuser is in position of power; defn also includes pornography and exhibitionism; must be considered w/ any vaginal foreign body; majority of cases involve someone the victim knows socially.

Forensic sampling: If an assault occurred within 72 hrs, forensic sampling should be performed. The most commonly used marker for semen is acid phophatase (detectable < 72 hrs); motile sperm can be recovered 8 hrs after assault (nonmotile up to 26 hrs); test for STIs!

PE red flags – Damage to 6 o’clock gu region rather than classic 12 o’clock as seen in straddle injuries; hymenal-vaginal tears, enlarged hymenal opening > 1cm, resting anal dilation (>2cm) in absence of stool;

Ambiguous genitalia: medical emergency; do not assign gender in delivery room if unsure; every case should be considered as congenital adrenal hyperplasia until proven otherwise because of serious consequences

Ellicit a pertinent history and focused PE based on the patient’s age (equipment, positioning, adjuncts):
Younger children may best be examined while sitting on mother’s lap, even for the pelvic exam. An older child may be examined in the supine position w/ knees apart and feet together or in the knee chest position. Child should never be restrained for
the exam. Distal vagina can be visualized by gently retracting the inferior labia downward. Knee-chest position can be used to visualize vagina w/o speculum for girls>2 yo. Rectal exam should be performed if genital tract bleeding, pelvic pain, suspicion of a foreign body or pelvic mass (normal prepubertal uterus and ovaries are not palpable). Relative size of cervix to uterus is 2:1.

**Precocious Puberty:**

Definition: evidence of secondary sexual characteristics, including breast or pubic hair development, at an age < 2.5 SDs below the mean (< 6yo for Afr Am and < 7yo for Caucasian).

Principal causes: can be divided into GnRH-dependent (complete, true) and GnRH independent (incomplete, pseudo).

Heterosexual precocious puberty: premature virilization in a female child

Isosexual precocious puberty: non-virilizing sexual characteristics in a female

Prepubertal thelarche: isolated unilateral or bilateral breast development is the only sign of secondary sexual maturation; normal in neonates and may persist to 6 mo old; also can occur ages 1-4 yo w/o nipple development; usually benign and self-limiting; girls need to be followed for other signs of precocious puberty

Premature pubarche or adrenarche: isolated public hair and/or axillary hair w/o other secondary sexual characteristics; need to follow closely for virilization, bone age should not be advanced; some have abnormal EEGs w/o neurological disease; thought to be due to excess DHEA and DHEA-S by the adrenal glands.

GnRH-dependent: premature maturation of the hypothalamic-pituitary-ovarian axis: normal menses, ovulation, pregnancy possible; increased estrogen

- 70% of cases are idiopathic
- girls have increased basal FSH/LH, estrogen
- occasionally develop follicular cysts
- many have abnormal EEGs
- may be associated w/ gelastic seizures (seizures w/ inappropriate laughter)

Etiologies: include inflammatory, degenerative, neoplastic, congenital defects

CNS lesions: located near hypothalamus in region of 3rd ventricle, tuber cinereum or mammillary bodies;
CNS diseases: TB, encephalitis, trauma, hydrocephalus, neurofibromatosis, granulomas, hamartomas, teratomas, craniopharyngiomas, cranial irradiation, congenital brain defects; Pathophysiology of how CNS disease can cause precocious puberty is poorly understood, but it is known that hamartomas may secrete GnRH;

GnRH-independent: premature female sexual maturation and uterine bleeding w/o associated ovulation; secretion of estrogen independent of hypothalamic control

Estrogen-secreting ovarian tumors: most common cause, esp granulosa cell tumors (60% of cases). Granulosa cell tumors usually >8cm and can be palpated. Other tumors: thecomas, luteomas, teratomas, Sertoli-Leydig, choriocarcinomas, benign follicular cysts.

McCune-Albright: polyostotic fibrous dysplasia, triad of café-au-lait spots, fibrous dysplasia, cysts of the skull of the long bones; 40% of girls w/ this have isosexual precocious puberty

Adrenocortical neoplasms: can produce either isosexual or heterosexual precocious puberty; congenital adrenal hyperplasia can result in normal puberty if treated infancy, heterosexual precocious puberty if not treated and isosexual precocious puberty if treated in late childhood.

Hypothyroidism: usually associated w/ delayed puberty but instances can result in precocious puberty; due to decreased TSH

Iatrogenic/factitious: when a young female uses estrogen cream or ingests oral estrogen or OCPs.

Work-up of Precocious Puberty:
- Meticulous H&PE,
- Labs: FSH, LH, prolactin, TSH, T3, T4, estradiol, DHEA, hCG, androstenedione, 17-hydroxyprogesterone
- Imaging studies of the brain: CT, MRI
- Hand-wrist films for bone age to compare w/ standards at patient’s age;
  - Hand-wrist films should be repeated q6 months to evaluate rate of skeletal growth;
  - Advancement of bone age more than 95% of the norm for the child’s age documents a peripheral estrogen effect;
- Abdominal imaging: CT abd/pelvis and/or pelvic sono to assess ovaries, uterus, adrenal glands
GnRH stimulation test

Management of Precocious Puberty:
Depends on the cause, extent and progression;
For premature maturation of the hypothalamic-pituitary-ovarian axis:
  Girls w/ menarche b/4 8yo, progressive thelarche and pubarche and bone age more than 2 yrs greater than chronological age should be treated. Treatment is GnRH agonists w/ optimal dosage determined by estradiol levels being in normal prepubertal range.
For McCune-Albright:
  Testolactone – an aromatase inhibitor, which prevents conversion of estrogen precursors to biologically active estrogens

Long-term prognosis for patients with precocious puberty:
These girls will have a shorter than normal adult height due to premature epiphyseal closure. Without therapy, 50% of girls will not reach an adult height > 5 ft.

Adolescent Gynecology
Normal and abnormal pubertal development

Normal sequence of development:
Breast development (thelarche) → axillary/pubic hair (pubarche) → maximal growth velocity → menarche (menarche may occur b/4 pubarche in 10% of normal females)

Tanner Stages: Breast Development

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prepubertal</td>
</tr>
<tr>
<td>2</td>
<td>Breast bud stage with elevation of breast and papilla; enlargement of areola</td>
</tr>
<tr>
<td>3</td>
<td>Further enlargement of breast and areola; no separation of their contour</td>
</tr>
<tr>
<td>4</td>
<td>Areola and papilla form a secondary mound above level of breast</td>
</tr>
<tr>
<td>5</td>
<td>Mature stage: projection of papilla only, related to recession of areola</td>
</tr>
</tbody>
</table>
Tanner Breast Development Stages I-V

Tanner Stage: Pubic Hair

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prepubertal</td>
</tr>
<tr>
<td>2</td>
<td>Sparse growth of long, slightly pigmented hair, straight or curled</td>
</tr>
<tr>
<td>3</td>
<td>Darker, coarser and more curled hair, spreading sparsely over junction of pubes</td>
</tr>
<tr>
<td>4</td>
<td>Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs</td>
</tr>
<tr>
<td>5</td>
<td>Adult in type and quantity, with horizontal distribution</td>
</tr>
</tbody>
</table>

Tanner Pubic Hair for Girls Stage I-V


**Delayed puberty:**

**Defn:** a girl who has not experienced any pubertal development by the age of 13 is more than 2 SDs beyond the normal age of initiating puberty and warrants work-up
**REI CREOG REVIEW**

**Causes:** Multiple, including anatomic abnormalities, chromosomal disorders, neoplasm

**Work-up:** x-rays for bone age, brain imaging if hypogonadotropic, FSH, LH, PRL, adrenal and gonadal steroid measurements, thyroid function tests.

May characterize by FSH level (hypogonadotrophic vs hypergonadotrophic)

<table>
<thead>
<tr>
<th>FSH Level:</th>
<th>Differential Diagnosis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt;30mIU/ml)</td>
<td>Turner’s syndrome</td>
</tr>
<tr>
<td>Hypergonadotropic Hypogonadism</td>
<td>Sweyer’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Primary ovarian failure</td>
</tr>
<tr>
<td>Low (&lt;30mIU/ml)</td>
<td>Constitutional delay</td>
</tr>
<tr>
<td>Hypogonadotropic Hypogonadism</td>
<td>Intracranial neoplasms</td>
</tr>
<tr>
<td></td>
<td>Isolated gonadotropin deficiencies</td>
</tr>
<tr>
<td></td>
<td>Hormone deficiencies</td>
</tr>
<tr>
<td></td>
<td>Kallmann syndrome</td>
</tr>
<tr>
<td></td>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td></td>
<td>Laurence-Moon-Biedl syndrome</td>
</tr>
<tr>
<td></td>
<td>Chronic disease and malnutrition</td>
</tr>
<tr>
<td>Normal FSH</td>
<td>Anatomic deformities that result in normal development with primary amenorrhea</td>
</tr>
<tr>
<td>Eugonadism</td>
<td></td>
</tr>
</tbody>
</table>

**Hypergonadotropic Hypogonadism:**
Gonadotropins present but end organs not responsive;
Turner syndrome (45,X):
Swyer syndrome (46, XY):
Primary ovarian failure: causes include chemo/radiation, galactosemia, gonadotropin resistance, autoimmune, infection

**Treatment:** Administration of exogenous estrogen and progesterone to avoid osteoporosis and facilitate development of secondary sexual characteristics

**Hypogonadotropic Hypogonadism:**
**Chronic malnutrition or disease:** Thought to disrupt GnRH production. Includes anorexia nervosa, cystic fibrosis, Crohn’s, DM, inflammatory diseases, hypothyroidism

**Constitutional Delay:** Delay in the GnRH pulse generator postpones the normal physiologic events of puberty.
**Intracranial neoplasms:** including craniopharangiomas and pituitary adenomas

**Isolated gonadotropin deficiencies:** often genetic mutations affecting GnRH, LH, FSH

**Hyperprolactinemia:** can cause a decrease in FSH and LH levels and thus delay puberty

**Kallman syndrome:** sporadic or X-linked syndrome with classic triad of anosmia, hypogonadism, color blindness

**Prader-Labhart-Willi syndrome:** autosomal dominant w/ extreme obesity, emotional instability and delayed puberty due to hypothalamic dysfunction

**Laurence-Moon syndrome:** rare autosomal disorder; retinitis pigmentosa, hypogonadism, spastic paraplegia

**Bardet-Biedl syndrome:** rare autosomal recessive; retinitis pigmentosa, hypogonadism and postaxial polydactyly

Treatment: treat specific cause; hormonal therapy as needed

**Eugonadism (Normal FSH):**

Presents as primary amenorrhea as reviewed in other section; causes include imperforate hymen, transverse vaginal septum, mullerian agenesis, vaginal atresia, androgen insensitivity

**Menstrual and Endocrine Disorders**

A. Dysmenorrhea
   a. Primary: recurrent crampy lower abdominal pain during menses in the absence of pelvic disease
   b. Secondary: as above, in the presence of pelvic pathology
   c. Risk Factors
      i. Endometriosis
      ii. Adenomyosis
      iii. PID
      iv. Presentation at <30 yo
      v. BMI <20
      vi. Menarche prior to 12
      vii. Longer cycles/duration of bleeding
      viii. Irregular or heavy flow
ix. Premenstrual symptoms
x. PID
xi. Sterilization
xii. h/o sexual assault
xiii. Heavy smoking
d. Pathogenesis:
i. Association with frequent, prolonged uterine contractions that result in uterine ischemia or decrease in blood flow to myometrium
ii. Doppler studies show higher uterine and arcuate artery resistance on the first day of menses in those with PD compared to controls
iii. E + P \rightarrow \text{Arachidonic Acid} \rightarrow \text{PGF2, PGE2, Leukotrienes} \rightarrow \text{uterine contractions}
iv. Uterine Pressure > Arterial pressure \rightarrow \text{anaerobic metabolites} \rightarrow C fibers

8. Diagnosis:
i. EMBx
ii. Microbiology of genital tract
iii. Pelvic Ultrasound
iv. HSC, Lsc
v. CT, MRI

9. Treatment
i. Heat
ii. NSAIDS (80-86%)
iii. Exercise
iv. OCP
v. IUD
vi. Tocolytics (questionable)
vii. TENS (trancutaneous electrical nerve stimulation)
viii. Surgical interuption of nerve pathways (LUNA)<(LPSN)
ix. Raises threshold fr pain signals
x. Stimulates endorpin release
xi. Laparoscopy (80% with have endo)
xii. After 2-3 failed cycles with medical
xiii. GnRH treatment to empirically dx Endo

10. Causes:
i. Endometriosis
ii. Acute Endometritis:
   1. Pelvic Inflammatory Disease
   2. Sexually transmitted diseases
   3. Surgical procedures
4. Uncommon complication
5. 2/927
6. ACOG does not recommend antibiotic prophylaxis prior to hysteroscopy, IUD insertion, endometrial biopsy, routine D&C, ablation
7. Does recommend prior to surgical termination of pregnancy: Doxycycline 100mg prior to procedure and 200mg after completion or Flagyl 500 bid x 5 days

iii. Chronic Endometritis
   1. Detected histologically in 8% of endometrial specimens
   2. No apparent etiology in one third
   3. Present with abnormal uterine bleeding
   4. Many women are asymptomatic
   5. Endometrial Biopsy will show plasma cells in the endometrial stroma

B. Amenorrhea
   a. Definition Primary:
      i. No menses by 16 yo
      ii. Failure of any signs of puberty by 13
      iii. Consider if cyclic pain without menses by 12-14
   b. Etiology
      i. Chromosomal abnormalities causing gonadal dysgenesis (ovarian failure) – 50%
      ii. Hypothalamic Hypogonadism – 20%
      iii. Absence of uterus, cervix, vagina, mullerian agenesis – 15%
      iv. Transverse vaginal septum or imperforate hymen – 5%
      v. Pituitary disease – 5%
   c. Congenital Causes:
      i. Vaginal Agenesis
         1. Differential:
            a. Androgen Insensitivity
               i. Male range testosterone
            b. Low Lying transverse septum
               i. Between hymenal ring and cervix
            c. Imperforate Hymen
               i. Hematocolpos
               ii. Diagnosed by physical exam
            d. Mayer-Rokitansy-Kuster-Hauser
REI CREOG REVIEW

i. No vagina, variable
development of uterus

ii. 7-10% with normal but
obstructed uterus with
functional endometrium

iii. NORMAL testosterone

d. FSH in primary amenorrhea
   i. Normal FSH $\rightarrow$ high FSH/LH
      1. Functional hypothalamic amenorrhea
      2. Abnormal GnRH secretion, decreased
gonadotropins, no follicular development
   3. Eating disorders
   4. Congenital: Kallmans (anosmia)
   5. AD, AR, Xlinked, 2/3 sporadic
   6. Constitutional Delay
      a. Common in boys, uncommon in girls
   7. Infiltrative diseases/tumors
      a. Check MRI – check in all with primary
         hypogonaditropic hypogonadism!

8. PRL

9. Check autoimmune thyroid/adrenal

e. Low FSH
   i. PRL

f. High FSH
   i. Check Karyotype
   ii. Gonadal dysgenesis $\rightarrow$ premature depletion of ovarian
       follicles
      1. Turners
         a. Most common
         b. 45 X
         c. Can be secondary amenorrhea is
            mosaicism
         d. Web neck
         e. Short stature
         f. Sheild Chest
         g. Widely spaced nipples
         h. BP in both arms $\rightarrow$ Coarctation Ao
     iii. PCOS
     iv. Autoimmune

9. Genetic Causes:
   i. Androgen Insensitivity
REI CREOG REVIEW

1. 46 XY
2. Phenotypically female with palpable testes
3. Defect in androgen receptor
4. Breast development
5. Excise testis at puberty due to risk CA

ii. 5 alpha reductase
   1. Onset of virilization at puberty
   2. Present non-DHT features: muscle mass, voice deepening, male pattern hair growth

iii. 17 alpha reductase

iv. CYP17 gene
   1. 46 XX or XY
   2. Decrease cortisol, overproduction ACTH
   3. Phenotypically females with HTN

v. Vanishing testes syndrome
   1. 46 XY
   2. Streak gonads, no MIS
   3. Female internal and external if early, if later streak testes
   4. High FSH, high risk gonadal tumors

vi. Absent testis determining factor
   1. Ullrich-Turner syndrome
   2. 46 XY
   3. Female internal and external

h. Other
   i. Neonatal crisis: CAH vs hypothalamic
   ii. Symptoms of virilization: PCOS vs androgen/adrenal tumor, Y chromosome material
   iii. Medications (heroin, methadone)

i. Review:
   i. Uterus absent: test for testosterone
      1. Androgen insensitivity
      2. MRKH
   ii. 5 alpha reductase

j. Uterus present: check FSH (+/- Karyotype)
   i. Primary ovarian failure
   ii. Hypothalamic (check MRI)
   iii. Thyroid/PRL, testosterone (tumor), if HTN progesterone for CYP17
### REI CREOG REVIEW

#### k. Secondary Amenorrhea

<table>
<thead>
<tr>
<th>Cause</th>
<th>%</th>
<th>W/U</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
<td>40</td>
<td>FSH, DHEA-S, Test</td>
<td>PCOS, premature ovarian failure (check karyotype), tumor</td>
</tr>
<tr>
<td>Hypothalamic Dysfunction</td>
<td>35</td>
<td>FSH/ LH, low leptin</td>
<td>Anorexia, stress</td>
</tr>
<tr>
<td>Pituitary Disease</td>
<td>19</td>
<td>PRL, TSH, MRI, Fe, FSH/LH</td>
<td>Infiltrative lesions, prolactinoma, empty sella, thyroid disease</td>
</tr>
<tr>
<td>Uterine disease</td>
<td>5</td>
<td>HSG, pelvic sono, attempt w/d bleed</td>
<td>Ashermans</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>HCG</td>
<td>pregnancy</td>
</tr>
</tbody>
</table>

#### C. PMS/PMDD

a. cyclic changes in E and P cause marked changes in GABA and serotonin systems.
b. Pt with PMS have lower serotonin levels and uptake
c. Aleviated with SSRI- even if only taken cyclically

#### D. PCOS

a. NIH:
   i. Menstrual irregularity
   ii. Evidence hyperandrogenism (clinical or lab)
   iii. Exclusion of other causes
b. Rotterdam: (2/3)
   i. Oligo- or anovulation (<9 in yr)
   ii. Clinical/biochem hyperandrogenism
   iii. PCOS
c. Insulin resistance (no data to test without Sx)
d. Labs: total testosterone, DHEAS, 17 OHprogesterone
e. Differential: nonclassical CAH, androgen tumors, hyperPRL
f. Increased risk for metabolic syndrome, DM, CV disease
g. Caveat: adolescent: multifollicular ovaries can be nml.
   Hyperandrogenism is critical factor.
h. Rx: weight loss, Rx hirsutism. Endometrial protection!! OCP. If desires pregnancy clomid works well

#### E. Hirsutism
a. Caused by androgens
   i. Testosterone (ovarian)
   ii. DHEA-S (adrenal)
   iii. Androstenedione (adrenal/ovarian)
b. PCOS
c. CAH – late onset form (nonclassical) → 21 hydroxylase leading to excess 17 hydroxypregesterone and androstenedione
d. Ovarian Tumors (sertoli leydig, granulosa theca cell, hilus-cell) → high test >200ng/dl
e. Adrenal tumors → DHEA-S and DHEA, cortisol
f. Treatment
   i. Ferriman Gallwey System
      1. Mild (score 8-15) – nonpharmacologic or pharmacologic alone
      2. Severe (>15) – multimodel or >1 medication
   ii. Androgens increase follicle size, hair fiber diameter, proportion of time in anagen phase
      1. Cause differentiation into terminal hair
   iii. Nonandrogenic hair growth
      1. Langugo: vellus
      2. Hypertrichosis: diffuse, commonly by drugs
   iv. Will take 4-6 months for effects
   v. If treatment isn't continuous most relapse in 6 months
   vi. Nonpharmacologic
      1. Shaving
      2. Depilatories/bleaching
      3. Electrolysis
      4. Laser Treatment
   vii. OCP
      1. Start with 35mg EE with norethindrone acetate, increase NEA as needed. If breakthrough bleeding 35mg EE plus ethynodiol diacetate
         a. Increase SBG
         b. Inhibit LH, therefore ovarian androgen
         c. Inhibit adrenal androgen secretion
      2. Antiandrogens
         a. Spironolactone
         b. Inhibit testosterone binding to receptors
         c. 100mg
         d. S/E: hyperkalemia, GI
      3. Flutamide
         a. Inhibit testosterone binding to receptors
REI CREOG REVIEW

b. Liver failure

4. Finasteride
   a. Alpha reductase inhibitor
   b. Less effective

F. Recurrent Pregnancy Loss:
   a. Definition: >3 consecutive pregnancy losses <20 weeks gestation
   b. 1 SAB: 15%
   c. 2 SAB: 2%
   d. 3 SAB: 0.3 – 1%
   e. Risk after two consecutive miscarriages: 24-29%
   f. Causes:
      i. Genetic
      ii. Chromosome number or structure
      iii. 3-5% with major chromosomal rearrangements
      iv. 60% reciprocal translocation
      v. 40% Robertsonian
      vi. Uterine
      vii. Anomalies (10-15%) – most commonly septate
      viii. Fibroids (submucosal)
      ix. Synechiae- commonly from D&C prior to weeks with damage to basalis \(\rightarrow\) granulation tissue creating bridges
      x. Cervical incompetence
      xi. Immunologic
      xii. APS (5-15%) test 6-8 weeks apart, need two values mid to high positive (anticardiolipin AB, RVV)
      xiii. Failure of maternal immune protection (ie expression of compliment, etc)
      xiv. Poorly controlled DM
      xv. Endocrine
      xvi. Thyroid: high thyroid antibody concentration
      xvii. PCOS (20-40%)
      xviii. PRL
      xix. Luteal phase
      xx. Thrombophilias (thrombosis of spiral arteries)
      xxi. Male Factor
         1. Poor sperm morphology
         2. Defects in chromatin condensation and irregular nuclei
      xxii. Infection
         1. Listeria, toxo, CMV, primary HSV (mostly sporadic)
      xxiii. Celiac Disease
xxiv. Miscarriage Rate by Age
   1. 20-30 → 9-17%
   2. 35 → 20%
   3. 40 → 40%
   4. 45 → 80%

xxv. Evaluation
   1. Some Eval after 2 losses
   2. US, HSG, sonohysterogram
   3. TSH, HgA1c if symptomatic
   4. APS workup
   5. Thrombophilia (factor V, prothrombin mutation, protein C/S, antithrombin 3)
   6. Karyotype – last and if all else negative
   7. No studies to support treatment of luteal phase defect
   8. Nothing to support IVIG
   9. Cultures are not beneficial

IV. Infertility
   A. Evaluation
      a. Primary vs Secondary
         i. Primary:
         ii. Secondary:
      b. Causes:
         i. Primary:
            1. anovulation
            2. endocrine (hyperprolactinemia, hypothyroid, PCOS)
            3. structural (septate uterus, fibroids)
            4. endometrial (endometriosis, synechiae)
            5. tubal (PID, endo)
            6. male (azzoospermia, oligospermia, teratospermia, etc)
         ii. Secondary: as above
         iii. Male factor — 23 percent
         iv. Ovulatory dysfunction — 18 percent
         v. Tubal damage — 14 percent
         vi. Endometriosis — 9 percent
         vii. Coital problems — 5 percent
         viii. Cervical factor — 3 percent
         ix. Unexplained — 28 percent
      c. Tests
REI CREOG REVIEW

i. Ovulation: BBT, LH kits
ii. Male: Semen Analysis
iii. Endocrine: TSH, Prl, PCOS
iv. Endometrial: US
v. Tubal: HSG
vi. Cervical: postcoital (usually when on clomid to assess)
vii. Laparoscopy as last test
d. Treatment:
e. Reproductive technologies
   i. IUI
   ii. ICSI: Intracytoplasmic Sperm Injection
       1. Single Sperm is microinjected into the oocyte after passage through the zona pellucida and the oolema
       2. Done for:
          a. Severe Male factor infertility
          b. Azoospermia, Oligospermia, Oligoasthenospermia, Oligoasthenoteratozoospermia, Antisperm antibodies
          c. Spinal cord injury
          d. Ejaculatory disturbances
          e. Repeated Fertilization Failure
          f. PGD (enhance fertilization, less contamination)
          g. Those who cryopreserved sperm prior to chemo, vasectomy
       3. Done with epididymal or testicular sperm
       4. May pass on male infertility, increase chromosomal problems
iii. GIFT
iv. ZIFT
v. PGD (Preimplantation genetic diagnosis)
   1. Biopsy one or two cells at 6 - 8 cell stage OR remove polar body
   2. Diagnosis of chromosomal anomalies (CF, etc) does NOT diagnose non-cytogeneic or single gene anomalies
   3. Must occur by 6th day (pre-implantation)
   4. Benefits
REI CREOG REVIEW

a. Can select for sex (X linked disorders)
b. Reduce risks of SAB by selecting chromosomally normal

5. Draw Backs
a. Requires IVF
b. Manipulation may result in loss of normal embryo
c. May fail to diagnose
d. May be contaminated with ambient DNA (nonembryonic) -> therefore do ICSI with all PGD case
e. Increases risk of monozygotic twinning
f. PCR failure rate with nested primers of 5-10%, including complications of allele drop out \( \rightarrow \) this is a problem for dx of nucleotide repeat disorders (Huntingtons, myotonic dystrophy, Fragile X)

6. Procedure:
a. Biopsy 6 – 8 cell embryo via mechanical (razor/laser) or chemical (enzymatic) disruption of zona pellucida, followed by pipelle aspiration
b. Polar body biopsy diagnoses at division of meiosis I, (NOT meiosis II, therefore misses paternal genotype, misses cross-over). Diagnosis by exclusion (ie this is NOT the DNA)
c. Can do FISH with chromosome specific probes

7. Clinical pregnancy rate 17% (ESHRE)

8. Single Gene disorders tested for in PGD
a. CF
b. B-thal
c. Spinal muscular atrophy
d. Sickle cell
Management of Climacteric Period
A. Diagnosis:
   a. Genetically programmed loss of follicles
   b. Mean Age 51.4
   c. “Menopausal transition:” begins with variation in menstrual cycle length and elevated FSH, ends with final menses. Can have hot flashes
   d. “Perimenopause:” around the menopause (beings with variable cycle length thru 12 months after menses)
   e. “Menopause:” 12 months of amenorrhea after final menses. Complete or near complete follicle depletion
   f. “Postmenopause:” first five years → stage one. s/p five years to death → stage two

B. Symptoms:
   a. 70% get hot flashes, usually resolved in 1-5 years
   b. vaginal mucosal atrophy → dryness. Also increase in pH
   c. sexual dysfunction due to lack of lubrication and decrease blood flow
   d. may have recurrent UTI due to change in flora/vaginal pH
   e. depression
   f. eventually: osteoporosis, cardiovascular disease, dementia

C. Endocrine:
   a. Follicular phase length gradually shortens
   b. In early menopausal transition:
      i. inhibin B decreases due to decrease in follicular number
      ii. Therefore, FSH rises
      iii. Estradiol remains roughly same due to increase in aromatase.
      iv. Progesterone levels are lower in luteal phase
   c. Late transition
      i. Cycle variability increases, variety in FSH/estradiol levels increase

D. Evaluation
REI CREOG REVIEW

a. Chronic anovulation, progesterone deficiency leads to long periods unopposed estrogen, may necessitate EMBx
b. May treat with low dose OCP or progestin, or HRT
c. Always consider hyperthyroidism, pregnancy in differential

E. Management
   a. Treat to manage moderate/severe symptoms
   b. Do not use for “prevention”
   c. Avoid estrogen treatment in those with history of thromboembolism, breast cancer, CAD, stroke, high risks of these diseases
d. WHI and HERS trials
e. Doses: lowest dose of estrogen effective
f. Add progesterone in all women who have not had hysterectomy
g. in WHI risk of breast cancer with estrogen-progesterone therapies didn’t increase until 4th year
h. Newer data suggests effects on CHD are limited to elderly postmenopausal
i. HABITS trial for info on breast cancer/HRT