General

- Sex Hormones (both male and female)
  - Very Pulsatile GnRH (Hypothalamus)
    - Mildly Pulsatile FSH/LH (Pituitary)
      - FSH stimulates germ cell production and estrogen/progesterone/inhibin production (Sertoli/Granulosa Cells)
      - LH stimulates testosterone steriodogenesis and estrogen precursor production (Leydig/Theca Cells)
  - NB estrogen also made by corpus luteum, placenta, liver, adrenals, breasts (which are important secondary sources during post-menopausal period) estrogen is responsible for secondary sex characteristics and endometrial thickening
  - NB feedback inhibition by androgens/estrogens(except during mid cycle)/progesterones on gonads/pituitary and also Inhibin
  - Steroids activated in target tissue (prostate, fat), inactivated in non-target tissue (uterus, kidney), metabolized in peripheral tissue (liver, skin), testosterone converted to estradiol by Ledyig aromotase and ? by adipose ?
- Gametogenesis
  - Spermatogonia → Spermatozoa
  - Oogonia → Follicle (w/ each menstrual cycle releasing a Oocyte/Corpus Luteum)
- Ejaculation+Ovulation then Fertilization to form Zygote
- Embryogenesis
  - Day 1: Zygote → Day 2: Morula → Day 6: Blastulocyst → Day 16: Gastrula → Fetus → Baby
    - 3rd Week: Trilaminar division w/ Ectoderm (CNS, Skin, Eye) + Mesoderm (Everything Else) + Endoderm (GI)
    - 7th Week: Heart
    - 8th Week: Most Other Organs except Kidney/Lung
    - 9th Week: Kidney
    - 24th Week: Lung (but sufficient surfactant for life is after 30 therefore b/t 24-30 you can give surfactant and infant is fine)
    - NB
      - Determination of Totipotent Cells (any type of cell) to Pleuripotent Cells (one type of cell for a germ layer) them Differentiation of Pleuripotent Cells to Stem Cells
      - Marrow: Yolk Sac 3-8, Liver 6-8, Spleen 9-28, BM >28
      - PGE1 opens PDA while Indomethacin/O2 closes PDA
      - High AFP (multiple gestations, neural tube defects, gastrochesis)
      - Low AFP (trisomy 21,18
- Sex Chromosomal Disorders
  - Sex chromosome aberrations are better tolerated than autosomal disorders b/c:
    - one of the X-chromosomes are lyonized or inactivated
    - there is really only a modest amount of genetic material on the sex chromosomes
  - Features of sex chromosome disorders
    - cause subtle, chronic problems that are related to sexual development and fertility
    - difficult to diagnose at birth w/ most recognized at puberty
    - higher number of X chromosomes → greater likelihood of mental retardation
  - Sex is actually very ambiguous and can be defined in different ways:
    - Genetic sex – determined by the presence or absence of a Y chromosome; no matter how many X chromosomes one has it is the Y that confers maleness
    - Gonadal sex – because femaleness is default for gonadal development w/ the Y chromosome triggering male differentiation sex can be based on the histologic appearance of the gonads
    - Ductal sex – similarly determined by the presence of Mullerian or Wolffian duct derivatives
    - Phenotypic (genital) sex – based on the appearance of external genitalia (note differentiate from gonadal sex)
    - True hermaphrodite (refer)
    - Pseudohermaphrodite (refer)
  - Klinefelter Syndrome
    - General
      - Incidence of 1/800 boys and thus 1/1600 babies
      - RF: advanced maternal age
      - Male Hypogonadism 2/2 to 2 or more X chromosomes and 1 or more Y chromosomes (XX+Y+)
    - Type of Defect
      - 80% (47,XXY) due to nondisjunction in 1 of parents during meiosis of germ cells
      - 20% mosaic (46,XY/47,XXY)
    - Clinical Features
      - Tall w/ Arm Span > Height, Eunuchoid Body Habitus w/ Escutcheon, High Voice, Decreased Body Hair, Gynecomastia (increased r/o breast cancer)

- Hypogonadism w/ Small/Firm Testes and Small Penis w/ Infertility
- Very Mild MR, antisocial behavior
- Breast Cancer
- Lymphoma
- Autoimmune (Hashimotos)

▪ Tx: testosterone starting at puberty

o Turner's Syndrome
▪ General
- Incidence of 1/2500 girls and thus 1/5000 babies
- RF: NOT RELATED TO ADVANCED MATERNAL AGE
- Female Hypogonadism 2/2 complete or partial monosomy of the X chromosome
- only 1% of 45,X fetuses live to birth but those that do live live a normal life span

▪ Type of Defect
- 55% 45,X (worst one)
  - Recurrence Risk is same as general population
- 25% structural abnormalities of the X chromosome these partial monosomies include:
  - whole deletion of the small arm resulting in isochromosome of the long arm 46,X,i(X)(q10)
  - partial deletions of both small and long arms resulting in ring chromosome 46,X,r(X)
  - partial deletions of either small or long arms 46,X,del,(Xq or p)
- 15% mosaics 45,X w/ either of the following: 46,XX, 46,XY, 47,XXX, 46,X,i(X)(q10)
- *Noonan's Syndrome*
  - pts have a normal karyotype but a syndrome similar to Turner's
  - mutation maps to chromosome 12

▪ Clinical Features (many girls are diagnosed not at birth but at puberty)
- Phenotype: Short, Small Mandible and Narrow Maxilla, Low Posterior Hairline, Webbing of Neck (Pterygium Colli) 2/2 Cystic Hygroma (distended lymphatic channels), Shield Shaped Chest w/ Small Breasts and Widely Spaced Nipples, Cubitus Valgus, Lymphedema of Hands and Feet, Multiple Pigmented Nevi, Obesity
- Organ: Renal Anomalies, Congenital Heart Disease esp coarctation of aorta and bicuspid aortic valve (cause of death), Autoimmune Thyroiditis = Hypothyroidism, DM, OP
- Hypogonadism ("Streaked Ovaries")
  - Primary Amenorrhea 2/2 Low Estrogen (during oogenesis normally both X chromosome become active now since there is only one X there is an accelerated loss of oocytes (menopause occurs before menarche)
  - Failure to develop normal secondary sex characteristics, breast development is inadequate
  - Gonadoblastoma (tumor of abdominally located gonads)
- NORMAL Mental Status just only nonverbal, hearing and visual spatial defects

▪ Tx: E+P, TTE Q4yrs, TFTs Qyr, excise ovaries b/c of cancer risk

- Genitalia
  - Internal: Undifferentiated Gonads + Mullerian/Wolffian Ducts
    - Female (XX): Ovaries (-SRY) + FallopianTube/Uterus/Vagina (-AMH) (being female is default)
    - Male (XY): Testis (+SRY) + Epididymis/VasDeferens/SeminalVesicles (+AMH) (hence male needs hormones made by Y chromosome)
  - External: Tubercle
    - Female: Clitoris/Labia + Female 2° Characteristics (being female is default)
    - Male: Penis/Scrotum (dihydrotesterone) + Male 2° Characteristics (testosterone)
  - Ambiguous
    - True Hermaphroditism
      - Person (no such thing as male or female just hermaphorditism b/c always mosaicism w/ 46,XX/46,XY)
        - Mixture of Hormones
          - ±SRY/±AMH = both male and female internal genitalia
          - ±T/±DHT = both male and female external genitalia and both male and female secondary characteristics (usually more male therefore usually raised as boys)
    - Psuedo Hermaphroditism
      - Genetic Male (46,XY)
        - Various Enzyme Defects Resulting in Impaired Testosterone Synthesis
          - +SRY/+AMH = normal internal male
          - –T/–DHT = default external female and female secondary characteristics

        - NB disastrous b/c pt is grown up as a female but then during puberty she doesn't menstruate and when she goes to doctor she realizes that she in fact a male
    - 5alpha-Reductase or Receptor Defect Resulting in Impaired Androgen Synthesis or Inactivity
        - +SRY/+AMH = normal male internal genitalia
        - +T/–DHT = default external female but male secondary characteristics
        - NB Disastrous b/c pt is grown up as a female but then develops male characteristics at puberty and when she goes to doctor she realizes that she in fact a male
- Genetic Female (46,XX)
    - Congenital Adrenal Hyperplasia
        - –SRY/AMH = normal internal female
        - +T/–DHT = normal external female but male secondary characteristics w/ clitoral hypertrophy, labiosacrotal fusion, virilization of ext genitalia, ambiguous genitalia

Tanner	Gonadarche (Gonads)		Adrenarche (Adrenal Gland)
	External Female	**External Male**	**Pubic Hair**
I (pre-adolescence)	NONE NB infants can have breasts and periods b/c of maternal estrogens withdrawal	NONE	NONE
II	(11yr) Breast Bud aka Thelarche	(12yr) Testes enlarges	(F11.5yo, M12.5yo) Sparse, Straight, Slightly Pigmented Downy Hair at Penis Base and Middle of Labia
III	(12yo) Enlarges but No Contours Growth Peak	(13yo) Testes enlarges even more Penis Lengthens	(F12.5yo, M13.5yo) More, Curly, Darker, Coarser Hair
IV	(13yo) Enlarges w/ Second Mound Areola and Papilla Project Menarche	(14yo) Testes enlarges even more Penis Widens Growth Peak	(F13.5yo, M14.5yo) Adult looking but does not include Medial Thighs
V (adult)	(15yo) Mature	(15yo) Mature	(F14.5yo, M15.5yo) Mature Inverse Triangle

Precocious Female <6yoAA <7yoW	**Precocious Male <9yo**
(1) Idiopathic (2) Exogenous Estrogen/Testosterone (3) Ovarian Estrogen Granulosa Cell Tumor vs Testicular Leydig Cell Tumor (4) Any CNS process increasing gonadotropin release (5) ONLY FEMALE McCune-Albright Syndrome (ovarian cysts secreting estrogen w/ also café-au-lait spots) Tx underlying cause or if idiopathic then Tx w/ GnRH agonists to prevent premature epiphyseal closure and arrest puberty until appropriate age	
Delayed Female >13yo	**Delayed Male >14yo**
(1) Constitutional 2/2 idiopathic or various endocrine/systemic disorders (2) Primary Ovarian Failure 2/2 Turner's, Surgery, Radiation, Autoimmune vs Primary Testicular Failure 2/2 Klinefelter's, Cryptochordism, Dysgenesis, Congenital ("Vanishing Testis Syndrome") Surgery, Radiation, Autoimmune, Infection, Chemo (3) Hypogonadotropic Hypogonadism 2/2 Kallman's (X-linked, anosmia + cleft lip / palate + midline defect), Hypopituitarism, Tumors, Prader-Willi, Anorexia	

- Menstrual Cycle (28 + 7d, ovary/endometrial phase)
    - Menstruation 4 ± 2d, 40 ± 20mL
    - Follicular/Proliferative Phase (varied duration)
        - ↓E and ↓P from unfertilization during L/S phase → ↑FSH → Follicle Growth → ↑E → Endometrial Growth (NB initial rise in E inhibits FSH but as it rise further it stimulates FSH so then there is another spike in FSH)
        - ? → ↑LH → Follicle Rupture → Ovulation →↓E b/c the follicle dies & Leutinizaton aka Corpus Luteum Formation from follicle remnants
    - Luteal/Secretory Phase (fixed duration)
        - ↑P (from corpus luteum) → prepares endometrium for implantation
        - ↑E (from corpus luteum) → (not sure what E does during this phase)

        - X
        - If NO Fertilization → NO placenta to make beta-hCG (~LH/FSH) → corpus luteum involutes → ↓P and ↓E → Endometrial Degeneration aka Menstruation
        - If YES Fertilization → YES placenta to make beta-hCG (~LH/FSH) → corpus luteum lives → ↑E and ↑P

Hormones

- **Normal Physiology**
    - Estrogen
        - Source: ovary (estrone/estradiol), placenta (estriol), fat (estriol)
        - Action: endometrial growth, external genital development, female fat distribution, various metabolic actions, etc
    - Progesterone
        - Source: ovary, corpus luteum, adrenal gland
        - Action: maintains endometrium by stimulating spiral artery development, uterine smooth muscle relaxation, etc
- **Types**
    - Estrogen Agonists (eg. conjugated estrogen, estradiol, esterefied estrogen, etc), Estrogen Antagonists (eg. fulvestrant, etc), SERMs (eg, tamoxiphene, raloxifene), Aromatase Inhinitors (eg. clomiphene, anastrazole, etc)
    - Progestin Agonists (eg. progesterone, medroxyprogesterone, hydroxyprogesterone, norethindrone, norgestrel, etc), Progestin Antagonists (eg. mifepristone-RU486)
- **Morning After Emergency Contraceptives**
    - NB some use the anti-progestin mifepristone (RU486) as the drop in progesterone signals menses
    - Does NOT cause an abortion
    - "Morning After Pill" (Plan B / Proven (progestin-levonorgestrel only, more effective ~85% and less N 6%) vs YUZA (combo progestin and estrogen, less effective ~75% and more N 40%)
    - SEs: Severe bloating, N, V
    - Must be taken within 72hrs teratogenic effects if pill fails
    - (two doses, 12hrs apart, very HIGH doses of E+P, with first dose must be taken within 72-120hrs of sex, also give an antiemetic, inhibits ovulation/fertilization depending on when taken)
- **Contraceptives**
    - **Sterilization**
        - **Vasectomy** (Ligation of vas deferens, Can be reversed (success rate: 65%) using reanastomosis, safer, less expensive, can be performed as outpt under local anesthesia unlike tubal ligation, Not immediately effective b/c sperm can remain viable in proximal collecting system therefore use other forms of contraception for up to 6-8wks after procedure and then check sperm count x2, Antisperm Antibody, NB ejaculation still occurs)
        - **Tubal Sterilization** (Postpartum: (subumbilical incision), Ligation w/ electrocautery, Ligation w/ sutures using Pomeroy Tech, NON Postpartum: (laparoscopy), Banding w/ Falope Rings or Clipping w/ Hulka/Felchie clips, Can be reversed (success rate: clips 85%, bands 70%, Pomeroy 50%, Cauterize 40%)) using tubal microplasty if pt wants many pregnancies or IVF if pt just wants one more pregnancy, Post-Tubal Ligation Syndrome (pain and menstrual disturbances)
    - **Natural Methods** (least effective but good for pts w/ religious/philosophic objections)
        - **Periodic Abstinence** (chance of pregnancy highest from 5d before ovulation to day of ovulation and then drops down to zero therefore engage in intercourse only from 2d after ovulation to when menstrual cycles starts then after menstrual cycle ends begin to abstain, a women can understand cycle by tracking menstruation, basal body temp, cervical mucus, and/or symptoms)
        - **Coitus Interruptus** ("pull out" but remember that pre-ejaculate has sperm)
    - **Mechanical Barriers**
        - **Condoms**
        - **Diaphragm** (can last 5yrs if stable weight, Must be fitted and prescribed by a doctor therefore $$$, must be left in place 7hrs after intercourse, must use spermicidal jelly)
        - **Cervical Cap** (similar to diaphragm but smaller, Hard to place/remove in addition DISLODGEMENT is a problem)
        - **Spermicides** (nono-xynol-9 or octo-xynol-9 which disrupt sperm cell membranes AND acts as a mechanical barrier
    - **Intra Uterine Device (IUD)** increasing use in Asia with decreasing use in US overall most common form on contraception in the world!!!, prescribed/removed/Introduced into uterine cavity by doctor with string hanging out to detect expulsion or migration, good for women who have OCP contraindications, low risk for STDs, and are in a monogamous multigravid relationship, contraindication (pregnancy, undx VB, infection or h/o PID), SEs: pain, bleeding, expulsion, abortion, perforation, infection (ESPECIALLY insertion related PID during 1st 20d due to contamination therefore very common to prophylactically treat with antibiotics during insertion)
        - **ParaGard (Copper-T)** Q10y (foreign-body material elicits a sterile spermicidal inflammatory response resulting in sperm being engulfed, immobilized, and destroyed by inflammatory cells)

        - **Progestasert (Progesterone-T)** Q1y (similar to above but also progesterone thickens cervical mucus and atrophies endometrium to prevent implantation)
        - **Mirena (Levonorgestrel-T)** Q5y (similar to above)
    - **Oral Contraceptive Pill (OCP)**
        - Mech: pill places the body in a "pseudo-pregnant" state by giving body E and/or P which feedback and inhibits release of FSH and LH (instead of the spike seen in cycle levels of E, P, LH, FSH are always constant) which in turn suppresses ovulation, in addition progesterone thickens cervical mucus and atrophies endometrium to prevent implantation
        - Types
            - E+P: you can catch up if you miss a few pills unlike P only, Acne (Ortho-Tri-Cyclen, Yasmin), PMS (Yasmin, Loestrin), Migrains (Seasonique, Mircetta), Menorrhagia (Yasmin), 4 Periods /yr (Seasonique, Seasonale
            - P alone: NOT as effective as combinations pills but they have no E therefore good for nursing mothers and women who have E contraindications, cannot catch up if you miss a pill, if you are greater than 4hrs later you must use a backup method, Progestin Only (good more women who cannot take estrogen like during breast-feeding or b/c of estrogen SEs), must take every day and it must very regular b/c if not then slightly higher failure rate, The Minipill, Depo-Provera (Q3mo IM/SC)
        - **Monophasic** (pt takes a fixed dosage of E+P for 1st 21d and then last 7d takes a placebo which results in sloughing and thus a period, can be taken continuously and thus no periods at all which is best for pts w/ endometriosis) vs **Tri/Multiphasic** (pt takes an increasing dosage of P with =E each week for… such that pt actually received less total hormones in end but with same effect)
        - **Contraindications:** pregnancy / lactating, fibroids, migraines w/ increased r/o CVA, CAD, stroke, HTN, HL, h/o thromboembolic disorders, **35+yo and smoking (increases risk 11x),** 40+yo and high risk for cardiovascular dz, depression, undiagnosed VB, E dependent cancer malignancy, benign/malignant liver tumor or acute/chronic liver dz or biliary tract dz
        - E Side-Effects: nausea, break thru bleeding, breast tenderness vs P Side-Effects: breast tenderness, HA, HTN, androgenic effects
        - Best time to start: first day of menses, Take at bedtime or dinner which decreases N compared to in morning
        - Monophasic pills have less breakthrough bleeding
- **HRT**
    - Women's Health Initiative (WHI) study was a very large/long study looking into the r/o certain conditions with HRT
    - Inaccurate to use the term replacement b/c the doses given are often a fraction of the of the levels seen in non-menopausal women
    - If pt is having S/S 2/2 menopause then talk to pt about the balance b/t the relief of Sx w/ HRT vs the increased r/o certain conditions
    - Use estrogen only HRT except if pt has uterus then use estrogen+progesterone HRT b/c unopposed estrogen causes endometrial cancer
    - What you need to remember is that the change in risk is marginal in the order 1/1000
    - Always do a complete pelvic exam b/f stating HRT
    - If pt is very obese consider just progestin only HRT b/c their fat can produce a fair amount of estrogen
    - HRT good for treating vasomotor/atrophic dz and some neuropsych Sx (like mood changes / insomnia), there is evidence that E+P can be helpful for OP/MI/CRC/Breast Cancer but can increase CVA/DVT/MI/Breast Cancer depending on the type (refer below)
    - If pt is not having vasomotor/atrophic Sx don't use estrogen to Tx OP/neuropsych Sx use other agents even though in it works b/c there are other agents are out there
    - Take lowest effective dose for the shortest duration of time, try to decrease dose Q6mo and do so through a tapering method never acutely from day to the other
    - Should only be used for acute-subacute Sx never for prevention of chronic conditions
    - Key is to discuss w/ each pt
    - SEs: breast TTP and VVB
    - PO, TD, Vaginally
    - E-HRT Premarin (Conjugated Equine Estrogen)
        - Increased Risk: **CVA** (1.2 more women for every 1000), **DVT** (0.8 more women for every 1000), **CRC** (0.1 more women for every 1000)
        - Decreased Risk: Breast CA (0.6 fewer women for every 1000), OP Fracture (0.6 fewer women for every 1000), MI (0.3 fewer women for every 1000)
    - E+P-HRT Pempro (Conjugated Equine Estrogen + Medroxyprogesterone Acetate)
        - Increased Risk: **DVT** (1.8 more women for every 1000), **Breast CA** (0.8 more women for every 1000), **CVA** (0.7 more women for every 1000), **MI** (0.6 more women for every 1000)
        - Decreased Risk: CRC (0.6 fewer women for every 1000), OP Fracture (0.5 fewer women for every 1000)
    - If pt has a h/o of any of the above bold (+Hx or Active Dz) and also UnDx VB would favor against use

Infertility

- General
  - 1° women never able to get pregnant 2° woman has gotten pregnant in past can't the past year
  - Def: inability to conceive after 1yr of unprotected intercourse
  - Incidence has remained unchanged past 30yrs but office visits has tripled
  - normal fecundity rate (likelihood of achieving pregnancy in one month) in a couple with normal fertility is 25%/mo
  - in couples with fertility problems 50% will eventually become pregnant with assistance
  - First: semen analysis after 48hrs of abstinence and b/f 2hrs post-ejaculation, Second: confirm ovulation in women by checking BBT which should increase by 0.5-1F during luteal phase, Third: hysterosalpingogram, Fourth: ex-lap to explore for adhesions/endometriosis
- Male (30%)
  - Endocrine: hypothalamic-pituitary-gonadal axis dysfunction, hyperprolactinemia, exogenous androgens, liver, thyroid dz, adrenal hyperplasia, Check hormone levels, Check testicular size
  - Anatomic: STDs, mumps, chemicals, radiation, heat, varicocele, cryptorchidism, hernia repair, check environmental exposure and presence of varicocele/crypt, ligation of varicocele
  - Sperm: low counts (azospemia), antisperm antibodies, Kartagener's syndrome, drugs, check sperm count, volume, motility, morphology, pH, WBC, Postcoital Test (assess interaction b/t sperm and cervical mucus 2-8hrs after coitus, healthy if a large # of sperm are seen moving forward) Normal: Volume: >2mL, [ ]: >20million sperm/mL, Motility: >50% forward, Morphology: >40% normal Quit smoking, drinking, using lubricants, Washed Sperm for Intrauterine Insemination (for low volume), ICSI aka Intra-Cytoplasmic Sperm Injection (inject sperm into egg and then place in female via IFV or ZIFT, sperm can be retrieved from semen or aspirated from testis (TSE - Testicular Sperm Extraction), or aspirated from epipidymis (MESA – Microsurgical Epididymal Sperm Aspiration), Donor Sperm
  - Dysfunction: retrograde ejaculation, impotence, decreased libido, Better Coital Practice (sex Q2d during ovulation, female on bottom, female on back with knees on chest for 15min after sex, male avoid tight underwear and heat)
- Female (30%)
  - Cervix (10%): DES Exposure, Cervical Stenosis (2/2 conization, multiple dilations, cauterizations), Hostile Cervical Mucus, Chronic Cervicitis, check cervical mucus for amount, quantity, color, spinnnbarkieit aka stretchability, fluidity, ferning, Postcoital Test, IUI which bypasses the cervix
  - Uterus (10%): Submucosal Fibroids, Congenital Uterine Septums, Intrauterine Synechiae (Asherman's Syndrome), Endometrial Cancer, Hysterosalphingogram (dye is injection into cervix), Saline Sonohystogram , Pelvic US, Hysteroscopy, Laparascopy, Fibroids (myomectomy), Synechia/Septae (ligation), Tubuloplasty
  - Tubal/Peritoneal (40%): Endometriosis (invasion causes inflammation), Adhesions (2/2 PID, surgery, infection, ruptured viscus), Endometriosis (S/S refer(, Adhesions (pain w/ lifting motions), Endometriosis (Dx refer),m Endometriosis (Rx refer but note that Danazol GnRH analogs, Provera, or continuous OCPs do NOT increase fertility but do fix endometriosis), Adhesions (laparoscopic ligation, excision, coagulation, fulguration, vaporization)
  - Ovarian (40%): WHO Class I (H-P Axis Failure), WHO Class II (H-P Axis Dysfunction), WHO Class III (Ovarian Failure), Check hormone levels, Check past-ovulation by monitoring menstruation, temp, mucus, and progesterone, WHO Class I (GnRH analogues or gonadotropins), WHO Class II (1st clomiphene citrate 2nd gonadotropins + ART), WHO Class III (no Rx thus only egg donation or adoption)
- Both 20%
- Unknown 20%: Confirm by rechecking the more rare causes above (abnormalities in sperm transport, sperm antibodies, problems with penetration) if still no cause then studies indicate that most Rx have NO higher success rates than no Rx at all HOWEVER the pregnancy rate eventually reaches 60% in the next 5 years regardless BUT if not then consider abortion or donor sperm/egg
- Advanced Reproductive Technologies: Oocytes production is stimulated by inducers below, harvested transvaginally, and then… (-IFTs slightly better than IVF) (1) Intra-Uterine Insemination (IUI), (2) 20% success rate, In-Vitro Infertilization (IVF) sperm is allowed to fertilize egg outside (if bad sperm then Intra-Cytoplasmic Sperm Injection (ICSI) and then zygote is placed in uterus using a catheter, (3) 25% success rate, Gamete Intra-Fallopian Transfer (GIFT) laparoscopically placing eggs and sperm into tubes, (4) 30% success rate, Zygote Intra-Fallopian Transfer (ZIFT) sperm is allowed to fertilize egg outside and then zygote is laparoscopically placed into tube, SEs: multiple gestations (35%) important b/c carry higher rates of maternal complications (preeclampsia, gestational diabetes, previa, premature delivery, postpartum hemorrhage) and fetal complications (IUGR, RDS), Ovulation inducers can be used to support these methods: Clomiphene Citrate (Clomid) binds ER in hypothalamus preventing E feedback inhibition resulting in increased release of GnRH, SEs: antiE effects (hot flashes, ab distension and bloating, emotional lability, depression, visual changes), multiple gestations (8%) hMGs aka GnRH analogues (Pergonal): SEs: multiple gestations (20%) and ovarian hyperstimulation (range from mild symptoms to rupture and death)

Amenorrhea (**NB Primary:** no menses by 16yo (nl avg age 11.5) in a pt w/ 2° sex characteristics OR no menses by 14yo in a pt w/ NO 2° sex characteristics vs **Secondary:** no menses for >6mo in a woman w/ prior nl menses OR no menses for >12mo in a woman w/ prior irregular menses)

- 1st rule out Pregnancy

- 2nd rule out Virilization (skip if no S/S)
    - S/S: Hirsutism (excessive sexual (aka not asexual as in hypertrichosis) terminal (aka not vellus) hair on face/chest/ab/eustacheon), Oily Skin/Adult Acne/Alopecia/Deep Voice, Clitoromegaly/Breast Atrophy/Muscle Weight, Infertility, Amenorrhea
    - Where are the androgens coming from?
        - Idiopathic: increased activity of 5α-reductase at end-organ tissue therefore normal testosterone/DHEAS
        - Exogenous Drugs: anabolic steroids, phenytoin, cyclosporine, etc
        - Ovary: increased production free testosterone therefore normal DHEAS
            - Sertoli-Leydig Ovarian Cancer but any type of ovarian cancer can produce androgens (refer)
            - Thecal-Lutein Cyst (refer)
            - Hyperthecosis
            - PolyCystic Ovarian Syndrome (PCOS) aka Stein-Leventhal Syndrome
                - Mech: for unclear reason the ovaries begin to produce more estrogen which is the converted to androgens, the high estrogen inhibits FSH but stimulates LH such that the ratio of LH:FSH is >3
                - S/S: Virilization (rarely full virilization often just hirsutism and amenorrhea/infertility, endometrial hyperplasia/cancer) + Obesity + T2DM + CAD
                - Dx: Labs (L:H >2:1), high testosterone, US (multiple ovarian follicles at different maturation stages forming a "pearl necklace" sign)
                - Tx (for all: Weight Loss, Metformin, etc)
                    - No Hirsutism and No Desire for Pregnancy: P-Hormones
                    - Hirsutism and NO Desire for Pregnancy: E+P-Hormones
                    - Hirsutism and Desire for Pregnancy: Clomiphene
        - Adrenal Gland: increased production of DHEA-S and subsequent conversion to testosterone therefore high free testosterone
            - Tumor (refer)
            - Cushing (refer)
            - Congenital Adrenal Hyperplasia: 21α-Hydroxylase (95%), 11β-Hydroxylase (rare), etc Defect (refer)
    - Work-Up: CT-A/P, TV-US, Free Testosterone (nl: ~200ng/dL), DHEA-S (nl: ~7ng/dL) and based on these studies pursue adrenal work-up w/ ACTH, cortisol, dexamethasone suppression test, 17-OH progesterone during follicular phase, etc vs ovarian work-up w/ LH, FSH, etc, also check Total testosterone, SHBG (sex hormone binding globulin)
    - Tx: OCP, peripheral androgens blockers (flutamide, aldactone)
- 3rd rule out Male Psuedohermaphroditism (skip if no S/S)
- 4th assess "hypothalamic-pituitary/ovary/uterus-vagina axis" by measuring LH&FSH and perform 10d Medroxyprogesterone challenge and check for withdrawal bleeding, if withdrawal bleeding at 2wks then there is enough estrogen to prime the endometrium for progesterone and the rest of the tract (uterus/vagina) is normal therefore there is a HP problem therefore check LH, FSH, TSH, Prolactin vs If NO withdrawal bleeding at 2wks then there is NOT enough estrogen to prime the endometrium for progesterone therefore there is a problem w/ ovary or uterus/vagina check Estrogen and TVUS or give E+P x2mo and see if menses resume
    - **HP** (decreased LH & FSH aka Secondary Hypogonadism): tumor, malformation, radiation, infiltrative process, trauma, hyperprolactinemia, Constitutional Delay (some part of the brain is delaying development but eventually it happens "late bloomer"), Chronic Hypothalamic Anovulation aka CHA (most common, nl LH and FSH, respond to progesterone), chronic illness, malnutrition, eating disorder, stress, exercise, hypothyroidism, Cushing, Kallman's Syndrome (delayed puberty + anosmia), drugs (recreational, steroids, haldol, reglan), Sheehan, Empty Sella Syndrome, Infiltration, Radiation/Surgery, Drugs (Lupron Depot, Depo-Provera for up to 2yrs even after one dose of 150mg), hyperprolactinemia, hyperthyroidism
    - **Ovary** (increased LH & FSH aka Primary Hypogonadism)
        - Pure/Partial Gonadal Dysgenesis
        - Turner's Syndrome
        - PCOS
        - Hyperthecosis
        - Ovary Damage (surgery, tumors, chemo, radiation)
        - Premature Ovarian Failure aka amenorrhea <40yo, often 2/2 autoimmune as part of PGA Type I, idiopathic, chemo related, XRT, chromosome abnormalities, viral illness
        - Savage Syndrome (germ cells cannot bind FSH)
    - **Uterus/Vagina** (normal LH & FSH): anatomical anomalies

Menopause aka NON-Premature Ovarian Failure

- Dx: amenorrhea >6-12mo + FSH >30 ± S/S

- Types: “natural” (avg 51yo, often correlates w/ mother but otherwise no other predictors, can be sooner in smokers or those exposed to chemo/XRT), “surgical” aka bilateral oopherectomy, “medical” aka GnRH antagonist use, “premature ovarian failure” refer to amenorrhea section
- Climacteric aka Peri-Menopause: termination of reproductive phase but pt is still menstruating though irregularly = there is endometrial change but no oocytes are being released, lasts up to 2-8yrs, 30% of women begin to develop S/S of menopause during this time despite still menstruating)
- FSH: nl (10mU/mL) Peri-Menopause (20mU/mL but note that it still fluctuates during menstrual cycle therefore not reliable) Menopause (>30mU/mL)
- S/S
    - Hyperactive Vasomotor Sx: hot flashes (intense diaphoresis of face/neck/chest, lasts 30sec-5min, often a prodome of HA/weakness/palpitations occurs, can often awake a pt from sleep, “Cascade Effect” hot flashes lead to interrupted sleep leads to fatigue and mood changes, always r/o secondary causes like niacin, carcinoid, pheo, etc), Tx w/ (1) HRT and/or non-hormonal methods: Rx (clonidine, fluoxetine, gabapentin, venlafaxine) Herbals (black cohosh, red clover, dong quai, vitB6), lifestyle changes (paced slow respiration, weight loss, light clothing, fan, cool food, soy protein, exercise, avoid exacerbating foods like caffeine, alcohol, spicy foods, fat)
    - Urogenital Atrophic Sx: vaginitis w/ pruritus/dyspareunia, non-infectious urethritis/cystitis, Tx w/ estrogen creams
    - Neuropsych Sx: depression/anxiety/”moody”, insomnia, decreased memory, decreased libido, decreased cognitive fxn
    - Virilization Sx: mild (refer)
    - Osteoporosis
    - CVD
    - Breast Cancer

Pelvic Pain

- Non-Menstrual
    - Acute: infection
    - Chronic: multifactorial process including neur/MS/endo/psych factors, very ill-defined Sx, rarely is a Dx made, Tx is difficult if a Dx is not made and some try oral progestins and psych meds b/c often pysch dz confounds Sx and also reassure the pt, goal is to try to reproduce pain during Pelvic Exam, DDx: endometriosis, adhesions, IBS, intertistial aka non-infectious cystitis
- Menstrual
    - Menstruation = **Dysmenorrhea**
        - S/S: lower abdominal cramping
        - Types
            - Primary: typically <20yo, NO pathologic cause and thus a DOE after ruling secondary dysmenorrhea w/ H&P, underling cause is increased endometrial production of prostaglandins 2/2 decreasing levels of E/P which causes uterine contraction and subsequent pain, Tx: similar to Premenstrual Disorders below
            - Secondary: typically >20yo, YES pathologic cause therefore requires a work-up with TV-US, Tx: etiology specific
                - Endometriosis (refer below)
                - Adenomyosis (refer below)
                - Fibroids
                - Pelvic Adhesions
                - PID
    - Follicular/Proliferative = usually there are no problems during this phase but occasionally pts may describe pain during the period of ovulation termed **Mittleshmerz**
    - Luteal/Secretory = **Premenstrual Disorder** (Sx that appear during this phase and then diminish/disappear w/ menstruation)
        - **Premenstrual Symptoms** (mild Sx, 60% of women)
            - S/S
                - Physical: HA, breast tenderness, D/C, N w/ lack of appetite, ab cramps, bloating, weight gain, extremity swelling, fatigue, palpitations, acne
                - Emotional: irritability, depression, sadness, nervousness, anger, rage, over-sensitivity, anxiety
                - Behavioral: food cravings, increased food intake, decreased interest in work, decreased interest in social relationships, decreased concentration, sleep disturbance, change in sexual interest
            - Tx
                - Education, Exercise, Balanced Diet w/o Caffeine/Alcohol,
                - 1° NSAIDs (eg. OTC Midol good for HA, breast tenderness, etc but can worsen GI Sx) and OCPs (keeps E/P higher during luteal phase)
                - 2° VitB1 (Thiamine), VitB6 (Pyridoxine), Vit E, Omega-3-FAs, Mg

        - Intermittent Aldactone for weight gain and edema, breast tenderness, mood changes
        - SSRIs for mood changes
        - Last Line: GnRH agonists, Danazol, Oopherectomy
    - **Premenstrual Syndrome aka PMS** (mod Sx, 20% of women)
    - **Premenstrual Dysphoric Disorder aka PMDD** (severe Sx w/ functional impairment, 4% of women)

Abnormal Uterine Bleeding (statistically every women b/t menarche and menopause will experience at least one episode of abnormal uterine bleeding = bleeding that differs in frequency, duration or amount from the pattern observed in a normal cycle)

- **Post-Menopausal**
    - Etiology: Endometrial/Vaginal Atrophy (70%), Exogenous Estrogen w/o P (20%), Endometrial/Cervical Cancer (10%), Endometrial Polyps, Hyperplasia, et al. (7%) **regardless assume cancer until proven otherwise**
        - **Vulva**
            - **Cancer**: 4th most common gyn cancer, post-menopausal but there are some cases in young women, RF: age, HPV, etc Type: VIN to SCC (90%), Melanoma (7%) BCC (3%) Lymph Metastasis, S/S: ranges in appearance from a cauliflower lesion to an indurated ulcer, always consider when a pruritic inflamed area does not respond to topical anti-fungal, Tx: surgery + radiation + chemo, Remember: Young Pt: cervical cancer vs Middle-Aged Pt: vaginal cancer vs Old Pt: vulvar cancer
        - **Vagina**
            - **Cancer**: very rare gyn cancer, RFs: HPV?, chronic irritation from pressaries, DES, etc, VAIN to SCC (90%) Adenocarcinoma (10%), Tx: surgery + radiation + chemo
    - Dx: Pelvic Exam, TVUS measure endometrial thickness - ET (<5mm excludes a uterine process) to first rule out endometrial cancer then consider endometrial Bx - EMB or D&C
- **Non-Menopausal**
    - First r/o pregnancy b/c of first trimester bleeding, coagulopathy or use of AC, hyperthyroidism, certain contraceptives esp Depo, OCPs, or IUD
    - Rule Out non-genital bleeding (GI & Urinary)
    - Occurs when pt is ovulating therefore further workup is warranted b/c likely pathologic
        - Hz: **Oligomenorrhea** (menstruation occurs >35d apart) vs **Polymenorrhea** (menstruation occurs <24d apart)
        - Amount/Duration: **Menorrhagia** (excessive amount (>80mL or >24pads) and/or duration (>8d) during menstruation) vs **Hypomenorrhea** (deceased amount and/or duration)
        - Other: **Metrorrhagia** (bleeding b/t menstruaton that is usually less than or equal to in volume and duration to normal periods but if not then it is called **Menometrorrhagia**)
        - DDx
            - Above
            - Ovary: ovarian tumor (rare)
            - Uterus: Endometriosis, Adenomyosis, Endometrial Hyperplasia, Leiomyoma/Fibroids, Endometrial Carcinoma, Leimyosarcoma (most common)
            - Cervix: tumor (rare)
            - Vagina: foreign body, trauma, tumor, atrophy (rare)
        - Dx: endometrial Bx, TVUS, Hysterosalpingogram, Hysteroscopy
        - Tx: treat underlying cause but if unknown then give brief high dose E followed by OCP, also consider NSAIDs, If medical therapy fails then D&C, endometrial ablation, electrocautery, hysterectomy
    - Occurs when pt is NOT ovulating therefore not as important b/c most likely DUB
        - **Dysfunctional Uterine Bleeding (DUB)** when no cause of abnormal uterine bleeding is found above then most likely due to anovulation resulting in constant estrogen production without progesterone production by corpus luteum and thus the endometrium grows and grows but is never maintained and thus eventually outgrows blood supply and then sloughs off resulting in bleeding that is more frequent and heavier but also unpredictable (usually around menarche or menopause b/c secondary to anovulation)
            - **Mild:** give P (medroxyprogesterone acetate 5-10mg PO Qd x10d) and if it works and pt does not desire contraception then take the first 10d of each calendar month but if it does not work or pt does desire contraception then give E+P (OCP, Depo, Levonorgesterol IUD)
            - **Mod:** give high dose E for a brief period of time and then OCP as above
            - **Severe & Medical Therapy Fails:** D&C, endometrial ablation, hysterectomy

Vulva

- **Other**: Labial Fusion, Eczema, Seborrheic Dermatitis, Lichen Sclerosus, Lichen Planus, Squamous Cell Hyperplasia 2/2 chronic scratching resulting in thickening, Bx is required to r/o cancer
- **Cysts**: Epidermal Inclusion, Sebaceous Duct, Apocrine Sweat Gland, Skene/Paraurethral Gland, Bartholin's Duct Cyst: not the most common but they are more symptomatic as they can grow quite large compared to other cysts and cause pain

even when just walking, Complications: (1) cancer (2) infection, Tx: unlike other cysts these cysts cannot be repaired alone using I&D b/c they often recur, therefore, one of two methods can be used (1) Word Catheterization (I&D then a word catheter is placed which has a balloon tip which fills up inside the cyst, over a 4-6wk period the balloon slowly decreases in size allowing epithelialization to fill entire cyst while preventing fluid/abscess formation) and (2) Marsupialization (I&D then the resulting space is sewn open therefore no space even exists for fluid/abscess formation and thus epitheliazation to occur)

Vagina

- Vaginal Obstructions: imperforate/septate hymen, Transverse Vaginal Septum, vaginal atresia vs Vaginal Agenesis: 2/2 congenital absence from Mayer-Rokitansky-Kuster-Hauser (MRKH) Syndrome or androgen excess resulting in absence of not only vagina but also everything proximal to it, Tx: create vagina by doing serial dilation of perineal body or using split-thickness skin grafts

Uterus

- Anatomic Anomalies
  - Genetic: **Unicornuate Uterus** (uterus attached to one fallopian tube), **Uterus Didelphis** (two separate uteri with two separate cervixes with two separate vagina each attached to one fallopian tube), **Septate Uterus** (septum itself comes off of fundus downward toward cervix and is made of collagen and lacks a vascular supply thus during pregnancy a placenta that attaches to it cannot survive resulting in 1st trimester SAB), **Bicornuate Uterus** (entire fundus dips downward toward cervix and thus unlike a septum is made of the same tissue as normal uterine wall therefore blood supply is not a problem rather mere mass effect on a growing fetus is the main problem resulting in 2nd and 3rd trimester SAB or preterm labor)
  - Acquired: **Pregnancy Trauma, Asherman Syndrome** (intrauterine adhesions 2/2 DIC, uterine surgery, etc), **Synechiae** (after IUD placement/miscarriage/D&C/ablation), **Cervical Stenosis** (2/2 scarring 2/2 surgery/radiation, 2/2 obstruction 2/2 cyst/polyp/fibroid/neoplasm, problem for pregnant women: poor dilation for delivery of fetus, problem for non-pregnant women causing dysmenorrheal, Tx: dilation via surgery or laminaria (seaweed that is inserted into os and dilates by absorbing water) **Cervical Polyps, Cysts, etc**
- **Endometriosis**
  - History: first described by von Rakitansky in 1860
  - Def: ectopic functional endometrial tissue
  - Mechanism w/ Three Possible Theories: (1) Halban Theory: during menstruation endometrial tissue is transported via lymphatic system, (2) Meyer Theory: multipotential cells in non-endometrial tissue undergoes metaplastic transformation into endometrium, (3) Sampson Theory: during menstruation endometrial tissue is transported retrograde through fallopian tubes into abdomen
  - Epidemiology: 10-15% of child-bearing women, average age: 27y, W>AA
  - RFs: unopposed estrogen, less pregnancies, etc
  - Location (most to least common (near uterus to away from uterus): 1° ovary (50% of pts have both ovaries involved, classically called "chocolate cysts"), 2° GI (rectosigmoid → appendix → ileum), post cul-de-sac, ant uterovesicle pouch, broad ligament, uterosacral ligament, fallopian tube, rectovaginal septum, 3° cervix, vulva, vagina, umbilicus, pelvic/ab scars, ureter, bladder, arm, leg, lung, brain
  - Mech: undergo normal menstrual changes → cyclic growth and sloughing of tissue → irritation to serosa and progressive invasion of intestinal wall causing deeper damage characterized by fibrosis and muscle hypertrophy
  - S/S: 30% asymptomatic but if symptomatic (usually cyclic but not always) then pain (2/2 nerve impingement, serosal inflammation, etc), change in bowel habits, partial obstruction 2/2 adhesions, appendicitis from obstructing endometrioma, small bowel intussusception, infertility (most common cause), uterosacral ligament nodularity on PEx, fixed retroverted uterus on PEx 2/2 adhesions, cul-de-sac nodular induration on PEx, tender adnexal mass representing a fixed ovarian mass on PEx (always perform exams before andafter menstruation)
  - Dx: clinical (cyclic Sx in women, DDx: IBS), Endoscopy (rarely can lesions be seen unless severe demonstrating extrinsic compression or strictures), Laparoscopic Visualization w/ Biopsy (many different visual manifestations w/ early raspberry colored bumps to late powder-burn lesions w/ surrounding fibrosis), no radiographic imaging is pathognomonic
  - Tx: NSAIDs → Chronic Low Dose Acyclic E+P so as to keep all hormones in chronically low, acyclic states which in turn inhibits endometrial growth → GnRH Agonist (leuprolide-Lupron) decreases E and P even more by inhibiting release of LH/FSH → CO_2 ablation during surgery, Excision, LAH, TAHBSO
- **Adenomyosis**
  - Def: diffuse endometrial invasion of myometrium esp at posterior uterine wall causing myometrial hypertrophy/hyperplasia
  - Epidemiology: 15% of women, seen in post-parous women
  - Dx: unlike endometeriosis in which the tissue "lies on top" of other tissues adenomyosis is an invasion and thus cannot be visualized by laparoscopy therefore cannot only be assessed w/ TVUS, diffusely/symmetrically enlarged soft uterus (adenomyosis) vs. focally enlarged firm uterus (fibroids)
  - Mechanism: high levels of E stimulates hyperplasia of basalis layer of endometrium followed by destruction of barrier b/t endometrium and myometrium 2/2 to endomyometritis following delivery of baby

- S/S: 30% asymptomatic but sometimes you have symptoms similar to endometriosis but does not change w/ menstruation
- Tx: if symptomatic then NSAIDs → Hysterectomy is the only definitive treatment (it is imperative to perform a Bx to r/o endometrial carcinoma) NB does NOT respond to hormones

- **Leiomyoma aka Fibroid**
  - Def: multiple local proliferation of myometrium with compressed surrounding tissue forming a "psuedocapule" 1° Intramural vs 2° Submucosal/Subserosal
  - Epidemiology: 25% of women, AA>W, any high estrogen state as estrogen stimulates muscle
  - Dx: TVUS, hysteroscopy, HSG
  - S/S: as the fibroid enlarges it outgrows its vascular supply, infarcts, and degenerates (in one of five ways: (1) hyaline, (2) cystic, (3) hemorrhagic, (4) calcific, and (5) sarcomatous) resulting in pelvic pain (INFARCTION OFTEN OCCURS DURING PREGNANCY B/C (1) HIGH ESTROGEN STIMULATES GROWTH AND THUS INCREASED REQUIREMENTS FOR BLD and (2) SOME OF THE BLD SUPPLY THAT DOES EXIST GOES TO THE BABY)
  - *** fibroids have NO malignant potential***
  - NB either of these can beceome pedunculated when the subserosal one does, attaches to pelvic viscera/omentum, and develops its own blood supply then it is called a parasitic leiomyoma
  - S/S: asymptomatic (55%), longer/heavier bleeding aka menorrhagia (most common of the symptoms esp for submucosal fibroids), as it grows it can cause a mass effect resulting in urinary frequency / retention, constipation, and general pelvic pressure / bloating and as it grows even more it infarcts manifesting as pelvic pain (esp for subserosal fibroids) or prolapsed into cervix, infertility however most women with fibroids are able to conceive just fine rather more common is IUGR, malpresentation, dystocia necessitating CS, pre-term, nontender, solid, "lumpy-bumpy", irregularly enlarged uterus on palpation on PEx, Sequalae: hyaline degeneration, calcification, red degeneration (hemorrhage during pregnancy), cystic degeneration (rupture)
  - Tx: (MOST COMMON INDICATION FOR SURGERY IN WOMEN REPRESENTING ~1/3 OF ALL HYSTERECTOMIES) HOWEVER it is imperative that you r/o other types of pelvic masses esp leiomyosarcomas which appear as RAPIDLY growing masses in POSTmenopausal women
    - IF ASYMPTOMATIC THEN **expectant management** aka just observe
    - IF SYMPTOMATIC PAIN THEN
      - **Decrease Estrogenic Effects** myometrium contains ER (+growth) (problem is that once meds are discontinued tumors usually resume growth therefore use for perimenopausal women until they reach menopause on their own) give Provera (P) so that E does not act unopposed or give Danazol or give GnRH agonists which decrease both E and P
      - **Uterine Artery Embolization** (UAE) decreases bld supply to fibroid (problem is that rest of uterus and ovaries can be also be compromised therefore only for women who do not want to become pregnant)
      - **Myomectomy** (best for patients who want preserve fertility) (problem is that fibroids recur in 50% of pts and adhesions frequently form after removal carrying with the their own set of problems)
      - **Hysterectomy** (definitive treatment but obviously lose fertility)

- **Leiomyosarcoma**
  - solitary (leiomyosarcoma) vs. multiple (leiomyoma)
  - h/o radiation to pelvis
  - fast growing
  - post-menopausal
  - Tx: TAHBSO + LND + Peritoneal Washing + Adjuvant Chemo

- **Endometrial Hyperplasia**
  - Def. normally endometrium proliferates during the follicular/proliferative phase of the menstrual cycle, however, when the endometrium is exposed to continuous E in the absence of P endometrial proliferation → endometrial hyperplasia + architectural changes + cytologic atypia
  - *Simple*: no architectural changes b/c BOTH glandular AND stromal elements proliferate such that everything looks nl just a lot more tissue than nl vs *Complex*: architectural changes occur b/c ONLT glandular elements proliferate without stromal element proliferation thus glands are crowded back to back and are of varying size and shape
  - *Typical*: nl vs *Atypical*: large nuclei with increased N/C ratio, loss of polarity, and prominent nucleoli
  - *** unlike fibroids, endometrial hyperplasia can have malignant potential depending on architecture and cytologic atypia ***

Architecture	Cytologic Atypia	Progression to Cancer	Rx
Simple	Absent (Typical)	1%	Progestin Therapy + D&C
Complex	Absent (Typical)	3%	Progestin Therapy + D&C
Simple	Present (ATypical)	9%	Progestin Therapy + TAHBSO
Complex	Present (ATypical)	29%	Progestin Therapy + TAHBSO

  - Epidemiology: peri- or menopausal women OR right after menarche, RFs: unopposed E exposure (obesity, chronic anovulation, low to nulli parity, early menarche / late menopause , exogenous E w/o P, PCOD, E producing tumor)

- Dx: (NO GOOD SCREENING TEST LIKE FOR CERVICAL AND BREAST) 1° Bx, 2° Hysteroscopy and D&C if Bx cannot be performed 2/2 pt discomfort, cervical stenosis, or insufficient tissue
- S/S: abnl bleeding (postmenopausal, menorrhagia, postcoital, intermenstrual) usually uterus is normal on PEx but in late stages cervix mare be firm/protruding and uterus enlarged

- **Endometrial AdenoCarcinoma**
  - Def: glandular (not stromal) proliferation

	Estrogen-Dependent Cancer 25%	**Estrogen-INDependent Cancer 75%**
Pt	Young, White, Perimenopausal	Old, Asian/AA Postmenopausal
RFs	Unopposed estrogen exposure	NOT unopposed estrogen exposure
Pre-Neoplasm	Yes	No
Differentiation and Prognosis	Well and Good	Poor and Bad

  - Epidemiology: estrogen dependent neoplasm therefore higher when you have more unopposed estrogen
  - Sx: post-menopausal bleeding, sometimes abnl pap
  - Dx: >5mm endometrial strip on US, then D&C
  - most common gyn cancer but 3rd cause of gyn cancer death
  - Four Routes of Metastasis: 1° Direct Extension 2° Lymphatics 3° Shed Into Fallopian Tube into Ab 4° Hematogenous
  - Prognostic Factors: 1° Histologic Grade 2° Depth of Myometrial Invasion (much worse if invaded >1/3 of myometrium) 3° Histologic Type (adenocarcinoma much better prognosis than the other more rare variants such as clear cell)
  - RFs: same + HTN + DM + endometrial hyperplasia
  - Prevention: OCP
  - Rx: TAHBSO + LND + Chemo (controversial) + Radiation w/ f/u Q3mo for 2yrs and then Q6mo for 3yrs and then Q1yr b/c high recurrence rate

Fallopian Tubes

- **Pelvic Inflammatory Disease (PID) aka Salpingitis**
- **Adenocarcinoma** (unknown cause, exceedingly rare, similar to surface epithelial cell ovarian tumors in terms of metastasis and Rx, usually asymptomatic but pt develops triad of symptoms (pelvic pain + profuse watery discharge + menorrhagia = "hydrops tubae profluens") it is considered pathognomonic for fallopian tube adenocarcinoma)

Ovary

- **Tubo-Ovarian Abscess (TAO)**
- Cysts (75% of "masses")
  - Types
    - 1° **Follicular Cysts:** form when follicle fails to rupture during follicular phase, most resolve w/in 2mo therefore no Tx, if Sx then give OCPs, if not resolved after 2mo then surgery b/c then there might be concern for cancer, Unilateral, small (<8cm), more softer, unilocular, asymptomatic if small (3cm), chronic dull pain if large (8cm), acute sharp pain if torsion or rupture
    - **2° Corpus Luteum Cysts**: form when corpus luteum fails to regress during luteal phase, unilateral, large (>8cm), more solid, multilocular, amenorrhea, chronic dull pain if expanding, acute sharp pain if torsion or rupture
    - **3° Thecal Lutein Cysts:** when pregnant mother is exposed to very high levels of bHCG as in GTDs, PCOD, Multiple gestation, etc the increase in number of theca cells results in androgen production exceeding capacity of granulose cells to aromatize to estrones hence virlization/hirsutism, bilateral, large, more solid, multilocula, virilization/hirsutism
  - Dx: US (cystic vs solid neoplastic mass) CA-125 level to r/o common cancer
  - Tx: based on age/size

Premenarchal	#cm	Laparoscopic exploration b/c more likely neoplasm than cyst and if confirmed then oopherectomy
Reproductive	<5cm	Observe for 2mo then repeat US b/c most likely follicular cyst which usually disappear within 2mo
Reproductive	5-8cm	Uniliocular: (above b/c more likely follicular cyst) Multilocular: (below b/c more likely corpus luteum cyst) US
Reproductive	>8cm	Laparoscopic exploration b/c more likely corpus luteum cyst and if confirmed then cystectomy
Postmenopausal	#cm	Laparoscopic exploration b/c more likely neoplasm than cyst and if confirmed then oopherectomy

- Tumor (25% of masses)
  - Epidemiology: 80% Benign 20% Malignant, women have a 1:60 chance of developing ovarian cancer during lifetime with median age of 61yo, although 3rd most common gyn tumor it is the 1st most deadly gyn tumor 2/2 lack of effective screening tools and b/c ovaries are in peritoneal cavity and thus spread very easily

- Met: 1° direct exfoliation into ab resulting in ascites and encasement of bowel with tumor resulting in bowel obstruction (*carcinomatous ileus*) 2° hematogeneous to brain/lung
- RFs: ovulation disrupts epithelium of ovary and activates cellular repair therefore when ovulation is allowed to continue uninterrupted for a long period eventually mutations accrue (as seen in nulliparity or just few parity or even just delayed childbearing, late onset menopause, ovulation induction w/ fertility drugs) NO OCP use b/c ovulation is not being suppressed therefore OCP use decreases risk, Familial Cancer Syndrome (80% BRCA1>2 and 20% Lynch) then Qyr Ca-125, pelvic exam w/ TVUS or pt should undergo prophylactic oophorectomy, High Dietary Fat, Mumps, Asbestos , Lactose Intolerance, Industrialized countries, Age (post-menopausal, ~55yo, rare in women <20yo)
- S/S: often asymptomatic until advanced at which stage 2/2 peritoneal spread pt presents w/ vague GI/urinary complaints along w/ solid fixed adnexal pelvic mass and ascites on PEx (Sister Mary Joseph's Nodule aka met to umbilicus) mets to abdomen, pleura, LN (very rarely lung, liver, bone, CNS)
- Screening: b/c low prevalence and tests poor screening is not indicated
- Dx: (NEVER FNA b/c malignant cells spread thru tract) 1° US and Serum Tumor Markers
  - Benign: mobile, cystic, unilateral, smooth Cul-De-Sac, <8cm, unilocular
  - Malignant: fixed, solid, bilateral, nodualer Cul-De-Sac, >8cm, multilocular
- Prognosis (based on Stage): I Ovary 90% 5yr survival, II pelvis 70%, III ab 25%, IV met 5%

	Surface Epi	**Non-Epi**		
	Surface Epithelial Cell Tumors (cells on the surface of the ovary)	**Germ Cell Tumors** (germ cells aka oocyte)	**Sex Cord or Stromal Cell Tumors** (undifferentiated germ cells or non-functioning fibroblasts that support germ cells)	**Mets**
%	80%	10%	5%	5%
Pt Age	Post-Menopausal (>50yo)	Young (<30yo)	Post-Menopausal (>50yo)	20+yo
% Malignant	98%	5%	1%	
Types	(1) Serous Cystadenoma (B) 20% (2) Serous Adenocarcinoma (M) 20% (3) Mucinous Cystadenoma (B) 7.5% (4) Mucinous Adenocarcinoma (M) 7.5% (5) Endometrioid Tumor (B) 7.5% (6) Clear Cell Tumor (B) 5% (7) Brenner Tumor (B) 5% (8) Undifferentiated (M) 5%	(1) Mature Teratoma (B) (2) Immature Teratoma (M) CA-125 (3) Dysgerminoma (M) LDH, CA-125 (4) Endodermal Sinus (Yolk Sac) (B) AFP, most aggressive (5) Choriocarcinoma (M) hCG (6) Embryonal Cell Carcinoma (B) (7) Mixed Germ Cell Tumor (B)	(1) Granulosa-Theca Cell Tumor (B) (2) Sertoli-Leydig Cell Tumor (B) (3) Fibroma (B)	(1) GI (Gastric, Colon, etc) (M) aka called Krukenberg tumors if the cell is a signet ring cell (2) Breast (M) (3) Endometrium (M)
Markers	CA-125 (80% sens, very low spec) • Cancers (Fallopian Tube, Endometrial, Pancreatic, Lung, Breast, Colon • Other (Pregnancy, Endometriosis, Fibroids, PID, Pancreatitis, Cirrhosis, Peritonitis, Recent Laparotomy)	hCG, AFP, LDH, CA-125	G-T Cell Tumors produce estrogens S-L Cell Tumors produce androgens	
Notes	• Slow growing thus most (75%) diagnosed only after tumor is very large (Stage III) with symptoms reflecting metastasis therefore poor prognosis (5yr of 20%) • Malignant epithelial cell tumors actually rarely invade the ovary itself • Bilateral 65% of the time • +CA-125 80% of the time, good for tracking changes b/c sensitive but not good for screening but not specific • Most common complication: torsion during pregnancy	• Fast growing thus most diagnosed early on while tumor is still small with symptoms reflecting a fast growing structure against adjacent tissue that cannot accommodate (pelvic pain and rapidly enlarging adnexal mass) and not metastasis therefore good prognosis (5yr of 60-85%) • Teratomas sometimes have hidden SCC and some undergo torsion	• Slow growing but symptomatic (produces specific hormones) thus most diagnosed early on therefore good prognosis (5yr of 90%) • Fibroma is sometimes associated with Meig's Syndrome (ovarian tumor, ascites, and R hydrothorax) • Recurrence is very common • G-T Cell Tumor often associated with endometrial carcinoma b/c of estrogen production, precocious puberty, postmenopausal	

	• Often burst leading to psuedomyxoma peritoneii	• Dermoid Cyst (Benign Cystic Teratomas) • Dermoid Cyst that predominantly contains fxnal thyroid tissue is called a "Struma Ovarii" • Often unilateral • Often occur during pregnancy	bleeding • S-L Cell Tumor (virilization)	
Rx	Stage I (confined to ovary) 80% 5yr Stage II (to pelvis) 50% Stage III (to peritoneum) 25% Stage IV (metastatic) 5% TAHBSO/Omentectomy w/ ex-lap (RPLND, ab organ & diaphragm eval, random Bx, peritoneal cavity washings) for all b/c can't assess stage unless you do surgery, also check CA-125, CXR, CT-A/P Ab US prior Platinum based chemo for all stages except low grade (1/2) stage IA/B XRT for Stage III/IV Follow pts Q3mo x2yrs, Q6mo x1yr, then Qyr w/ CA-125 and pelvic exam and if + CA-125 then >90% are recurrence then restart chemo NB the presence of tumor after surgery is the most important unfavorable RF hence it was advocated that pts undergo "2nd look lap" but studies show no survival benefit	Unilateral Oopherectomy ↓ Multi-Drug Chemo (Cisplatin/Etoposide/Bleomycin) IMPORTANT: Dysgerminomas are exquisitely sensitive to radiation but rarely used b/c of sterility	TAHBSO IMPORTANT: Chemo is typically ineffective	

Obstetrics

General

- Beta-hCG becomes + after 2wks of conception
- S/S: amenorrhea, morning sickness, Hegar Sign (softening of uterus), Chadwick Sign (darkening of vulva), Melasma, Linea Nigra, weight gain (28lbs) , heavy breasts, increased pigmentation of areolae, stria gravidarum, LE edema, GERD, polyuria, Quickening @18wks
- Labs/Studies: Pap w/ GC&Ch, UA Qvisit and Tx asympt UTI, CBC, blood type and Rh type and ab screen, Syphilis, Rubella, DM screen, Triple Screen (@15-20wks, AFP + beta-hCG + Estriol, AFP low w/ aneuploid like Down's and high w/ neural tube defects), genetic counseling w/ Amnio at14-16wks, Group B Strep, hCG (double Q2d in 1st trimester), HIV, PPD, Sickle Cell, HBV, OGTT at 26-28wks, RhoGam at 28wks, fetal heart tones w/ Doppler, uterine size, TVUS, other tests (amniocentesis, chorionic villous sampling), general labs should be normal except increase in AlkPhos and a decrease in Cr
- Meds: folate supplementation is most important during 1st trimester, avoid teratogenic meds, HIV (ziduvidine at 14wks and continue in newborn for 6wks post partum)
- Physiology: CV (decrease in BP, increase in HR, increase in CO), Pulm (increase in RR, increase in TV), GI (decrease resting LES tone, prolonged transit time, etc)
- Abortion (most are 1st trimester and are spontaneous aka miscarriage, Threatened (bleeding, ½ of women have nl pregnancy), Inevitable (bleeding w/ cervical dilation), Missed (fetal death w/o expulsion, need D&C), Incomplete (partial expulsion, need D&C), Complete (complete expulsion, follow HCG), Induced (<20wks, legalized 1973 w/ Roe vs Wade, b/f 3mo every state allows but after 3mo it varies from state to state based on their definitions of viability), Etiology: recurrent consider infection (syphilis, Listeria, Mycoplasma, Toxo), environmental (alcohol, tobacco, drugs), metabolic (DM, hypoTH), autoimmune (antiphospholipid syndrome), anatomic (cervical incompetence, fibroids), genetic (chromosomal abnormalities))

First/Second Trimester

- **GI (usually non-liver stuff & less serious compared to GI problems later in pregnancy, refer to GI)**
- **Ectopic**: S/S (S/S of pregnancy but also pain, adnexal mass, small uterus for GA), RFs (STDs, PID, endometriosis, prior, pelvic surgery, use of IUD), Dx (US w/ 99% at ampulla of fallopian tube, 1% other), Tx (if unruptured then MTX but if ruptured then surgical resection)
- **Oligohydramnios**: 2/2 PROM, Renal Agenesis (Potter's Disease) = Pulmonary Hypoplasia, Cutaneous/Skeletal Abnormalities, Hypoxia 2/2 Cord Compression vs **Polyhydramnios**: 2/2 Maternal Diabetes, Multiple Gestation, Neural Tube Defects, GI anomalies, Hydrops Fetalis = Postpartum Uterine Atony w/ Subsequent Hemorrhage, Maternal Dyspnea, Malpresentation (NB Amniotic Fluid Produced by kidney vs Absorded by GI/Membranes)
- **Multiple Gestation**: results in premature labor, determine if monozygotic/identical (not inherited, worse complications) vs dizygotic/fraternal (not inherited, complications not as bad), r/o maternal (anemia, HTN, postpartum uterine atony, postpartum hemorrhage) vs fetus (polyhydramnios, malpresentation, placenta previa, abruption placenta, vasa previa, umbilical cord prolapsed, IUGR, congenital anomalies), Tx: if vertex-vertex presentation then VD otherwise do a CS Twins
- **DM**: Complications: Maternal (polyhydramnios, pre-eclampsia, DM complications), Fetal (macrosomia, IUGR, RDS, CV/Colon/Craniofacia/CNS defects, Caudal Regression Syndrome in which lower half of body is not completely formed), Tx: diet, exercise, insulin, NO oral hypoglycemic
- **Rh Incompatibility**: when Rh-mother has exposure to Rh+ blood (prior pregnancy w/ Rh+ infant, transfusions, etc) warn mother that with pregnancy w/ Rh+ infant there is r/o fetal hydrops w/ hemolysis hence to prevent this give Rh-Ig during first pregnancy at specific times to prevent sensitization

Second/Third Trimester

- **GI (usually liver stuff & more serious compared to GI problems early in pregnancy, refer to GI)**
- **Trophoblastic Hydatidorm Moles:** Mech (proliferation of products of conception, can be complete vs incomplete), S/S (painless bleeding early in pregnancy and pre-eclampsia b/f 3rd trimester w/ expulsion of grape like vesicles), Dx (elevated hCG levels that does not return to zero after delivery, snow-storm pattern on US), Tx (D&C and then follow hCG and if does not fall to zero then likely invasive mole, choriocarcinoma or trophoblastic tumor and pt needs TAH and chemo)
- **Placenta Previa** (placenta over internal os instead of normally over posterior wall, S/S: painless bleeding, RFs: multiparity/gestation, age, prior previas, etc, Dx: US, Tx: bedrest b/c sometimes resolves but if not then CS)
- **Fetal Vessel Rupture** (Velamentous Placenta = vessels insert b/t amnion and chorion vs Vasa Previa = vessels pass over os vs Succentruriate Placenta = placenta has extra lobe such that vessels that connect lobes are exposed, S/S: painless bleeding, RFs: multiple gestation, Dx: US w/ Apt Test indicating fetal not maternal blood, Tx: CS)
- **Abruption** (separation of placenta from uterus, S/S: painful bleeding w/ strong contractions but sometimes blood is not visible b/c it collects behind placenta, RFs: HTN, trauma, polyhydramnios, cocaine, tobacco, premature-PROM, Dx: US, Tx: VD, NB can also cause DIC and shock)

L&D

- If concerned about fetal well being then check BPP (BioPhysical Profile) which consists of US eval of (1) HR, (2) amniotic fluid index, (3) breathing movements, (4) body movements and if low BPP then check Contraction Stress Test (mother given oxytocin and fetal heart strip is monitored)
    - Early Decel = deceleration in HR occurs during contraction = normal head compression
    - Variable Decel = deceleration = bad cord compression = " " (below)
    - Late Decel = deceleration in HR occurs after contraction = bad uterine-placental insufficiency = place mother in L lateral decub, oxygen, stop oxytocin then give tocolytic and IVF then measure fetal oxygen saturation and scalp pH
- **Pre/Post-Term**
    - Pre-Term: <37wks, NB not viable <24wks, Complications: general increase in M&M w/ RDS, Intraventricular Hemorrhage, PDA, Bronchopulmonary Dysplasia, Sepsis, Necrotizing Enterocolitis, Retinopathy, RFs: PROM, chorioamnioitis, multiple gestations, anatomic anomalies, overweight mother, abruption, eclampsia, etc, Tx: lateral decubitus, bed/pelvic rest, IVF, oxygen then tocolytics (saline, MgSO4, beta agonists, nifedipine) which only buy you 48hrs therefore only enough time to give steroids, if fetal lungs are immature i.e. lecithin:sphingomyelin ratio <2:1 and negative phosphatidylglycerol in amniocentesis and fetus is b/t 26-24wks then give steroids
    - Post-Term: >42wks, Complications: general increase in M&M w/ macrosomia, oligohydramnios, meconium aspiration, Tx: if gestational age is confirmed as accurate then induce but some wait to 43wks
- **PROM** (rupture of amniotic sac b/f onset of labor and is called preterm PROM if bf/f 37wks, Dx: pooling of amniotic fluid, fern pattern of amniotic fluid is dried on microscope slide, + nitrazine test of amniotic fluid then US, Tx: if labor does not occur in 6-8hrs and then mother is term than induce, Complications: chorioamnionitis: infection, S/S: F and inflamed uterus, RFs: PROM, Tx: abx, Complications: chorioamnionitis, abruption, cord prolapsed)
- Labor
    - Check Fetal Position w/ Leopold Maneuver
    - Check if membranes have ruptured
    - Check cervix for Dilation(widening) / Effacement(thinness) / Station(baby-position) / Consistency(softness) / Position using Bishop Score
    - Check fetal position in cervix (vertex vs breech, head up/down/left/right w/ most common head down)
    - True Labor (contractions regularly Q10-1min and w/ cervical changes) vs False Labor aka Braxton-Hicks Contractions (contractions irregularly and w/o cervical changes)

- Vaginal Deliver (baby faces left/right, head comes out facing posterior and extending back, then head turns to left/right, anterior shoulder then posterior shoulder, the rest of body, suction baby, clamp cord and cut)
- Protraction/Arrest/Failure to Progress/Dystocia: Etiology (consider abnormal lie like breech, cephalopelvic disproportion or shoulder dystocia), Tx (episiotomy, forceps, vacuum extraction, CS)
- CS (do in women w/ active herpes, classic/vertical vs new/horizontal incision, increased r/o uterine rupture w/ future pregnancies) w/ or w/o Epidural Anesthesia
- Placental Separation (fresh blood per vagina, lengthening of umbilical cord, rising of fundus, uterus becomes firm)

Post-Partum

- Hemorrhage (NB complication of Sheehan Syndrome, if pt is in shock but there is no bleeding then consider Amniotic Fluid Embolism or Concealed Hemorrhage where uterus is bleeding into peritoneal cavity)
  - **Uterine Rupture** (rupture of uterus, RFs: previous uterine surgery, trauma, oxytocin, multiparity/gestation, polyhydramnios, CPD, S/S: sudden painful bleeding leading to shock w/ fetal parts palable in ab and change in ab contour, Dx: US, Tx: ex-lap)
  - **Uterine Atony** (overdistension of uterus 2/2 multiple gestation, polyhydramnios, macrosomia, etc, prolonged labor, oxytoxin usage, grandmultiparity, precipitous labor aka lasting <3hrs) S/S: soft boggy uterus, Tx: bimanual compression and massage while giving dilute oxytocin infusion and if fails then try ergonovine or PGF2 and if fails then TAH
  - **Placenta Acreta/Increta/Percreta** where placenta has invaded uterine wall and thus during delivery of placentathere is retained products of conception, Tx remove placenta manually and if fails then curettage and if fails then TAH
  - **Uterine Inversion** 2/2 pulling too hard, Tx put uterus back in place
  - **Coagulopathy, Episiotomy, Laceration, CS Site Dehiscence**
- Fever: Breast Engorgement, UTI, Mastitis, Endomyometritis (RFs: CS, PROM, Prolonged Labor, Retained Placental Tissue, S/S: tender uterus, foul smelling lochia, Tx: abx but if fails then concerning for pelvic abscess or pelvic thrombophlebitis which requires either surgery or AC)
- Post Partum Blues/Depression/Psychosis
- Lactation Teaching
- Future Contraception (pelvic rest for 6wks, P only OCPs if breastfeeding or P+E OCPs if not breastfeeding b/c E decreases milk production, all other contraceptives are fine except for those the rely on cervix like cap or diaphragm b/c cervix still has abnormal shape)