CREOG review
REI

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Basic Science/Mechanism of Disease

- Mullerian Development
  - Wolffian and Mullerian Ducts co-exist thru 8 weeks
  - By 3rd month nonfunctioning ducts disappear
Mullerian Development

- Paramesonephric ducts contact in midline to form Y shape → primordial uterus, tubes, upper 1/3 vagina
- By 10th week: fallopian tubes, uterus, upper vagina
- 20th uterine mucosa is differentiated into endometrium
- 22nd uterine cavity, cervical canal, vagina
Abnormal Mullerian Development

- Failure of the midline ducts to fuse, connect to urogenital sinus, create appropriate lumen/resorption of central vaginal cells
- Septate (35%)
- Unicornuate (10%)
- Didelphus (8%)
- Bicornuate (26%)
Mullerian Anomaly Classes

- Class I-hypoplasia/agenesis
  - uterine/cervical agenesis or hypoplasia.
  - Mayer-Rokitansky-Kuster-Hauser syndrome
Class II (unicornuate uterus):

- unicornuate uterus is the result of complete, or almost complete, arrest of development of 1 müllerian duct
- If incomplete, as in 90% of patients, a rudimentary horn with or without functioning endometrium is present.
- If obstructed, it may come to surgical attention when presenting as an enlarging pelvic mass.
- Earlier SAB, ectopics, malpresentation, IUGR, PTL
Uterus Didelphys

- Class III (didelphys uterus):
  - complete nonfusion of both müllerian ducts
  - individual horns are fully developed and almost normal in size
  - Two cervices are inevitably present
  - longitudinal or transverse vaginal septum may be noted (can be obstructed, ipsilateral kidney)
  - Didelphys uteri have the highest association with transverse vaginal septa, but septa also may be observed in other anomalies.
  - Consider metroplasty; however, since each horn is almost a fully developed uterus, patients have been known to carry pregnancies to full term.
Uterus Didelphys - MRI
Bicornuate Uterus

- Class IV - bicornuate uterus
  - results from partial nonfusion of the müllerian ducts
  - The central myometrium may extend to the level of the internal cervical os (bicornuate unicollis) or external cervical os (bicornuate bicollis).
  - demonstrates some degree of fusion between the 2 horns
  - horns of the bicornuate uteri are not fully developed; typically, they are smaller than those of didelphys uteri.
  - Some patients are surgical candidates for metroplasty.
Bicornuate Uterus – MRI and HSG
Septate Uterus

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

- Class VI-arcuate uterus
  - single uterine cavity with a convex or flat uterine fundus
  - considered a normal variant because it is not significantly associated with the increased risks of pregnancy loss and the complications found in other subtypes
Arcuate Uterus - HSG
DES Anomaly

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

- **Hypothalamic-pituitary axis**
  - Hypothalamic hormones are small peptides generally active only at high concentrations.
  - Anterior Pituitary: bathed in capillary network of pituitary blood containing hormones released in median eminence.
    - ACTH, MSH, endorphins, GH, LH, FSH, TSH, PRL
  - Posterior Pituitary: contains axons and nerve terminals from SON, PVN.
<table>
<thead>
<tr>
<th>Hypothalamic stimulatory hormones</th>
<th>Pituitary hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin-releasing hormone - from PVN, SON and arcuate nuclei and limbic system</td>
<td>ACTH - basophilic corticotrophs, product of proopiomelanocortin (POMC) gene</td>
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<tr>
<td></td>
<td>MSH - alternate product of POMC gene</td>
</tr>
<tr>
<td></td>
<td>Endorphins - also products of POMC gene</td>
</tr>
<tr>
<td>GHRH - two forms, 40 and 44 amino acids</td>
<td>GH - acidophilic somatotrophs</td>
</tr>
<tr>
<td>GnRH- mostly released from preoptic neurons</td>
<td>LH and FSH</td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone - three amino acids; released from anterior hypothalamic area</td>
<td>Thyroid-stimulating hormone - thyrotropes represent about five percent of anterior pituitary cells</td>
</tr>
<tr>
<td>Prolactin-releasing factors - include serotonin, acetylcholine, opiates, and estrogens</td>
<td>Prolactin - lactotrophs represent 10 to 30 percent of anterior pituitary cells</td>
</tr>
</tbody>
</table>
### Hypothalamic inhibitory hormones

<table>
<thead>
<tr>
<th></th>
<th>Somatostatin - 14 amino acids</th>
<th>Inhibits the release of growth hormone</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Prolactin-inhibiting factors - includes dopamine</td>
<td>Major prolactin control is inhibitory</td>
</tr>
</tbody>
</table>
Thyroid Hormone

- Critical Determinants of brain and somatic development in infants
- Critical in metabolic activity in adults
- Major targets include: skeleton, heart, metabolic regulation
- Many drugs alter thyroxine absorption/metabolism: retinoic acid agonists, cigarettes, PCBs, iodine
TRH STIMULATION

INHIBITION

Free Hormone ↔ Bound Hormone

T4, T3

Thyroid Binding Proteins

Liver

Pituitary

Hypothalamus

TSH STIMULATION

Thyroid
T3

- T3 modifies gene transcription in virtually all tissues to alter rates of protein synthesis and substrate turnover
- 20% from direct thyroid secretion
- 80% from conversion from T4
Adrenal Steroid and Catecholamine Synthesis
Osteoporosis – bone formation
Pituitary Microadenoma

- **Prolactin**
  - 198 amino acid polypeptide
  - Structure similar to growth hormone
  - Produced by lactotrophs of anterior pituitary
  - Dopamine inhibits prolactin secretion
  - TRH stimulates release of prolactin via gene transcription
  - Estrogen stimulates prolactin via gene transcription, lactotroph proliferation, increases TRH receptors, decreases dopaminergic activity
Pituitary Microadenoma

- Hyperprolactinemia:
  - Induced hypogonadism
  - Typically causes oligomenorrhea or amenorrhea
  - Galactorrhea
Causes

- Pregnancy
- Hypothyroid
- Renal or Liver Disease
- Ectopic Secretion (bronchogenic/renal cell cancers)
- Stress
- Breast Stimulation
- Radiation
- Trauma
- Infiltration
  - Tumors
  - Granulomatous Lesions
  - Infection
- Medication
  - Estrogen, neuroleptic drugs, reglan, antidepressant drugs, cimetidine, methyldopa, verapamil, risperidone
Pituitary Microadenoma

- MRI should be obtained with elevated Prolatin levels
- Macroadenoma: >1cm
  - Treatment essential when causes neurological symptoms
- Microadenoma: <1cm
  - 95% do not enlarge during 4-6 years of observation
  - Treatment when causes hypogonadism
Treatment

- Dopamine agonist
  - Decrease hyperprolactinemia and size of lactotroph adenomas
  - Cabergoline (ergot dopamine agonist)
  - Bromocriptine (ergot derivative)
  - Pergolide (ergot derivative)
Treatment

- Decrease in prolactin within 2-3 weeks
- Usually precedes the decrease in size (6 weeks)
Other Options

- **Surgical management should be considered when**
  - Medical treatment unsuccessful
  - >3cm giant lactotroph

- **Usual Transsphenoidal**

- **Radiation**
  - Slow fall in prolactin (up to 10 years)
Menstrual Cycle

- FSH
- LH
- Estradiol
- Progesterone
- Basal Body Temperature

- Day 1: Menstruation Phase
- Day 7: Menstruation Phase
- Day 14: Ovulation
- Day 21: Secretory Phase
- Day 28: Menstruation Phase
Ovarian Histology

- Recruited Follicle
- Maturing Follicle
- Ovulation
- Corpus Luteum
- Degenerate C. Luteum

Body Temperature

37°C

36°C

Estradiol

Follicle-Stimulating Hormone

Luteinizing Hormone

Progesterone

Hormones

Follicular Phase

Luteal Phase

Menstruation

Endometrial Histology

Day of Menstrual Cycle

(Average values. Durations and values may differ between different females or different cycles.)
Menstrual Cycle

- Follicular Phase: onset of menses to LH surge
- Early Follicular Phase
  - Ovary least active: low E and P
  - Release from negative feedback results in increase in GnRH pulse frequency
  - Increase in FSH $\rightarrow$ recruitment of next cohort of follicles
  - Follicles secrete inhibin B $\rightarrow$ inhibit FSH
  - Increase in LH pulse frequency
Menstrual Cycle

- **Mid-Follicular Phase:**
  - Modest increase in FSH stimulates folliculogenesis and E2 production
  - Follicles reach antral phase
  - E2 and inhibin A increase
  - E2 feedback inhibits FSH and LH pulse frequency
  - GnRH pulse generator increases
  - Endometrium proliferates, increase in gland numbers
Menstrual Cycle

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

- **Luteal Phase: LH surge to onset menses**
  - Serum E2 increases until one day before ovulation
  - LH surge occurs due to positive feedback
  - Small increase in FSH
  - Oocyte in dominant follicle complete first meiotic division
  - Granulosa cells around dominant follicle luteinize and produce progesterone which slows the pulse generator
  - 36 hours later oocyte released
  - Endometrium changes due to progesterone increase → cessation of mitosis and organization of glands. Loss of triple stripe
Menstrual Cycle

- Increase in progesterone from corpus luteum
- Slowing of LH pulses
- Inhibin A produced by corpus luteum
- E and P decline if fertilization does not occur
- Endometrium: loss of blood supply, sloughing, onset menses.
- H-P axis is released from neg feedback as E and P decline, next cycle begins
Dysmenorrhea

- **Primary**: recurrent crampy lower abdominal pain during menses in the absence of pelvic disease
- **Secondary**: as above, in the presence of pelvic pathology
  - Endometriosis
  - Adenomyosis
  - PID
Risk Factors

- Presentation at <30 yo
- BMI <20
- Menarche prior to 12
- Longer cycles/duration of bleeding
- Irregular or heavy flow
- Premenstrual symptoms
- PID
- Sterilization
- h/o sexual assault
- Heavy smoking
Pathogenesis

- Association with frequent, prolonged uterine contractions that result in uterine ischemia or decrease in blood flow to myometrium
- Doppler studies show higher uterine and arcuate artery resistance on the first day of menses in those with PD compared to controls
Pathogenesis

- E + P $\rightarrow$ Arachidonic Acid $\rightarrow$ PGF2, PGE2, Leukotrienes $\rightarrow$ uterine contractions
- Uterine Pressure $>$ Arterial pressure $\rightarrow$ anaerobic metabolites $\rightarrow$ C fibers
Diagnosis (exclusion)

- EMBx
- Microbiology of genital tract
- Pelvic Ultrasound
- HSC, Lsc
- CT, MRI
Treatment

- Heat
- NSAIDS (80-86%)
- Exercise
- OCP
- IUD
- Tocolytics (questionable)
- TENS (trancutaneous electrical nerve stimulation)
- Surgical interruption of nerve pathways (LUNA)<(LPSN)
  - Raises threshold for pain signals
  - Stimulates endorphin release
Treatment Failures

- Laparoscopy (80% with have endo)
  - After 2-3 failed cycles with medical
- GnRH treatment to empirically dx Endo
Endometriosis
Endometritis

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

- Chronic Endometritis
  - Detected histologically in 8% of endometrial specimens
  - No apparent etiology in one third
  - Present with abnormal uterine bleeding
  - Many women are asymptomatic
  - Endometrial Biopsy will show plasma cells in the endometrial stroma
Amenorrhea

- PREGNANCY
- PREGNANCY
Diagnosis

- No menses by 16 yo
- Failure of any signs of puberty by 13
- Consider if cyclic pain without menses by 12-14
Etiology of Primary Amenorrhea

- Chromosomal abnormalities causing gonadal dysgenesis (ovarian failure) – 50%
- Hypothalamic Hypogonadism – 20%
- Absence of uterus, cervix, vagina, mullerian agenesis – 15%
- Transverse vaginal septum or imperforate hymen – 5%
- Pituitary disease – 5%
Primary Amenorrhea

- Presence Vagina/Uterus
  - High FSH
    - Gonadal Dysgenesis
  - Normal FSH
    - Hypothalamic
- Absence Vagina
  - Absence Uterus (nml FSH)
  - Presence Uterus
    - MKRH
    - Imperforate Hymen
    - Androgen Insensitivity
    - Transverse Vaginal Septum
Congenital Causes

- Vaginal Agenesis
  - Differential:
    - Androgen Insensitivity
      - Male range testosterone
    - Low Lying transverse septum
      - Between hymenal ring and cervix
    - Imperforate Hymen
      - Hematocolpos
      - Diagnosed by physical exam
  - Mayer-Rokitansy-Kuster-Hauser
    - No vagina, variable development of uterus
    - 7-10% with normal but obstructed uterus with functional endometrium
    - NORMAL testosterone
FSH in primary amenorrhea

- Normal FSH → high FSH/LH
  - Functional hypothalamic amenorrhea
  - Abnormal GnRH secretion, decreased gonadatopins, no follicular development
    - Eating disorders
  - Congenital: Kallmans (anosmia)
    - AD, AR, Xlinked, 2/3 sporadic
  - Constitutional Delay
    - Common in boys, uncommon in girls
  - Infiltrative diseases/tumors
    - Check MRI – check in all with primary ypogonaditropic hypogonadism!
- PRL
  - Check autoimmune thyroid/adrenal
- Low FSH
  - PRL
FSH in primary amenorrhea

- High FSH
  - Check Karyotype
  - Gonadal dysgenesis → premature depletion of ovarian follicles
- Turners
  - Most common
  - 45 X
  - Can be secondary amenorrhea is mosaicism
  - To Treat: GH before hormonal
- PCOS
- Autoimmune
Genetic Causes

- **Androgen Insensitivity**
  - 46 XY
  - Phenotypically female with palpable testes
  - Defect in androgen receptor
  - Breast development
  - Excise testis at puberty due to risk CA

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

- **17 alpha reductase**
  - CYP17 gene
  - 46 XX or XY
  - Decrease cortisol, overproduction ACTH
  - Phenotypically females with HTN

- **Vanishing testes syndrome**
  - 46 XY
  - Streak gonads, no MIS
  - Female internal and external if early, if later streak testes
  - High FSH, high risk gonadal tumors

- **Absent testis determining factor**
  - Ullrich-Turner syndrome
  - 46 XY
  - Female internal and external
Primary Amenorrhea

- **Other:**
  - Neonatal crisis: CAH vs hypothalamic
  - Symptoms of virilization: PCOS vs androgen/adrenal tumor, Y chromosome material
  - Medications (heroin, methadone)
- Uterus absent: test for testosterone
  - Androgen insensitivity
  - MRKH
  - 5 alpha reductase

- Uterus present: check FSH (+/- Karyotype)
  - Primary ovarian failure
  - Hypothalamic (check MRI)
  - Thyroid/PRL, testosterone (tumor), if HTN progesterone for CYP17
Turners

- Web neck
- Short stature
- Sheild Chest
- Widely spaced nipples
- BP in both arms $\rightarrow$ Coarctation Ao
## 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><strong>FSH, DHEA-S, Test</strong></td>
<td><strong>PCOS, premature ovarian failure (check karyotype), tumor</strong></td>
</tr>
<tr>
<td>Hypothalamic Dysfunction</td>
<td>35</td>
<td><strong>FSH/LH, low leptin</strong></td>
<td><strong>Anorexia, stress</strong></td>
</tr>
<tr>
<td>Pituitary Disease</td>
<td>19</td>
<td><strong>PRL, TSH, MRI, Fe, FSH/LH</strong></td>
<td><strong>Infiltrative lesions, prolactinoma, empty sella, thyroid disease</strong></td>
</tr>
<tr>
<td>Uterine disease</td>
<td>5</td>
<td><strong>HSG, pelvic sono, attempt w/d bleed</strong></td>
<td><strong>Ashermans</strong></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td><strong>HCG</strong></td>
<td><strong>pregnancy</strong></td>
</tr>
</tbody>
</table>
Hirsutism

- Caused by androgens
  - Testosterone (ovarian)
  - DHEA-S (adrenal)
  - Androstenedione (adrenal/ovarian)
- PCOS
- CAH – late onset form (nonclassical) → 21 hydroxylase leading to excess 17 hydroxprogesterone and androstenedione
- Ovarian Tumors (sertoli leydig, granulosa theca cell, hilus-cell) → high test >200ng/dl
- Adrenal tumors → DHEA-S and DHEA, cortisol
- Ferriman Gallwey System
- Treatment:
  - Mild (score 8-15) – nonpharmacologic or pharmacologic alone
  - Severe (>15) – multimodel or >1 medication
Anagen (growth phase)

Catagen (involution phase)

Telogen (rest phase)
- Androgens increase follicle size, hair fiber diameter, proportion of time in anagen phase
- Cause differentiation into terminal hair
- Nonandrogenic hair growth
  - Langugo: vellus
  - Hypertrichosis: diffuse, commonly by drugs
Hirsutism

- Will take 4-6 months for effects
- If treatment isn’t continuous most relapse in 6 months
- Nonpharmacologic
  - Shaving
  - Depilatories/bleaching
  - Electrolysis
  - Laser Treatment
Hirsutism

- **OCP**
  - Start with 35mg EE with norethindrone acetate, increase NEA as needed. If breakthru bleeding 35mg EE plus ethynodoil diacetate
  - Increase SBG
  - Inhibit LH, therefore ovarian androgen
  - Inhibit arenal androgen secretion

- **Antiandrogens**
  - **Spironolactone**
    - Inhibit testosterone binding to receptors
    - 100mg
    - S/E: hyperkalemia, GI
  - **Flutamide**
    - Inhibit testosterone binding to receptors
    - Liver failure
  - **Finasteride**
    - Alpha reductase inhibitor
    - Less effective
Recurrent Pregnancy Loss

- **Definition:** >3 consecutive pregnancy losses <20 weeks gestation
  - 1 SAB: 15%
  - 2 SAB: 2%
  - 3 SAB: 0.3 – 1%

- **Risk after two consecutive miscarriages:** 24-29%
Causes of RPL

- **Genetic**
  - Chromosome number or structure
    - 3-5% with major chromosomal rearrangements
      - 60% reciprocal translocation
      - 40% Robersonian

- **Uterine**
  - Anomalies (10-15%) – most commonly septate
  - Fibroids (submucosal)
  - Synechiae - commonly from D&C prior to weeks with damage to basalis → granulation tissue creating bridges
  - Cervical incompetence

- **Immunologic**
  - APS (5-15%) test 6-8 weeks apart, need two values mid to high positive (anticardiolipin AB, RVV)
  - Failure of maternal immune protection (ie expression of compliment, etc)
  - Poorly controlled DM

- **Endocrine**
  - Thyroid: high thyroid antibody concentration
  - PCOS (20-40%)
  - PRL
  - Luteal phase
  - Thrombophillias (thrombosis of spiral arteries)
Causes RPL

- Male Factor
  - Poor sperm morphology
    - Defects in chromatin condensation and irregular nuclei
- Infection
  - Listeria, toxo, CMV, primary HSV (mostly sporadic)
- Celiac Disease
Age and Miscarriage Rate

- 20-30 → 9-17%
- 35 → 20%
- 40 → 40%
- 45 → 80%
Evaluation

- Some Eval after 2 losses
- US, HSG, sonohysterogram
- TSH, HgA1c if symptomatic
- APS workup
- Thrombophilia (factor V, prothrombin mutation, protein C/S, antithrombin 3)
- Karyotype – last and if all else negative
Treatment

- No studies to support luteal phase defect
- Nothing to support IVIG
- Cultures are not beneficial