**General**

**Reproductive Physiology**

**Menstrual Cycle**
- Endometrium sloughs off, then body starts to increase thickness of endometrium, gets ready for implantation of the ovum, if implantation doesn’t occur, it sloughs off and starts over again
- Follicular phase/Proliferative = begins cycle day 1 and ends with LH surge
  - Early: thin endometrium, not much happening in ovary, thickening of endometrium & cervical mucus
  - Mid: growth of a cohort of follicles (increase as estradiol level increases)
  - Late: dominant follicle is selected and the rest undergo atresia (oocyte grows inside follicle)
  - Mature size of follicle is 20-26mm
  - Leutinizing hormone has a peak around day 13 – LH surge pops ovary open, triggered by rising estradiol levels
  - This phase can change in length, luteal phase does not
- Ovulation: 14 days prior to period (regardless of how long the cycle is)
  - Caused by LH surge (10-fold increase)
  - Oocyte has its first mitotic division and is released 24-36 hrs after surge
  - Granulosa cells surround oocyte, become leutinized and start secreting progesterone
  - May cause a temperature spike (need to use basal thermometer)
- Luteal phase = last 14 days (progesterone rises in luteal phase (pre-gestation)
  - Begins with LH surge and ends with onset of menses
  - Lasts 14 days (fixed amount of time)
  - Progesterone level rises via corpus luteum (secretes estrogen as well)
  - Organization of endometrial glands from progesterone (become ready for implantation of fertilized oocyte)
  - Eventually there is a decreases in progesterone signal from GnRH, blood supply to endometrium gets smaller, it sloughs off and menses ensues
- Once the endometrium sloughs off, the pituitary starts releasing LH and the ovary starts producing estrogen

**Ovarian Cycle**
- Primary follicle begins producing estrogen
- Secondary follicle produces estrogen and progesterone
- Graafian follicle develops with zona pellucida $\rightarrow$ secondary oocyte released
- Remnant of corpus luteum $\rightarrow$ corpus albicans

**Adolescent Menstruation:**
- Cycles between 21 and 45 days (high variation)
- Initial cycles occur from negative feedback
- Age at menarche = when positive feedback occurs
- Day 1 of a cycle is the first day of menstruation

**Normal Menstrual Cycle**
- Duration of flow: 2-7 days
- Volume of flow: 20-45 ml (abnormal >80ml)
- Length of cycle: 21-35 days
- Cycles most consistent from 20-40 years old
*Anovulatory cycles are the ones that get messed up

**Definitions**
- Oligomenorrhea: Periods that are further than 35 days apart
- Polymenorrhea: periods that are less than 21 days apart
- Amenorrhea: absence of menstruation for at least 3 cycle lengths (6 months)
- Menorrhagia: regular intervals, but excessive flow and it lasts a long time
- Metrorrhagia: irregular intervals with frequent bleeding (between periods)
- Menometrorrhagia: irregular interval and excessive volume and duration of flow

**Gonadotropins and Hormones**
- From the anterior pituitary
  - FSH: recruits a follicle in an ovary to ovulates
  - LH: luteinizing hormone (LH surge causes oocyte in dominant follicle to undergo its first myotic division)
- Estrogen: secreted by the ovary
- Progesterone: secreted by the corpus luteum
  - Corpus Luteum: “yellow body” the remnants of an ovarian follicle after ovulation has occurred. The cells enlarge and begin secreting progesterone, the dominant female hormone during the second half of the menstrual cycle. Some estrogen is also secreted
  - Corpus Albicans is the scar tissue that replaces the corpus luteum, caused by the drop in LH levels

**The menstrual cycle**

![Diagram of the menstrual cycle](image-url)
**Uterine Embryonic Development**

- Formed from the mullerian or paramesonephric ducts, these develop laterally in the fetus and develop and fuse to make the uterus; if something goes wrong with this fusion, you may end up with a bifurcated uterus, two cervixes, etc.
- If the sertoli cells are secreted during embryonal development, the uterus regresses and you get a boy instead of a girl.

**Primary Amenorrhea**

- Absence of spontaneous menstruation by age 16 (gonadal agenesis, androgen insensitivity, imperforate hymen).

  - **Pathophysiology**
    - Type 1: Gonadal agenesis
    - Type 2: Androgen insensitivity
    - Type 3: Endocrine tumor
    - Type 4: Imperforate hymen

  - **Clinical Presentation**
    - Type 1: No secondary sex characteristics
    - Type 2: Breast development but no pubic or axillary hair
    - Type 3: Incomplete secondary sex characteristics
    - Type 4: Normal secondary sex characteristics

  - **Diagnosis**
    - Pregnancy test
    - Serum FSH, estrogen, prolactin, testosterone levels
    - Progesterone challenge test
    - Thyroid studies, MRI (pituitary or pelvis), genetic testing, pelvic and transvaginal US.

**Secondary Amenorrhea**

- In a woman who has previously menstruated = absence for 6 months or longer.

  - If estrogen is normal → Asherman’s or PCOS, low estrogen tumor, stress, sheehan’s, premature ovarian failure
  - Weight loss, excessive exercise
  - Galactorrhea may be present (indicates a prolactinoma)

- Tests → b-hcg, prolactin, TSH, FSH, estrogen, testosterone, transvaginal u/s

**Osteoporosis**

- Lifestyle measures should be adopted universally to reduce bone loss in postmenopausal women → adequate calcium and vitD, exercise, smoking cessation, counseling on fall prevention, avoidance of heavy alcohol use
  - 1200mg elemental calcium and 800 international units of vitD

- In addition to non-pharmacologic therapy, if someone has a T-score of <-2.5, treat with a pharmacologic agent

- If a woman is high-risk and post-menopausal women with osteopenia (-1 to -2.5), pharmacologic therapy is recommended

- 1st line = oral bisphosphonates (alendronate or risedronate)
  - Patients who have esophageal disorders (achalasia, strictures etc), GI intolerance to oral bisphosphonates, or inability to sit up for 30-60 min shouldn’t take oral bisphosphonates (can be IV)
  - Can also be treated with teriparatide (PTH hormone) or denosumab

- For patients starting on therapy, get a DXA of the hip and spine after 2 years looking at bone mineral density

- >65yo or <65yo with risk factors should get DEXA scan (no more than q2yrs)

- Tx: Calcium & Vit D supplementation, bisphosphonates, SERMs, calcitonin

**Domestic abuse/inter-partner violence/sexual assault**

- IPV → 10-69% of women
- Actual OR threatened psychological, physical, or sexual harm
- Often undiagnosed
- Risk factors → younger age, lower SES, family hx or personal hx of violence

- Clues:
  - Inconsistent explanation of injuries
  - Delay in seeking treatment
  - Frequent ED visits
  - Missed appointments
  - Late initiation of prenatal care
  - Repeated abortions
  - Medication nonadherence
  - Inappropriate affect
  - Overly attentive or verbally abusive partner
  - Social isolation
  - Reluctance to undress/have exam

- IPV is associated with overall poor health
- Common to have PMS, STDs, HIV, unintended pregnancy, chronic pelvic pain
- Also IBS, chronic pain, headaches, MSK pain
- Depression, SI, anxiety, eating disorder, substance abuse, PTSD, dissociative disorder

**Table 2: Classification of Abnormal Uterine Bleeding**

| P — polyph | C — coagulopathy |
| A — adenomyosis | O — ovulatory dysfunction |
| L — leiomyoma | E — endometrium |
| M — malignancy | I — iatrogenic |
| N — not yet classified |
### PMS
- 70% of women, debilitating in 10-40%, PMDD in 4% (dysfunction of daily living), associated with post-partum depression, goes away after menopause
- Most common symptom is mastodynia (can be treated with bromocriptine)
- Mood symptoms: irritability, sleep, anxiety, appetite changes (SSRIs started mid-cycle through first day of menses)
- Fluid retention → edema, weight gain, breast pain, bloating, constipation, and back ache (treat with spironolactone)
- Rule out thyroid problems, symptoms must begin 1-2 wks before menses (luteal phase), and and 1-2 days after the onset of menses, 2 consecutive cycles, require medical advice
- Must have a 7-day symptom free period in the follicular phase
- Better with OCPs, limit caffeine, tobacco, chocolate, sodium, stress, try cognitive therapy and aerobic exercise
- Over 150 symptoms

### Menopause
- Mean age is 51 (between 44-55) — family history is important
- Premature may be caused by genetics, mosaicism, autoimmune, mumps, smoking
- Surgical menopause → give estrogen till age 45
- Contraindications to treatment = undiagnosed vaginal bleeding, estrogen dependent tumors, VTE
- No hysterectomy, you need estrogen & progesterone
- Don’t give hormones for more than 3-4 years (DON’T START LATE ~5rs, increased risk of stroke/MI)
- SSRI, gabapentin, clonidine, soy
- Diagnosis → waist circumference, basal cell vaginal scrapings, low estrogen, no rugation, dry
- You CAN get pregnant during menopause
- Progestin challenge test → give for 10 days and the withdrawal (no bleeding = menopause)
- Hot flashes for 3-4 years (80%), some for 10
- Worse in thin, dark skinned women, alcohol, stress, smoking, spicy foods
- Vasomotor resolve within 2-3 yrs (3-6 months with estrogen therapy)
- First cycles get shorter and closer together, then they lengthen out

### Perimenopause & Menopausal Symptoms
- Average age of menopause = 51yo (~44-55yo)
- Premature menopause is <40yo
- Perimenopause lasts ~3-5yrs
- Sx:
  - Vasomotor sx (hot flashes) causing tiredness, insomnia, irritability → usually resolve in 2-3yrs, 3-6wks with estrogen replacement therapy
  - Urogenital atrophy causing poor lubrication, dyspareunia, dysuria, urge incontinence
  - Osteoporosis caused by accelerated bone loss
  - Sleep cycle changes
  - Skin thins, facial hair may increase, hair loss may increase, nails become brittle
  - Confusion, lethargy, depression, declined libido, loss of memory
- Dx: FSH >30miU/mL

### Premenstrual dysphoric disorder
- Repeated experiences of significant depression and related symptoms the week before menstruation (no longer in the DSM-V)
  - Sx of anger, irritability, anxiety/tension, depressed mood
  - Sx most severe during the 4 days before and first 2-3 days of menses
  - SSRIs → Agents: citalopram, escitalopram, fluoxetine, paroxetine (Paxil?), serotonin
    - A/Es – weight gain, drowsiness, insomnia, *sexual dysfunction, anxiety, HA
    - May be taken daily or luteal phase
  - SNRIs → Agents: Venlafaxine
  - CHCs – monophasic EE and drospirenon (Yaz), continuous cycle EE and levonorgestrel

### Postpartum Physiological Changes
- AKA puerperium → begins with the delivery of the baby and placenta, the end is less well defined but is often considered to be 6-8 wks after delivery (but some changes take up to a year)
- Shivering → “rigors” occur in 25-50% of women
- Uterine involution → ie contraction to get back to normal size (also helps minimize blood loss/hemorrhage), fundus should be nontender and firm
  - A boggy uterus with heavy vaginal bleeding suggests inadequate contraction (atony)
  - Fundus should be at the umbilicus within 24 hours of delivery, midway between symphysis and umbilicus within one week, and should be non-palpable by 2 wks
- Lochia → Should all pass over the course of a month
- Cervix → soft and floppy (normalizes at 2-3 months)
- Abdominal wall → diastasis recti may persist
- Hormones → Beta Hcg is usually gone within 2-4 wks after term delivery but can take longer, the concern in women with rising hcg levels postpartum is gestational trophoblastic disease
  - Gonadotropins and sex steroids are at low levels for the first 2-3 weeks, get period at 45-64 days
  - Breastfeeding delays the return of ovulation (prolactin induced inhibition of GNRH)
  - Some have hot flashes in postpartum period
- Skin & Hair → striae if present fade to a silvery color
  - Cloasma resolves (mask of pregnancy)
  - Hair loss (telogen effluvium) can occur 1-5 months after delivery, should cease at 6-15 months
- Weight Loss → ½ of gestational weight gain is lost in the first 6 wks, and the rest over 6 months
  - Mean weight loss from delivery is 13lbs, additional loss of fluid adds up to 5-15 lbs
- Other → hemorrhoids, urinary and anal incontinence, varicose veins, breast engorgement, afterpains, headaches, pruritis, thyroid disease (8%)
**Menopause Therapy**

- Lifestyle modifications → regular exercise
- No uterus → estrogen alone
- Intact uterus → estrogen + progesterone combination (estrogen + progesterone can increase risk for breast cancer)
- Selection of products
  - Urogenital sx only = vaginal preparations
  - Vasomotor & urogenital sx = systemic estrogen or combo therapy
- Osteoporosis: Calcium & Vit D supplementation, bisphosphonates, SERMs, calcitonin

**Estrogen therapy**

- Oral Estrogens (first pass effect)
  - Protect bone and relieve vasomotor sx in most women
  - Increase sex hormone-binding globulin
  - Ex: Estrace, Premarin, OCPs
- Transdermal patch = **preferred route of systemic therapy**
  - Avoids first pass liver metabolism
  - Less likely to affect sex hormone binding globulin vs. oral therapy
  - Deliver estradiol at continuous rate
- Topical Estrogen = Convention, but variability in drug absorption has been noted (contact precautions with children/pets)
- Vaginal estrogen = used for tx of urogenital sx
  - Femring vaginal ring = systemic
  - Lower systemic absorption vs. oral and transdermal formulations
  - Products: Vaginal tablets (Vagifem), Vaginal rings (Estring), Vaginal creams (Estrace)
- Unopposed estrogen → endometrial cancer

**Progestin products:**

- Mechanism – reduce estradiol receptor concentrations and decrease estrogen bioavailability
- Agents: Provera, Prometrium Aygestin
- Adverse effects = irritability, weight gain, bloating, headache

**Combination products**

- Cyclic (sequential therapy)
  - Estrogen admin daily, progestogen co-admin 12-14d
  - Progesterone causes scheduled withdrawal bleeding in ~90% women
- Agents: Premphase, Combipatch, etc.
- Continuous therapy → Increased risk for CVD, breast cancer, cognitive changes, perhaps migraine

**Risks of hormone therapy**

- CV disease: Increased risk in women 50-79yr old receiving combo HT, Earlier initiation asx with less risk than late (10yrs or more after menopause)
- Breast cancer: Increased risk of invasive breast cancer with combine estrogen-progesterone oral therapy
- Endometrial cancer: Estrogen therapy alone given to women with an intact uterus increases uterine cancer risk
- Ovarian cancer: Risk increased in women receiving estrogen-only therapy for more than 10yr
- VTE: Women taking oral estrogen therapy have a 2 fold increase in risk for VTE

- Zoloft & Prozac help sx of hot flashes/vasomotor in menopause

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**Breast**

**Histological & Physiological Changes in Breast During Lifespan**

- Mammary ridge forms at fetal development (milk duct system)
- Shrinking of the mammary glands begins around age 35
- Changes during menstrual cycle
  - Each month, estrogen stimulates the growth of milk ducts in the breasts, then progesterone stimulates formation of the milk glands (lead to tenderness)
  - Texture changes due to glands enlarging
- Pregnancy & Lactation
  - Areolas swell, some women have soreness or tingling of the nipples (as the duct system grows)
  - Breasts are capable of producing milk at month 5-6
  - Darkening of the areola may occur
- Menopause
  - Decrease in estrogen leads to reduction in glandular tissue of breasts, they become dehydrated and inelastic → sagging
  - Hormones therapy may cause tenderness

**Breast Abscess**

- Localized collection of pus in the breast tissue, usually occur when mastitis or cellulitis does not respond to abx treatment
- Mostly African americans, obese patients, and smokers
- Localized painful inflammation of breast with fever and malaise, fluctuant, tender, palpable mass (may develop up to a month after mastitis)
- Diagnosis made with u/s, u/s may be used for guided aspiration of the collection
- Can culture breast milk to select abx
- Most caused by staph (can be MRSA) → if it is recurrent, it may be anaerobic
- Tx = abx and drainage (needle or surgical)
- Abx = dicloxacillin or cephalixin, if MRSA → Bactrim or vanco
### Paget's Disease
- A form of DCIS that extends from nipple ducts into the contiguous skin of the nipple and areola.
- Nipple can appear fissured, ulcerated and oozing, can look like dermatitis
- Hallmark is involvement of the epidermis by malignant cells, called Paget cells.
- Persistent scaling, eczematous, or ulcerated lesion involving the nipple/areolar complex
- The hallmark is the presence of malignant intraepithelial adenocarcinoma cells (paget cells) within the epidermis of the nipple
- It is associated with an underlying breast cancer in 85-88% of cases (often without a breast mass)
- Diagnosis is made with a punch or full wedge biopsy
- Both mastectomy and breast conserving surgery followed by whole breast radiotherapy (RT) are acceptable treatment options

### Inflammatory Breast Cancer
- **Painless** erythema (usually at least 1/3 of breast), **Peau d'orange** changes may be present, **thick and firm, not painful**
- Rare and aggressive form of breast cancer (1% of all breast cancer)
- Characterized by diffuse erythema and edema involving 1/3 or more of the skin of the breast
- Diagnosis based on the presence of the following:
  - Rapid onset of breast erythema
  - Edema and peau d'orange → Evaluate with diagnostic mammogram and targeted ultrasound.
  - Duration of no more than 6 months
  - At least 1/3 of the breast
  - Pathologic confirmation
- For diagnosed cases, get CT of chest, abdomen, and pelvis (with contrast), and bone scan since many patients have metastatic disease at presentation, may do an u/s guided fine needle aspiration (FNA) if axillary lymph nodes are palpable
- If it is non-metastatic → neoadjuvant chemo followed by loco-regional treatment
- Suggest radical mastectomy

### Mastitis
- Inflammation of the breast (most frequently caused by bacteria that enters during breastfeeding)
- Most common during nursing
- Staph aureus enters through fissures in nipple
  - Sudden onset
  - Extremely painful
  - Obvious cellulitis
- Treated with antibiotics
- Incision & drainage or attempt at aspiration if abscess involved

### Mastodynia
- Most pain is associated with benign conditions such as cyclical pain and fibrocystic changes and cysts
  - Worse during luteal phase, rarely associated with breast cancer
- Most common in premenstrual women (cyclical)
- Peaks in times of hormonal irregularity, ie. teens/early 20s and again during peri-menopause (late 40s), generally quiets after menopause
- Usually worse before period and better after
- For any women with a suspicious clinical exam or history, a mammogram and u/s are performed
- For women <30, usually it is just an u/s if pain is cyclical
- For women with a focal finding (mass, tenderness) and concerning hx, a mammogram and targeted u/s are performed
- Tx → analgesics and supportive bras can be helpful
  - Can be treated with tamoxifen or danazol in severe cases, but these drugs have serious adverse effects

### Breast Mass Differential diagnosis:
- Breast cancer
- Fibroadenoma
- Phyllodes tumor
- Cyst
- Lipoma
- Fat necrosis/scar tissue
- Normal breast tissue

### Paget's Disease
- A form of DCIS that extends from nipple ducts into the contiguous skin of the nipple and areola.
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### Simple Cysts
- Fluid filled sac (filling of ducts and lobules), feels like fibroadenoma (mobile), but **tender to palpation**
- Confirm with u/s, can aspirate if it causes pain (simple = fluid only, complex = solid as well)
- Can occur at any age, but usually during reproductive years and go away with menopause

### Fibroadenomas
- Common benign tumor of breast, composed of fibrous and glandular tissue
- Sharply circumscribed, smooth borders, freely mobile, non-tender
- Occurs during reproductive years, do NOT increase cancer risk (biopsy just in case to rule out cancer)
<table>
<thead>
<tr>
<th>Nipple Discharge</th>
<th>Fat necrosis</th>
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| • Generally benign, physiologic – usually bilateral from multiple ducts with manipulation  
  o Benign = bilateral and multiple ducts, pathology = one duct, unilateral  
  • 90% of biopsy = *papilloma* (most common cause of bloody discharge) – usually <1cm, branching, grows into lactiferous ducts (too small to feel)  
  • Also could be pituitary tumor (check prolactin) | • Essentially scar tissue  
  • Focal necrosis of fat in the breast followed by inflammation, sharply localized process  
  • History of trauma, surgery or radiation therapy  
  • The fibrosis of tissue can create a palpable mass that can be confused with carcinoma.  
  • Can appear as a *calcified cyst (oil cyst)* on mammogram and ultrasound. |
| Phyllodes Tumor                                                                 | Mammogram (diagnostic & screening)                                             |
| • RARE, any age, looks like fibroadenoma **but it keeps growing**  
  • Low grade → may recur locally, high grade → can metastasize to distant sites in 1/3 of cases (malignant phyllodes, need to come out, **not technically cancer**  
  • Sometimes called “cytosarcoma phyllodes” | **Calcifications on Mammogram**  
  • Due to secretory material or necrotic debris, too small to palpate, usually benign (cysts, fibrocystic changes, fat necrosis, hyalinized fibroadenomas)  
  • Cancer = small, clustered, linear, branching  
  • Benign = scattered, layered, coarse, dystrophic |
| Breast Erythema Differential Diagnosis:  
  *Cellulitis* → will be accompanied by pain, sudden onset  
  *Fluid congestion/edema* → usually in someone who has had breast cancer in the past or radiation, erythema improves when patient is supine for several minutes (better in the morning)  
  *Inflammatory breast cancer* → painless erythema (usually at least 1/3 of breast), Peau d’orange changes may be present  
  *Dermatitis* → accompanied by pruritis | **Mammographic Density**  
  • White = cancer, invasive cancers usually present as mammographic density (speculated or irregular shape)  
  • Well circumscribed densities are mostly cysts or fibroadenomas |
| Atypical ductal hyperplasia (ADH) - High risk lesion  
  • Atypical ductal or atypical lobular hyperplasia (cells still look normal)  
  • Found on a breast biopsy  
  • Marker for increased risk of developing breast cancer **(just in the breast that it is found in)**  
  • If found on needle biopsy, excision of that tissue required to exclude possibility of surrounding breast cancer | **Lobular Carcinoma In-Situ (LCIS) - High risk lesion**  
  • Incidental finding on biopsy done for another reason.  
  • Rarely associated with calcifications and does not form a mass → **NOT cancer**  
  • LCIS is proliferation of one or more terminal ducts with cells that expand and distort the duct.  
  • LCIS is a marker for increased risk of developing breast cancer in **either breast.** |
| Ductal Carcinoma In-Situ (DCIS)  
  • Malignant population of cells that lack the capacity to invade through the basement membrane of the duct (non-invasive), contained within the wall of the milk duct  
  • Cells can spread through ductal system and produce extensive lesions involving an entire section of the breast  
  • If left untreated, DCIS will in some cases progress into an invasive cancer. **Check imaging to make sure biopsy didn’t miss invasive cancer.** | **Invasive Ductal Carcinoma**  
  • Most common type of breast cancer (70-80%), tumor cells arising in the milk duct have infiltrated through the wall of the duct into the surrounding tissue (just outside of the milk duct)  
  • Tumor cells now have potential to invade the lymphatic space, vascular space or perineural space, allowing for possible metastasis (treat more aggressively than DCIS) |
| Invasive Lobular Carcinoma  
  • Similar to invasive ductal, but appears differently histologically, hard to find since they have a more diffuse pattern/ more difficult to detect by physical exam or by imaging (snaky or nebulous)  
  • They are often larger than they appear on imaging. | **Breast Cancer Risk Factors**  
  • **Non-modifiable risk factors for breast cancer:**  
    o Advancing age  
    o Early menarche  
    o Nulliparity or Late first birth (30 years old +)  
    o Late menopause  
    o Family history of breast cancer  
    o History of atypical hyperplasia or LCIS on a biopsy  
  • **Modifiable risk factors for breast cancer:**  
    o HRT use after menopause (estrogen/progesterone)  
    o Excess body weight after menopause  
    o 3+ alcohol containing drinks per week  
    o Night shift work |
Receptor status

1) Estrogen Receptor (ER)
- If a cancer is ER+, it has working estrogen receptors, where circulating estrogen can bind and promote cell growth and division (much like a healthy breast cell).
- If a cancer is ER-, it no longer has functioning estrogen receptors.
- An ER+ breast cancer is good because it can be treated with endocrine therapy (SERM or aromatase inhibitor). ER is reported on invasive cancers and DCIS.

2) Progesterone Receptor (PR)
- If a cancer is PR+, it has functioning progesterone receptors, where circulating progesterone can bind and promote cell growth and division.
- If a cancer is PR-, it no longer has functioning progesterone receptors.
- A PR+ breast cancer can be treated with endocrine therapy (SERM or aromatase inhibitor). PR is reported on invasive cancers.

3) Her2/neu
- If a breast cancer has too much of a growth promoting protein called Her2/neu, it is considered Her2/neu+.
- Her2/neu negative if the cancer doesn’t put a lot of this protein out.
- It is a genetic change in the cell that leads to Her2 positivity.
- Her2/neu+ cancers tend to grow more aggressively.
- Her2/neu status is reported on invasive cancers.

Breast cancer treatment based on receptor status

- ER or PR positive cancers
  - Tend to grow more slowly than hormone negative cancers, prognosis better in short-term but some come back many years after treatment.
  - Can be treated with endocrine therapy.

- If ER and PR are both negative:
  - Do not respond to endocrine therapy, tend to be more aggressive.
  - If recurrence is going to occur, will usually occur within 1-2 years after treatment, and if they don’t recur then, they probably won’t at all.
  - More common in pre-menopausal women.

- Her2/neu Positive Cancers
  - Chemotherapy with drugs that target Her2 are almost always recommended:
    - Herceptin (Trastuzumab) and Pertuzumab.
  - Herceptin given concurrently with standard chemotherapy, (every 3 weeks for a year)
  - Pertuzumab given concurrently with Herceptin in neoadjuvant trials.
  - Herceptin binds to her2 receptors to mark cell for destruction by immune system. Also enhances effect of standard chemotherapy.

- Triple Negative
  - ER negative, PR negative and Her2/neu negative.
  - Endocrine therapies don’t work.
  - Tend to be more aggressive tumors.
  - No good options for therapy, chemotherapy is still an option for these tumors (only option).

Treatment Recommendation based on node status, hormone receptor status, age of patient, and sometimes Oncotype Dx score.

- Surgery: mainstay of tx
  - Lumpectomy: removing the tumor and some surrounding tissue.
  - Mastectomy: removing all of the breast tissue (does not include pectoralis muscle).
  - Sentinel Node dissection: removing the few lymph nodes that are the main “drainers” of the breast.
  - Full axillary node dissection: removing level I/II axillary nodes.
- Radiation
  - External beam radiation to whole breast is standard of care after lumpectomy. Usually started about a month after surgery, each week for 6 weeks.
- Chemotherapy → adriamycin
  - Adjuvant chemotherapy (given after surgery to reduce risk of recurrence).
  - Neoadjuvant chemotherapy (chemo given up front to reduce tumor size prior to surgery for better cosmetic result).
- Oncotype Dx → A genomic test that determines how likely a cancer will respond to chemotherapy.
  - Specimen sent for oncotype (result takes 2 weeks) and comes back with “recurrence score”. If low risk, chemotherapy not offered. If intermediate or high risk, chemotherapy offered.
  - Indicated for women with stage 1 or 2, ER+, Her2/neu negative, node negative breast cancer.

Endocrine therapy for breast cancer

- For hormone positive tumors, daily oral medication to begin once all other treatment ends. Standard is to take it for 5 years. Reduces risk of recurrence by 50%.
- Pre-menopausal → Tamoxifen (SERM) decreases the risk of 50%, increases risk of blood clots and uterine cancer by 1%.
- Post-menopausal → Aromatase Inhibitor (these do a little better).

SERMs (selective estrogen receptor modulators): can be used in pre & post-menopausal women, block estrogen receptors in breast.
- Tamoxifen: approved for treatment of ER or PR+ invasive breast cancer AND for prevention of breast cancer in high risk patients.
-Raloxifene (Evista): just as good as tamoxifen and doesn’t add the risk to the uterus, but does still increases clot risk, evista is just for prevention.

Aromatase Inhibitors: block the enzyme aromatase which converts androgens into estrogen in post-menopausal women.
- Arimidex (anastrozole), Femara (letrozole), Aromasin (exemestane).
**Breast Cancer Screening**
- "Average risk": no personal history of breast cancer, no personal history of LCIS or atypical hyperplasia, no known genetic predisposition, no first degree relative with breast cancer, no history of mantle radiation between age 10-30
- Women 40-44 → option to begin annual mammograms
- Women 45-54 → mammograms every year.
- Women 55+ → switch to having a mammogram every other year, or have the choice to continue yearly screening.
- **No clear benefit to clinical breast exam or breast self-exam so no longer recommended.**

**Bottom line:**
- Mammograms save lives, women should get them
- A discussion regarding when to start and how often to have them can be an individual decision
- Clinical breast exams and breast self-awareness have potential to detect cancer and can be recommended

**Uterine/Cervix/Adnexa/Ovaries**
- **Average uterus** = 7 cm and 70 g (size of lime)
- Uterine stripe: <4 mm normal, if >4 concern for hyperplasia
  - Tolerate up to 11 mm if no bleeding, concern for neoplasia when >4 mm and presence of bleeding
- **Leiomyomas**
  - Commonly occur in 4th decade of life
  - Depend on estrogen, appear with increased frequency in pts with endometrial hyperplasia, anovulatory states, estrogen-producing ovarian tumors
  - 4x increase risk for endometrial cancer, also a risk for spontaneous abortion
- **Signs & symptoms**
  - Asymptomatic, pelvic mass, pelvic pressure, menorrhagia, metrorrhagia, intermenstrual bleeding, dysmenorrhea (bleeding is most common presenting sx)
- **Diagnosis**
  - US, D&C, saline hysteroscopy, hysterosalpingography, laparoscopy
- **Management**
  - Observation vs. myomectomy vs. hysterectomy vs. D&C
  - Other options: uterine artery embolization, endometrial ablation, GnRH agonist, mifepristone
- **Dysmenorrhea**
- **Primary Dysmenorrhea**
  - Painful cramps without underlying pathology, physical exam is normal (ages 20-24 – peaks in late teens/twenties)
  - Prostaglandin E2 → painful smooth muscle contractions, N/V/D, reduce blood flow
  - Usually starts within 3-6 months of menarche
  - Cramps in lower central abdomen, radiating to back or thighs, **beginning around onset of menses, last 1-3 days**
  - Treatment → take prostaglandin inhibitor before cramps start
  - NSAIDs (2-3 days), heat, bed rest, OCPs, tocolytic agents, CCBs, progestogens
  - ***Membranous dysmenorrhea → entire endometrial cavity sheds at once, very rare***
- **Secondary Dysmenorrhea**
  - Due to pathology (endometriosis, PID, stenosed cervix, fibroids, polyps)
  - Usually affects women **over 25** and incidence increases with age, may involve prostaglandins
  - Treat underlying condition (remove IUD etc), hysterectomy, D&C, laparoscopy for diagnosis and treatment
  - Symptoms may also include bloating, menorrhagia, dyspareunia
  - ***Adenomyosis → endometrial tissue in the uterine wall (boogy uterus)**

**Endometriosis**
- Endometrial tissue is found outside endometrial cavity → commonly in pelvis or ovary
- Most commonly occurs in nulliparous women in late 20s or 30s
- Infertility is common
- S/sx → dysmenorrhea, dyspareunia, dyschezia, spotting, pelvic pain, infertility, tender nodularity of dul-de-sac and uterine ligaments, fixed uterus
- Dx → US and laparoscopy
- Treatment → NSAIDs, combined OCPs or progestins, surgery (danazol or GnRH agonist around surgery can improve fertility)

**High Risk Screening**
- **Definition of "high risk":**
  - Has a lifetime risk of developing breast cancer of 20% or more based on risk assessment models.
  - Has a known genetic predisposition to developing breast cancer (ie. BRCA 1 or BRCA 2 mutation)
  - Has a first degree relative with a known genetic mutation, and has not yet had testing herself.
  - Had chest wall radiation between ages 10 and 30.
- **High risk screening**
  - Clinical breast exam (CBE) q 6 months
  - Annual mammogram beginning 10 years before the youngest relative’s age at breast cancer diagnosis and no later than age 40. (BRCA 1 and 2 mutation carriers begin at age 30)
  - Annual screening breast MRI recommended for women with known genetic mutation (ie. Begin at age 25 for BRCA 1 or 2) and for women with history of mantle radiation between ages 10-30.
  - Annual screening breast MRI to be considered for women with lifetime risk of breast cancer > 20%.

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  - Dx → US and laparoscopy
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### Cervical Polyps
- Common, especially if >40
- Small, pedunculated, benign neoplasms of cervix composed of vascular connective tissue stroma covered by epithelium
- Commonly arise via focal hyperplasia of endocervix, and protrude from the cervical canal out of the external os
- Relatively common, rare before menarche but may arise after menopause
- Sx → asymptomatic, intermenstrual bleeding, postcoital bleeding
- Tx → Polyps should be removed when symptomatic (eg, bleeding, excessive discharge), large (≥3 cm), or appearing atypical → pathology should be done after removal

### Cervical Papillomas
- Very rare
- Arise from the ectocervix near the squamocolumnar junction (transformation zone) and are usually less than 1 cm in diameter. Microscopically, a central core of connecting tissue supports a covering of squamous cells.

### Abnormal/Dysfunctional Uterine Bleeding
- Abnormal bleeding in the absence of an anatomic lesion (polyps etc.), usually an axis problem
- Very common (10% of women), occurs shortly after menarche and around menopause (when ovulation is irregular)
- Most common cause = anovulatory bleeding, could be due to PCOS, obesity, adrenal hyperplasia
- Endometrium gets very thick without feedback signal to bleed, and then it occurs randomly
- Usually an unremarkable physical exam, but excessive bleeding (>80ml, <1 pad/hr)
- Do a CBC (anemia), PT, PTT, b-hcg, TSH, progesterone, LFTs, FSH, prolactin
- Maybe do a pap, endometrial biopsy (cancer), D&C (diagnostic and curative)
- Treatment → Iron replacement, treat acute hemorrhage with high dose IV/PO estrogens, if recurrent do cyclic estrogen/progestin (OCP) to the last 10-15 days of the cycle (may normalize in 3-6 months)
- If young, do progesterone only treatment
- If refractory to everything → hysterectomy or endometrial ablation

### General Characteristics
- Abnormal uterine bleeding in the absence of an anatomic lesion, usually caused by a problem with the hypothalamic-pituitary-ovarian hormonal axis
- Most commonly occurs shortly after menarche and during perimenopause because of anovulatory cycles (anovulatory bleeding is the most common cause)
- Other causes include PCOS, exogenous obesity and adrenal hyperplasia

### Pathophysiology
- Endometrium gets thicker and thicker without the regular feedback signal to bleed, happens randomly

### Clinical Presentation
- Abnormal bleeding with an unremarkable physical examination in young or perimenopausal women
- Excessive menstrual bleeding (>80ml - soaking through more than a pad an hour)

### Diagnosis/Lab Studies
- CBC (iron studies), PT and PTT, urine hCG, documentation of ovulation, thyroid function tests, serum progesterone, LFTs
- Prolactin and serum FSH levels
- MAYBE a pap smear, endometrial biopsy, pelvic u/s hystersalpingography, hysteroscopy, D&C

### Treatment
- Depends on bleeding severity (iron/volume replacement)
- Acute hemorrhage = IV or PO high-dose estrogens
- Cyclic estrogens with progestins added to the last 10-15 days of cycle for 3-6 months may establish a normal pattern
- OCPs (older), cyclic progestins alone (younger)
- D&C may be diagnostic AND curative
- Refractory: endometrial ablation or vaginal hysterectomy

### Dyspareunia
- Pain with intercourse, vaginismus, non-coital sexual pain (caused by non-penetrative sexual stimulation)
- Prevalence of painful intercourse up to 22%
- Risk factors → history of PID, depression, and anxiety
- Diagnosis is clinical, based on self-report
- A detailed history of the pain and PMH help assess anatomic sources, systemic, and psychosocial issues
- Can lead to significant anxiety regarding pelvic exams
- Goal of exam is to localize and recreate the pain
- Diagnostic studies → pH, microscopy, testing for infection, biopsy, pelvic imaging

### Tubo-ovarian Abscess
- Usually a complication of PID
- The risk factors for TOA are the same as for PID, and include the following: multiple sexual partners, age between 15 to 25 years, and a prior history of PID
- Typically polymicrobial, common organisms include Escherichia coli, aerobic streptococci, Bacteroides fragilis, Prevotella, and other anaerobes, such as Peptostreptococcus
- Sx: acute lower abdominal pain, fever, chills, and vaginal discharge (same for PID along)
- Dx: US, CT, leukocytosis, increased ESR/CRP
**PCOS**

- **General Characteristics**
  - Formerly known as Stein-Leventhal syndrome, it is the most common cause of androgen excess and hirsutism
  - Patients with PCOS have bilaterally enlarged polycystic ovaries, amenorrhea or oligomenorrhea, and infertility
  - Patients usually have a normal puberty and adolescence, followed by progressively longer episodes of amenorrhea
  - Irregular menstrual cycles, ovulation is occurring irregularly (if at all)
  - Effects 5-10% of women, Increased risk of DM and OSA, sx start in puberty usually, usually fewer than 6-8 periods a year

- **Pathophysiology**
  - High levels of androgens and LH and ovulation is not triggered
  - Hypothalamic pituitary dysfunction and insulin resistance, although the pathophysiology is not entirely clear
  - A genetic predisposition exists, patients are at increased risk for endometrial hyperplasia and carcinoma because of unopposed estrogen stimulation

- **Clinical Presentation**
  - Half of patients have hirsutism and show truncal obesity, male pattern baldness
  - Patients usually present for treatment of hirsutism or infertility, intractable acne, or menstrual irregularities (oligomenorrhea and amenorrhea), dark and discolored skin spots
  - Acanthosis nigricans sometimes occurs, hidradenitis suppurativa
  - Impaired glucose tolerance is present in 30%, DM type 2 is present in 8%

- **Diagnosis /Lab Studies**
  - Ultrasonography may demonstrate “string of pearls” appearance within the ovaries
  - Lab testing reveals mildly elevated serum androgen levels, increased LH/FSH ratio, lipid abnormalities and insulin resistance, pregnancy test, prolactin level, TSH
  - Women with PCOS have high levels of circulating insulin
  - Diagnosis is 2/3:
    - 1) irregular menses caused by anovulation or irregular ov
    - 2) evidence of elevated androgen levels
    - 3) polycystic ovaries on pelvic u/s

- **Treatment**
  - Weight reduction of 10% improves hirsutism, lipid and glucose parameters, and fertility
  - Hirsutism is treated with androgen lowering agents including OCPs
  - Metformin + progestin (may help with fertility)
  - Infertility usually is treated with clomiphene citrate, in refractory cases, wedge resection of ovary is used
  - Lipid/insulin abnormalities need to be managed
  - Get: blood glucose, lipid panel, if hirsutism (testosterone DHEA-S)

**Ovarian Cysts** → the most common ovarian growth

- Typically asymptomatic masses with pain and menstrual delay or hemorrhage d/t rupture
- Dx: US (mobile, simple, fluid-filled)
- Large (>8cm?) or persistent cysts require laparoscopic eval

**Functional cysts** →

- Functional cysts = have to do with ovulation (frequent in premenopausal women), often asymptomatic, caused by a follicle that never ruptures, most will resolve without treatment (seen on U/S), can cause abdominal pain, nausea
- Benign > malignant, BUT as you get older malignancy is more likely (we take a post-menopausal woman cyst more seriously)

**Dermoid Cysts (teratoma)** →

- Most common kind in women between 20-40
- Made up of ovarian germ cells, may have hair, teeth, fat
- Mostly benign, very seldom malignant

**Post-menopausal Bleeding** →

- Ddx: atrophy *, polyps *, cancer, postmenopausal hormone therapy, endometrial hyperplasia, leiomyomatous uteri, adenomyosis, infection, post-radiation, anticoagulants, supplements, disease of adjacent organs
- Dx: EMBX, TVUS

**Nabothian Cysts**

- A discrete mucous-filled cyst that looks like a small translucent or yellow elevation on cervix
- Sometimes columnar endocervical epithelial becomes covered by squamous epithelium, trapping the mucous secretions & forming cysts
-Typically asymptomatic but can cause dyspareunia
-Tx (if symptomatic): excision, electrocautery, cryotherapy
-Pregnancy, menopause, cervicitis are risk factors
-Other types of cervical cysts = mesonephric, endometrial,

**Ovarian Torsion**

- GYN emergency, can result in ischemia to the ovary
- Mostly occurs in women of reproductive age
- Primary risk factor is an ovarian mass, and is most common if the ovary is >5cm (can occur in pediatric population)
- Classic presentation is acute onset of pelvic pain, N/V
- Pelvic u/s is the first line imaging study for suspected torsion
- A definitive diagnosis is made by direct visualization of a rotated ovary at the time of surgical evaluation
- Ddx: ectopic pregnancy, tubo-ovarian abscess, appendicitis

**Treatment** → premenopausal women = detorsion and ovarian conservation rather than salpingo-oophorectomy
- Cystectomy is performed if a benign mass is present, if necrotic ovary is present, salpingo-oophorectomy is performed

*Note: * indicates a non-English term.
## Ovarian Cancer

#### General Characteristics
- High-risk women are older, nulliparous, white, and have a positive family history of ovarian or endometrial cancer
- **5th most common cancer in US** women and 3rd most common gynecological malignancy with highest mortality (60% die in 5 years)
- 1/70 lifetime risk of ovarian cancer
- Indications for referral: Ascites, family hx, CA 125>200 in pre-men, elevated CA 125 in post-menopausal, mets, fixed pelvic mass in post-men
- Most deadly gyn cancer

#### Pathophysiology
- 10% = genetic
- 90% = spontaneous
- Hereditary ovarian cancer has 2 forms:
  - Breast and ovarian syndrome (BOC)
  - Hereditary nonpolyposis colorectal cancer syndrome (HNPCC)
- Hormonally active: lots of testosterone \(\rightarrow\) clit growth, lots of estrogen \(\rightarrow\) bleeding
- Mets \(\rightarrow\) diaphragm, lung, stomach, “omenta caking” (can be caused by TB)
- Survival depends on age & stage
  - <50 – 5 yr 40%
  - >50 – 5 yr 15%

#### Clinical Presentation
- Diagnosis is often delayed because of a lack of specific symptoms (pressure, pain, urinary, irregular, bowel)
- May present with ascites, abdominal distention, vague GI symptoms, or a fixed mass
- Signs of malnutrition or dehydration, lymph nodes and spleen, abdominal exam, pelvic, rectal, nodularity in cul de sac
- Look at extremities (cancer may cause DVTs)
- Most patients are diagnosed between 40 and 60 (average age is 55-60)

#### Diagnosis / Lab Studies
- The BRCA1 gene is associated in 5% of cases, cancer antigen 125 (CA-125) may be used to follow treatment, especially in postmenopausal women
- An association exists with mutations in the P53 tumor suppressor gene
- Transvaginal or abdominal U/S is useful in distinguishing benign from potentially malignant masses
- Alpha-feta protein
- LDH, hcg, testosterone level, estrogen level
- Tumor markers (CEA), renal and hepatic fxn, CA 125, Pelvic ultrasound, CT
  - CA-125 in a woman with a mass
    - 98% accurate in post-menopausal women
    - 49% accurate in pre-menopausal women
    - **Can be elevated in endometriosis, IBS, any inflammation
- Paracentesis (tissue/pathology)

#### Treatment
- This involves surgery plus chemo and radiation
- Optimal cytoreduction – tumors <1cm, chemo depends on grade

#### Risks
- Nulliparity, infertility, early menarche/late menopause (more cycles), endometriosis, genetic (family hx, BRCA1/2, Lynch syndrome II HNPCC), talc?
- Women of Ashkenazi jewish women with it have a 40% chance of having BRCA ½

#### Protective factors
- OCPs \(\rightarrow\) Long-term OCP may be protective because of ovulation suppression
- Pregnancy, tubal ligation, oophorectomy (anything that decreases cycles)

### Vagina/External Genitalia

#### Bartholin Cysts
- Obstruction of gland (leads to retention of secretions), very painful, commonly form infections or abscess
- Duct usually empties into vestibule, once they are blocked you are more likely to get another, **must drain the cyst**, placement of a Word Catheter is helpful
- Obstruction is often caused by local or diffuse vulvar edema.
- Bartholin cysts are usually sterile and the gland is not affected
- Abscess = when obstructed duct becomes infected \(\rightarrow\) requires drainage, E. coli common, MRSA increasing

#### Candida
- 75% of women have this at one time, risks are antibiotics, high sugar intake, DM, immunosuppression, pregnancy, tight or wet clothes
- **Lower pH \(\rightarrow\) pH <4.5**, may cause erythema, dysuria (burning) can be STI, KOH will show hyphae & bus
- Treat with 1 dose fluconazole (difulcan), give cream too!
- Typically candida albicans (90%), flabratea (10%)
  - Normal pH <4.5, itching, dysuria, white cottage cheese w/ vulvar erythema/edema, KOH prep
<table>
<thead>
<tr>
<th>Trichomonas</th>
<th>Atrophic Vaginitis</th>
</tr>
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<tbody>
<tr>
<td>• Most common non-viral STI in US (unicellular flagellate protozoan, will see PMNs on wet mount as well)</td>
<td>• Little to no rugae, little blood flow, thinning walls, smooth muscle relaxation $\rightarrow$ increased susceptibility to pathogens, UTI, most common cause of post-menopausal bleeding</td>
</tr>
<tr>
<td>• Affects lower urinary tract in women and men (50% of women ax, 90% of men ax)</td>
<td>• 4-5 years after menopause 25-50% of women experience atrophic vaginitis symptoms</td>
</tr>
<tr>
<td>• pH $&gt;5$, profuse frothy green discharge, vulvar irritation, dyspareunia, dysuria, petechia $\rightarrow$ strawberry cervix</td>
<td>• Caused by drop in estrogen $\rightarrow$ dryness, irritation, itching, burning, UTI, incontinence, decreased libido</td>
</tr>
<tr>
<td>• Can confirm diagnosis with DNA probe (Affirm test), or culture and sensitivity</td>
<td>• Risk for rectoceles/cystoceles</td>
</tr>
<tr>
<td>• Treat with metronidazole (flagyl), resistance is growing, cream does not work!</td>
<td>• Urinary tract $\rightarrow$ mucosal thinning, urethral shortening, weakening of the sphincter, decreased bladder capacity, increased post-void residual urine volume</td>
</tr>
<tr>
<td>•</td>
<td>• Treat with vaginal estrogen cream (30% of absorbed systemically)</td>
</tr>
<tr>
<td>•</td>
<td>• ↑ susceptibility to pathogens (tx w/ vaginal cream, but 30% systemically absorbed)</td>
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<thead>
<tr>
<th>Vestibulitis/ Vulvodynia</th>
<th>Folliculitis $\rightarrow$ infectious or noninfectious</th>
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<tbody>
<tr>
<td>• AKA localized vulvar pain syndrome</td>
<td>• Infections may be due to either a staphylococcal bacterial or dermatophyte fungal etiology.</td>
</tr>
<tr>
<td>• Persistent vulvar pain consistently and precisely localized to the vulvar vestibule during physical examination, has no identifiable cause, and has been present for at least three months</td>
<td>• The presentations for these two types of infection are similar, although fungal folliculitis almost always occurs in the setting of tinea cruris (ringworm) on the upper inner thighs, whereas bacterial folliculitis occurs de novo as isolated lesions.</td>
</tr>
<tr>
<td>•</td>
<td>• Both infections manifest as scattered or groups of perifollicular, small (2 to 5 mm), red papules, most commonly on the hairy areas of the mons pubis, inner thighs, and buttocks, often in shaved areas</td>
</tr>
</tbody>
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<tr>
<th>Bacterial Vaginosis</th>
<th>Public Lice (Pediculus pubis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Most common cause of vaginitis, pH $&gt;4.5$, decrease in lactobacilli (H2O2), increases in gardnerella (produce amines that lead to fishy odor that is worse after sex), attach to epithelial cell border to make clue cells, don’t culture!</td>
<td>• Pediculosis pubis is usually sexually transmitted, and can extend beyond the pubic area to involve other areas of the body, including the eyelashes (pediculosis ciliaris).</td>
</tr>
<tr>
<td>• Treat with metronidazole (flagyl), or clindamycin if resistant</td>
<td>• Itching!! Pale blush 0.5 to 1 cm macules (maculae ceruleae) may develop in individuals with prolonged infestation, and are the result of injection of louse anticoagulant saliva during feeding</td>
</tr>
<tr>
<td>• Most common cause</td>
<td>• Diagnosis of pediculosis pubis is made by demonstration of the louse or nits (louse eggs); nits can easily be confirmed on microscopic examination</td>
</tr>
<tr>
<td>o ↓ lactobacilli / H2O2 = ↑ gardnerella = ↑ pH $&gt;4.5$</td>
<td>• Treatment = permethrin 1% cream rinse (applied to the affected areas and washed off after 10 minutes), o *Pyrethrins with piperonyl butoxide (applied to the affected areas and washed off after 10 minutes), malathion, ivermectin, and lindane</td>
</tr>
<tr>
<td>o Amines + whiff test, clue cells, fishy smell, thin milky gray-white discharge</td>
<td></td>
</tr>
<tr>
<td>o Affirm test (DNA probe)?</td>
<td></td>
</tr>
<tr>
<td>o Tx = metronidazole (flagyl)* PO 1xd x7d or clindamycin</td>
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<tr>
<th>Mass/neoplasm of Vulva or Vagina</th>
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<tbody>
<tr>
<td>• VIN = vulvar intraepithelial neoplasia $\rightarrow$ SCC (90%), melanoma, BCC, Bartholin gland carcinoma, sarcomas, lymphomas</td>
<td></td>
</tr>
<tr>
<td>• VAIN = vaginal intraepithelial neoplasia $\rightarrow$ SCC, melanoma, sarcoma, adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>• Asymptomatic, postmenopausal bleeding, bloody discharge, biopsy any pigmented vulvar lesion!</td>
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<th>VIN (Vulval intraepithelial neoplasia)</th>
<th>NOT vulvar cancer, but could turn into a cancer</th>
</tr>
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<tbody>
<tr>
<td>• There are abnormal cells in the surface layer of the vulva</td>
<td>o Squamous Cell Carcinoma: most common cancer of vulva, larger tumors spread to pelvic lymph nodes</td>
</tr>
<tr>
<td>• The term VIN is used to denote high-grade squamous lesions and is subdivided into usual-type VIN (including warty, basaloid, and mixed VIN) and differentiated VIN.</td>
<td>o Basal Cell Carcinoma (1-2%): Almost always labia majora</td>
</tr>
<tr>
<td>• Usual type VIN is associated with HPV infections</td>
<td>o Melanoma (5%) all pigmented lesions of the vulva are suspect and require excision biopsy with large margins</td>
</tr>
<tr>
<td>• Biopsy is indicated for any pigmented vulvar lesion</td>
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</table>
**Lichen Sclerosis/Planus**
- Most common non-neoplastic epithelial vulvar disorder (usually in post-menopausal women over 60 with atrophic vaginitis), NOT contagious, etiology unknown, thinning of vaginal epithelial lining
- Causes intense pruritus, shiny smooth white plaques, lichenification, and hyperkeratosis (can cause fissuring, bleeding, scarring, ecchymosis) – if mild the patient may have no symptoms, mostly genital/anal areas but can occur in breasts and upper arms
- Usually elderly, post-menopausal females, atrophic change, not considered precancerous, but associated with increased risk
  - **Sx:**
    - Chronically inflamed epithelial tissue and chronic thinning of epithelium, Most commonly pruritus is reported (can be ax)
    - Early: shiny, smooth, white papules
    - Later: atrophic wrinkled patches, with fissuring, bleeding (common cause of vulvar bleeding), discomfort or pain, ecchymosis, scarring of the introitus can occur
  - **Dx:** diagnosed by visual characteristics and biopsy
    - **ALWAYS biopsy** → high risk of squamous cell cancer (3-5%), but not considered precancerous
  - **Tx:**
    - Surgery not a good option due likelihood of recurrence
    - **High potency steroid:** daily initially, 2-3 times a week long term, regular follow-up by a doctor because using these creams and ointments for a long time can cause complications
    - Treat any underlying disorders: Low estrogen levels, Infection, Allergy to the medication
    - When creams and ointments don't work use Retinoids, or vitamin A-like drugs or Tacrolimus ointment
- Always biopsy → high rate of SCC, can lead to VIN

### Genitourinary

**Uterine Prolapse**
- Pelvic organ prolapse → happens in 3-11% of women
- **Risk factors:**
  - Increasing parity, Advancing age, Obesity, Hysterectomy, Women with chronic constipations, Jobs with heavy lifting, more in Latina/white women
  - Most common symptom is pelvic pressure/heaviness or protrusion of tissue from the vagina
  - Common for women to have pelvic floor complaints, urinary, bowel, and sexual complaints
  - Conservative treatment → vaginal pessaries and pelvic floor muscle exercises
  - Surgical candidates include women with symptomatic prolapse who have failed or declined conservative management

**Rectocele** → POP of the rectum
**Cystocele** → POP of the bladder

**Urinary Incontinence**
- Very common, especially in pregnancy
- **Risk factors**
  - Obesity → strongest risk factor (threelfold increase)
  - Parity → increased parity = risk for incontinence and pelvic organ prolapse
  - Vaginal delivery, Family history
  - Age → 38% of women >80
  - Ethnicity/race → may be higher in white women
  - Smoking, caffeine, DM, stroke, depression, fecal incontinence, atrophy, HRT, genitourinary surgery

**Stress Incontinence** → leakage of urine that occurs with increased intra-abdominal pressure (sneezing, laughing)
- Most common type in younger women (age 45-49)
- Can be caused by insufficient support of the pelvic floor muscles (urethral hypermobility), or intrinsic sphincteric deficiency
- **Tx** → after pelvic floor PT, and other initial tx
  - Pessaries
  - Meds → duloxetine (SNRI)
  - Mechanical devices, surgery

### Urgency Incontinence
- urge to void immediately right before or during involuntary leakage (the amount can range quite a bit), also termed “overactive bladder”, frequent small voids, can’t make it to the bathroom in time
- Most common in older women and may be associated with detrusor overactivity leading to involuntary contractions during bladder filling
- Found in 21% of elderly women
- **Tx** → Antimuscarinics, mirabegron, acupuncture, botox, tibial nerve stimulation, sacral neuromodulation, surgery

**Overflow Incontinence** → often presents with continuous urinary leakage or dribbling in the setting of incomplete bladder emptying
- Can cause weak or intermittent urinary stream, hesitancy, frequency, and nacturia
- When the bladder is very full, stress leakage can occur similar to stress/urge incontinence
- Caused by detrusor underactivity or bladder obstruction
- Painless loss of urine if detrusor, urine stream can occur with changes in position
- **Obstruction** → may need to strain to pass urine
- **Tx** → Outlet obstruction may need surgery (POP etc)
  - Detrusor → limited therapy
  - Other contributing factors
    - Vaginal atrophy, urethral diverticula (structural), neurologic causes, alcohol intake, caffeine, stool impaction, functional incontinence (decreased mobility), cognitive impairment
  - **Evaluation** → classify the type, always evaluate for UTI, medication reconciliation, voiding diaries, physical exam (atrophy, POP), cytology looking for malignancy
    - **Bladder stress test**
  - Treatment → often treated inadequately, pads, lifestyle modifications, pelvic floor PT (Kegel), weight loss, reduce alcohol, deal with constipation, smoking cessation, topical vaginal estrogen, pessaries
### Contraception, Family Planning and Infertility

#### Male Surgical Sterilization
- Vasectomy is the safest method of permanent sterilization
- Procedure → interruption or occlusion of the vas deferens and is performed under local anesthesia

#### Female Surgical Sterilization
- Tubal ligation → typical occludes the fallopian tubes
- Associated with risk of ectopic pregnancy if sterilization fails
- Risk factors for regret → young age, non-white race, marital status, postpartum timing, insurance status
- Can be done laparoscopically or hysteroscopically

#### EC (plan B & IUD)
- Prevent implantation after unprotected sex, prevent or delay ovulation, prevent fertilization by affecting cervical mucus or ability of sperm to bind the egg
- Do not harm existing pregnancy, most effective when taken as soon as possible
- Adverse effects: nausea & vomiting (40%)
- Regimens:
  - Progestin-only (levonorgestrel) = plan B 1-step, next choice 1 dose (generic), my way (generic) → most effective within 72hr, available OTC, no age restriction, no ID
  - Progestin receptor modulator: Uliprostal (Ella) → effective for up to 5 days
  - Combination OCs may also be used
  - Copper IUD insertion within 5 days

#### Medical abortion → pill or injection
- Can be administered within 9 weeks from LMP
- 97% effective
- Possible risks: Allergic reaction, Incomplete abortion, Failure to end pregnancy, Infection, Blood clots, Heavy bleeding
- Benefits: Can be done early, No anaesthesia, Can be completed at home, Women feel more control
- Side effects → dizziness, strong cramps, nausea, vomiting, abdominal pain, diarrhea, abdominal pain, mild fever
- Step 1: Mifepristone
  - Pill taken in the office → blocks progesterone and causes uterine breakdown
- Step 2: Misoprostol
  - Pills taken at home 1-2 days later → cause uterus to cramp, empty, bleed
  - 50% abort within 4-5 hours
- Methotrexate
  - Used when mifepristone is contraindicated (chronic adrenal failure, long-term corticosteroid use, hemorrhagic disorders)
  - Not used as much because mifepristone is more effective and quicker
- Step 3: Follow-up within two weeks for an ultrasound or blood test

#### D&E
- Performed during 2nd trimester (after 16wks post LMP)
- Procedure lasts ~30min
- Dilation of cervix with laminaria or synthetic dilator
- Paracervical block + sedative, or general anesthesia
- Suction cannula inserted to remove fetus
- Forceps used to remove larger pieces of tissue
- Curette removes remaining tissue from endometrium, suction may be used as final step
- **Advantages**: only option for 2nd trimester abortions
- **Disadvantages**: risks increase with surgical abortions performed in 2nd trimester

#### D&C - AKA vacuum aspiration, suction aspiration, suction curettage
- Used up to 16 weeks after LMP, 99.5% effective if first trimester
- Lasts 10-15 minutes, Local anesthetic to numb the cervix
- Use of seaweed (laminaria) absorbent rods to absorb moisture and widen the cervix
- Suction cannula is used
- Curette may be used to scrape remaining pregnancy from uterus

#### General complications of abortion
- Irregular bleeding first 2 weeks after surgery can be expected, fatigue, pain, cramping, light vaginal bleeding, N/D, constipation, HA
- Infection (bacteria enter uterus during procedure) → give antibiotics
- Perforation of uterus (usually occurs during dilation)
- Scarring intrauterine adhesions (Asherman’s syndrome)
- Occluded cervix, blocking blood flow, hemorrhage or blood clots

#### IUD insertion
- Placed at beginning or during period (to ensure not pregnant & cervix somewhat dilated)
- Can give misoprostol for cervical dilation (buccal or intravaginal) → 2hr before placement
- Pt can take ibuprofen 1hr before procedure
- IUD strings = want to cut ~2-3cm below uterus

#### Manual Vacuum Aspiration
- Can be used from 3-12 weeks from LMP (first trimester)
- 99.5% successful (0.01% complication rate, 0.5% failure rate)
- Handheld syringe is used to suction uterine contents
- 5-15 minute procedure, can leave office within 2 hours
- U/S to confirm pregnancy and success of the procedure
- Side Effects: cramping, pain, bleeding, nausea, sweating, spotting for 2 weeks following procedure
- Major complications: VERY rare: uterine or cervical perforation, pelvic infection, excess bleeding

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**Male & Female Infertility**

- **Inability for a couple to conceive after 12 months of regular intercourse without the use of contraception in women <35 and after 6 months in women >35**

**Male causes**
- HPA disease (secondary hypogonadism – GnRH deficiency)
- Genetic disorders of spermatogenesis
- Post-testicular defects in sperm transport
- Idiopathic → males with normal semen analysis
- Infection → mumps (orchitis)
- Drugs, radiation, smoking, hyperthermia, antisperm antibodies, systemic disorders, cryptorchidism

**Female causes**
- Ovulatory disorders (25%) → infrequent ovulation, oocyte aging, cysts,
- Endometriosis, Pelvic adhesions, Tubal blockage, Uterine leiomyomata
- Luteal phase defect → abnormal corpus luteum
- Cervical factors → cervical mucus, malformations
- Hyperprolactinemia
- Immune factors → antiphospholipid syndrome (immune rejection of early pregnancy), celiac
- Genetic causes

**Evaluation**
- Semen analysis, menstrual history, assessment of LH surge in urine prior to ovulation, and luteal phase progesterone level to assess ovulatory function
- Hysterosalpingography to assess tubal patency and the uterine cavity
- Day 3 serum FSH & estradiol levels
- TSH
- Pelvic ultrasound (myomas, ovarian cysts)
- Laparoscopy to identify endometriosis or other pelvic pathology
  - Assessment of ovarian reserve in women >35

**Treatment**
- Lifestyle modifications → smoking cessation, reduce caffeine and alcohol, appropriate timing of coitus
- Drug therapy, surgical procedures, IVF

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**STIs & Pelvic Infections**

**PID & Acute Salpingitis**
- Neighboring organs can be involved
- PID → caused by STI, ascends tract
- Endocervical infection with sexually transmitted pathogens can get through endocervical canal into sterile area
- Includes acute salpingitis, IUD-related cellulitis, tubo-ovarian abscess, pelvic abscess
- **Gonorrhea & chlamydia are most common agents**, and mycoplasma genitalium is also seen

**S/sx:**
- Lower abd pain, adnexal tenderness, cervical motion tenderness, abnormal uterine bleeding (post-coital bleeding, inter-menstrual bleeding, menorrhagia), non-specific complaints include urinary frequency and abnormal vaginal discharge, N/V

**Diagnostic tests:**
- B-HCG pregnancy test, wet mount microscopic exam of vaginal discharge, G/C tests, UA, CBC, consider pelvic US to eval for TOA, laparoscopy

**Treatment:**
- Inpatient = cefoxitin, cefotetan + doxy, clindamycin + gentamycin
- Outpatient = ceftriaxone + doxy +/- metronidazole, cefoxitin + doxy + probenecid +/- metronidazole,

**Complications:** infertility, Fitz-Hugh-Curtis Syndrome (perihepatitis), infertility and ectopic pregnancy, sex partners should be evaluated and treated

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**Acute & Chronic Pelvic Infections**
- Chronic pelvic pain is at least 6 months that occurs below the umbilicus and is severe enough to cause functional disability and require treatment
- Common etiologies
  - Endometriosis, OUD, adhesions, pelvic congestion syndrome, adenomyosis, ovarian cancer, leiomyoma, dysmenorrhea
- **Other**
  - Interstitial cystitis, IBS, IBD, diverticulitis, colon cancer, obstruction, chronic constipation, celiac, fibromyalgia, mental health issues, physical abuse, opiate dependency, depression
TSS
- Etiology: preformed exotoxins from Staph aureus (GAS)
- Clinical Findings: acute, high fevers, vomiting, diarrhea, signs of shock (>102.2F, tachycardic, hypotensive, dehydrated), diffuse sunburn-like rash, swelling & erythema (followed by ecchymosis & sloughing of skin)

**Diagnosis:**
- blood cultures (takes 8 to 24 hrs) - gram stain of involved tissue demonstrating gram-positive cocci in pairs and chains can provide an early diagnostic clue in many cases
- Isolation of GAS from a normally sterile site (eg, blood; cerebrospinal, pleural, or peritoneal fluid; tissue biopsy; or surgical wound) + hypotension + 2 of:
  - Renal or liver dysfunction, coagulopathy, ARDS, soft tissue necrosis, erythematous macular rash that may desquamate

**Treatment:** tx shock, surgical debridgement of infx site, antimicrobial therapy
- Empiric therapy initially: clindamycin + either carbapenem or PCN+beta-lactamase inhibitor
- Established Dx: Clindamycin + PCN G IV + IV immune globulin

HIV
- Heterosexual contact is the most commonly reported risk factor
- Candida vaginitis and HSV are more persistent and severe in HIV infected women
- HIV infected women have an increased risk for cervical dysplasia and cervical cancer
- Choice of contraception is complex (drug interactions and risk of transmission)

**GYN Oncology**
**Abnormal Pap Screening & management**
- <21 yrs → no screening
- 21-29 yrs → cytology alone every 3 years
- 30-65 yrs → HPV and cytology co-testing every 5 years, OR cytology alone every 3 years
- >65 yrs → no screening is necessary after adequate negative paps
  - ***women with a hx of CIN 2, CIN 3, or adenocarcinoma in situ should continue routine screening for 20 yrs
- Total hysterectomy → no screening for women who have never had CIN 2 or higher in which case they will have routine screening for 20 yrs, or if they have had cervical cancer at any point (can justs do cytology)
- Vaccinated women → same as unvaccinated patients
- HIV positive women → screening starts at age of first intercourse and does not stop at 65 (continues for whole lifetime), should have screening at time of diagnosis of HIV, LSIL → colpo, ASC-US → reflex HPV testing → colpo

**Cytology**
- Cytology negative → screen again in 3 yrs
- ASC-US cytology & reflex HPV negative → cotest 3 yrs
- All others → refer tp ASCCP guidelines

**Cotesting**
- Cytology & HPV negative → screen again in 5 yrs
- ASC-US cytology & HPV negative → screen in 3 yrs
- Cytology negative & HPV positive
  - 12 month follow up with co-testing (or test for genotypes 16 & 18, if positive do a colpo, if neg return in 12 mos)

**ASCCP guidelines**
- ASC-US →
  - Reflex negative = routine screening → Repeat again in 12 months, if negative twice, resume routine screening
  - Reflex positive = repeat cytology in 12 mos
  - If repeat is ASC or higher → colposcopy
- LSIL →
  - With negative HPV test → repeat contesting in 12 months → If ASC or higher, or HPV positive → colposcopy
  - LSIL with no HPV test or positive HPV test → colposcopy
  - Pregnant patients
    - No CIN 2 or 3 → postpartum f/u, CIN 2 or 3 → ASCCP guidelines
- ASC-H (can’t rule out high grade lesion)
  - Colposcopy regardless of HPV status
- HSIL →LEEP or Colpo
- Colpo → No CIN 2 or 3 → colpo and cytology every 6 months for 2 yrs (CIN 2 or 3 → LEEP)
- Atypical Glandular Cells (AGC) → colpo
- Atypical Endometrial Cells → endometrial and endocervical sampling
Von Willebrand’s Disease

General Characteristics

- Women with menorrhagia measured objectively have *13-20%* chance of having vWD – prevalence ~ 1% in general population
- Severe cases which require transfusions: 1/10,000 = abnormalities in bleeding: **deficiency and/or dysfunction** of von Willebrand factor - involve a hematologist, mucous membrane bleeding
- Factors that affect vWD:
  - Estrogen
  - Strenuous exercise, stress, caffeine, infection
- Blood type (type O is 25-30% lower than other blood types)

Pathophysiology

- vWB factor initiates the platelet adhesion, stabilizes and transports coagulation factor VIII, the symptoms most often are mucous membrane bleeding, and very difficult to control bleeding after a surgery like a tonsillectomy
- No change in fertility
- No increase in miscarriages
- Levels of factor VIII and von Willebrand’s factor rise spontaneously during pregnancy
- If Factor VIII levels are 30-40% of normal,
- low chance of bleeding during pregnancy
- May have late post-partum bleed as levels fall after delivery

Clinical Presentation

- Type 1: most common (55-80%) - decrease in the amount of the vWB factor, but it functions normally and has normal structure, but there is not enough
- Type 2: 2nd most common (20-40%) - there is enough of it, but there is abnormal structure or function
- Type 3: rare (3-10%), deficiency of vWF - homozygous autosomal recessive or double heterozygous, they have a low level of factor VIII and vWB factor

Diagnosis

- Level of VWF antigen, vWF function, TSH and estradiol (promote synthesis of vWB), test the function of vWB factor (NOT after someone has exercised, pregnant, or big inflammation) - can increase to 3x over baseline
- Thyroid hormone and estrogen increases the level of vWB
- Check blood type: type O blood has lower levels of vWB
- Both VWF and factor VIII are acute phase reactants: levels increase 1-3 X over baseline with exercise, adrenergic stimulation, inflammation, and pregnancy

Treatment

- Replace missing or malfunctioning vWF and factor VIII
- **Desmopressin** (synthetic antidiuretic hormone): it increases factor 8, and releases vWB from the stores, good for mild or moderate type 1
- VWF/Factor VIII concentrates for type 2B or type 3
- **Stimate** - use monthly with menses and before surgery
- Oral contraceptive pills
- Other Medications: GnRH agonists: Luprolide acetate, Danazol

Diethylstilbestrol Exposure (DES)

- Women who took DES during pregnancy have an increased risk of developing breast cancer
- Women exposed to DES in-utero are at increased risk:
  - Cervicovaginal clear cell adenocarcinoma
  - Congenital anomalies and epithelial changes
  - Infertility, ectopic pregnancy, pregnancy loss, preterm birth
  - Cervical intraepithelial neoplasia
  - Earlier menopause
- Do yearly cancer screenings and pregnancies should be monitored very closely
- Males exposed to DES in-utero have higher risk for benign epididymal cysts, cryptorchidism, testicular inflammation, infection
<table>
<thead>
<tr>
<th>Disorder</th>
<th>General Characteristics</th>
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<th>Clinical Presentation</th>
<th>Diagnosis/Lab Studies</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial vaginosis</strong></td>
<td></td>
<td>Complex change in vaginal flora: decrease in H2O2 by lactobacilli, increases growth of anaerobe gardnerella</td>
<td>Thin, milky, grayish white, “fishy” smelling discharge which is worse after unprotected sex</td>
<td>Don’t do a general culture (too much bacteria there)</td>
<td>Metronidazole (flagyl) oral or topical (some resistance)</td>
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<tr>
<td></td>
<td>Most common cause of vaginitis</td>
<td></td>
<td>(+) whiff test, CLUE CELLS → gardnerella adheres to the epithelial cells</td>
<td>Most people do a wet mount, home-use of the Vi-Sense panty liner, DNA probe is highly sensitive and often used</td>
<td>Clindamycin is another option for resistance or allergies</td>
</tr>
<tr>
<td></td>
<td>Vaginal pH rises &gt; 4.5 (increase in AMINES)</td>
<td></td>
<td>Risks: douching, anything other than soap and water, smoking, new sexual partner, or partner that is having other partners</td>
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<td><strong>Candida Vaginitis</strong></td>
<td>Yeast are everywhere! Very common, 75% of women will experience an episode vaginitis from candidiasis</td>
<td>Yeast risk factors: - Recent antibiotics - High Sugar intake - Diabetes - Immunosuppressed - Pregnancy - Tight Clothing, Wet Clothing</td>
<td><em>LOWER pH</em> pH&lt;4.5 ITCHING and white-cottage cheese w/ vulvar erythema or edema Dysuria “BURNING”</td>
<td>Repeat candida vaginitis requires investigation CAN be sexually transmitted KOH 10% Wet prep → will see hyphae and buds</td>
<td>One dose of fluconazole Also prescribe an anti fungal cream Diflucan</td>
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<td><strong>Trichomonas vaginitis</strong></td>
<td>Affects the lower urinary tract in men and women MOST COMMON NON-viral STI in the US 50% women and 90% men asymptomatic</td>
<td>Unicellular flagellate protozoan Also test for other STIs</td>
<td>Profuse, frothy, greenish, foul discharge pH &gt;5 (basic) Vaginal rugae erythematous, small petechia on vaginal walls and cervix (strawberry cervix) Vulvar irritation, dyspareunia, dysuria</td>
<td>Wet mount: many polymorphonuclear leukocytes and larger motile flagellate Clinical exam is compelling, but you need to confirm with wet mount or DNA probe (Affirm Test) Can also culture and Sensitivity for T Vaginalis</td>
<td>Treatment is Metronidazole (flayl) but trich is becoming resistant! It cannot be treated by a cream Partners need to be treated</td>
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<td><strong>Atrophic vaginitis</strong></td>
<td>Vaginal wall with little rugae = atrophic vaginitis Leads to increased susceptibility to pathogens, and an increase in urinary frequency Most common cause of postmenopausal uterine bleeding, 4-5 years after the menopause 25-50% of women experience symptoms due to atrophic vaginitis</td>
<td>When estrogen levels drop Not just postmenopausal women: - Lactating Women - Long-term Depo Provera - Oophorectomy - Chemotherapy</td>
<td>- Discomfort, dryness, irritation, itching, burning, urinary incontinence, UTIs, dyspareunia - Decreased Libido - Significant decrease in the quality of life</td>
<td>Postmenopausal vagina: decreased capillary blood flow and reduced smooth muscle relaxation, vaginal wall thins (lose the rugae, at risk for cystoceles, rectoceles) Urinary tract epithelium: urethral and bladder mucosal thinning, urethral shortening, weakening of the sphincter decreased bladder capacity, increased postvoid residual urine volume</td>
<td>- Ask about symptoms. Look for signs on exam. Ask again, and talk about it. - Replace the lost estrogen, usually vaginal cream 30% of vaginal estrogen is absorbed systemically, consider risks and give patient education Lifestyle, OTC products, Estrogens, SERM etc. under development</td>
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