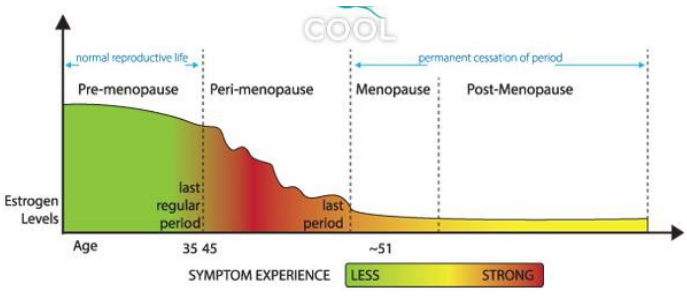
L9 – FEMALE REPRODUCTIVE AGENTS

ESTROGENS & PROGESTINS

Pathophysiology review

- Female sex hormones
  - Low testosterone VS High estrogen/progesterone
  - Production sites: ovarian cells, corpus luteum, placenta
    - Adipose tissue: transforms testosterone into estradiol
  - Control menstrual cycle: cyclical concentration variations → associated ovarian & uterine changes
- Sex hormone functions
  - Estrogen
    - Sex-related: menstrual cycle regulation, endometrial regeneration, reproductive organ maturation
    - Non-sex related: bone metabolism (↑ deposition), liver metabolism (fat regulation), CNS/brain (neuroprotective), pancreas (protective + ↑ insulin), hemostasis (both promote & inhibit!)
  - Progesterone
    - Pregnancy hormone!
    - Uses: endometrium thickening for implantation, uterine expansion + contraction inhibition, inhibits HPG (delays next menstrual cycle), breast alveoli development + lactation inhibition, immune tolerance to fetus
- Menstrual cycles: average length 28 days
- Female HPG (LH → FSH for follicle maturation → Estrogen for growth → LH surge = ovulation)
- Menopause
  - Amenorrhea for 1 year
  - Perimenopausal changes: decrease follicle numbers leading to ovaries atrophy, increased uterine thickness leading to heavy menses, vasomotor flushes → night sweats, dizziness, palpitations
  - Manifestations
    - ↓ Bone mass density (BMD) → ↑ osteoporosis
    - ↑ BP & dyslipidemia → ↑ coronary heart disease
    - Mood swings; migraine headaches; weight gain
    - Vaginal & uterine atrophy → ↓ lubrication & ↑ vaginitis
    - ↑ breast fat deposition → ↓ size & firmness



Estrogens

Clinical pharmacology

- Kinetics
  - Admin : PO, transdermal, intravaginal, parenteral
  - CYP1A2 & 3A4 metabolism
- Therapeutic uses
  - Menopausal hormone therapy
  - Cancer hormonotherapy (discussed last week)
  - Others: acne, female hypogonadism
- Contraindications (hormone replacemnet is not indicated in these cases)
  - DVT, pulmonary embolism, stroke/MI, liver disease, estrogen-dependent tumors, pregnancy
- Adverse effects
  - Endometrial hyperplasia → can lead to cancer
    - INTERVENTION: mitigation with concurrent admin of Progesterone = whole point of combining Estrogen + Progesterone
    - Progesterone in itself doesn't have a lot of benefits. The reason why it's added is really to counteract this.
  - Others : jaundice, nausea, migraine headache
- Interactions
  - CYP1A2 & CYP3A4 inducers/inhibitors
  - ↓ efficacy of antidiabetic drugs & thyroid replacement & anticoagulants

SERMs (Raloxifene) - REVIEW

- Selective Estrogen Receptor Modulators (agonist in some tissues & antagonist in others)
  - Advantage: we can increase the benefits for certain actions specifically (++ specificity)
- Actions
  - Agonist: bones, lipid metabolism, blood clotting
  - Antagonist: breast & endometrium
- Therapeutic uses
  - Postmenopausal osteoporosis
  - ER-positive breast cancer prevention
- Black box warning toxicity: DVT & PE
  - Discontinue if prolonged immobility (ex: travel, surgery)
- Adverse effects
  - Very serious teratogen → completely contraindicated during pregnancy

Estrogen VS Raloxifene

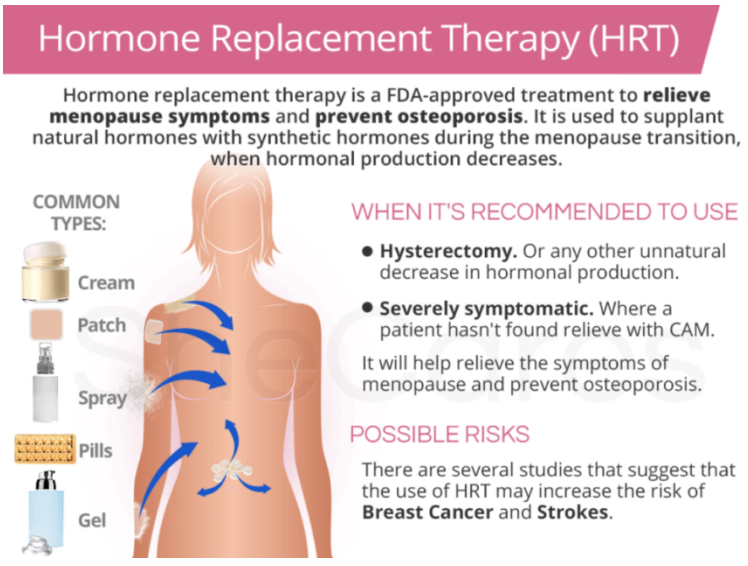
- **Estrogen:** ↑ BMD (reduces fracture risk), ↓ LDL cholesterol and ↑ HDL, alleviates menopausal symptoms (ex: hot flashes, vaginal dryness, itching) = PREFERRED FOR MENOPAUSAL REPLACEMENT THERAPY
- Raloxifene: protects against bone cancer, does not cause breast enlargement or pain, does not provide endometrial cancer and may offer protection, causes bleeding in 3-5% of postmenopausal women

Progestins

Clinical pharmacology

- Kinetics
  - Admin : PO, transdermal, intravaginal, parenteral
- Therapeutic uses
  - Menopausal hormone therapy → simply to ↓ estrogen endometrial cancer risk
  - Dysfunctional uterine bleeding → ↓ hemorrhage + promote regular monthly cycle
  - Others: amenorrhea, infertility, prematurity prevention
- Adverse effects
  - ↑ breast cancer risk & thromboembolic events (when combined with estrogen)
    - Risk benefit ratio to consider! Without progesterone, there is an increased risk of endometrial cancer BUT increased risk of breast cancer… so need to individualize! (pick according to what the pt is less likely to have)
      - Ex: If pt has a BRCA1 mutation, should give estrogen alone (bcs risk of endometrial would be less). But if pt doesn't have breast cancer risk, then you would give the combination
    - If progesterone was given alone, these AE would be very minimal! It's really about the combination
  - Others: abdominal discomfort, breast tenderness, irregular menses

Menopausal hormone therapy



Low-dose estrogen with/or without progestins

- We don't want to give a full replacement dose, we just want to give less than what the body is used to produce. Because menopause is caused by a drastic decrease of estrogen, the point here would be to taper it off over a few years (NOT to regain/replace everything!)

Controversy with MHT

- Pre-2000s → compulsatory MHT for everyone
  - Believed the benefits outweighed the risks
- Early 2000s → WHI & HERS-II landmark studies
  - MHT ↑ cardiovascular even risk & estrogen + progestin ↑ risk of breast cancer
  - Result: 80% decrease in MHT prescriptions
- 2010s → increased scrutiny insights into the landmark studies' data
  - Biased conclusions → age of participants & time on MHT was higher than best practice
  - In a study: For women between 50-59 taking MHT for 10 years or less
    - Cardiovascular risks were minimal → benefits outweighed the risk
    - After 59, you don't really need it anymore because the symptoms that you were trying to target are now pretty much gone
- Current guidelines
  - Use lowest effective dosage
  - Short term MHT (5 years or less) in early menopausal women → benefit > risk
  - Complication risks increase with age ☹
  - Long term MHT (5+ years) *regardless of age* → risks > benefits
    - SO even though patient is 45 yo, only for 5 years MAX
    - Most important factor is the time you are on the therapy rather than the age

Approved indications for MHT – Really well established benefits

- Moderate severe vasomotor symptoms
  - Vasomotor sx ↓ over time → short term MHT is safe (more intense in first few years of menopause) – no need to continue treatment after
  - Other options if MHT is contraindicated: Paroxetine (SSRI) – but less effective :/
- Moderate severe vulva & vaginal atrophy
  - Use topical estrogen to minimize toxicity
  - Allows longer-term therapy with minimal complications
- Osteoporosis prevention
  - Ideally we would need lifelong therapy → BUT ↑ MHT complication risks
  - ONLY considered for women at high risk of osteoporosis

Inappropriate usage

- Heart disease prevention
    - MHT ↑ risks of cardiovascular events
- Alzheimer's disease prevention
    - No evidence of delayed onset
    - Evidence of ↑ risk of dementia & possibly cognitive impairment

Risks VS benefits (over 5 years) – These are correlations (not well established benefits)

- Benefits: coronary heart disease, osteoporotic fractures, breast cancer, colorectal cancer, T2DM, mortality overall
    - Benefits – actually well established: vasomotor & urogenital symptom alleviation
- Risks: thromboembolism, stroke, breast cancer, cholecystitis

Other considerations

- Safety in younger women without uterus (SAFEST POPULATION)
    - Young women = safest group
    - No uterus → estrogen therapy only → safer than estrogen + progestin
        - Without uterus: give estrogen only (less toxicity) + 0 risk of uterine cancer!
- Discontinuing hormonal therapy
    - There will be a strong rebound (especially vasomotor symptoms)
    - No data on gradual tapering VS immediate cessation
    - Only decrease estrogen → keep progestin levels the same until estrogen is at 0 (then remove progesterone which is your protection against cancer)

BIRTH CONTROL

Birth control effectiveness

- Failure rate: 1 year % of unplanned pregnancies
- Theoretical use: % expected with proper use
- Actual use: % observes with day-to-day use (suboptimal!)

HCP should take the time to explain proper usage of contraceptives to maximize % efficacy BECAUSE
Our goal is: to make actual use as close as possible to theoretical use

Methods

- Extremely effective: subdermal implant, surgical sterilization, intrauterine devices
- Very effective: oral contraceptives, intramuscular injection, vaginal contraceptive ring, contraceptive patch
- Effective: condoms, diaphragm with spermicide
- Least effective: contraceptive sponge, spermicide alone, periodic abstinence, withdrawal

Considerations & selection

- Consider effectiveness / safety / personal preferences
    - Most effective = sterilization (vasectomy & fallopian tubes ligation)
    - Women 35+ smoking or high risk of thromboembolic events → avoid combination with OCs
    - Individuals in non-monogamous relationships (higher risk of STI) → avoid IUDs
        - They are very effective but they are more likely for bacteria development (can stick on it)
    - Convenience & accessibility → OCs & condom popularity
- Consider also family planning goals & intercourse frequency
    - Sterilization bad option if family goal not achieved – but best if family goals achieved
    - High coitus (sex) frequency or adherence problems → long-term contraceptive (ex: implants)
    - Infrequent intercourse → condoms & spermicides → no toxicity
    - Multiple partners → condoms + spermicides → pregnancy/STI prevention

Combination oral contraceptives: Estrogen + Progesterone pills

Overall, it's the best for efficacy & safety (it's the most popular)

Actions

- FSH inhibition → ↓ follicular maturation
- LH surge inhibition → anovulation (Ø ovulation) = prevents pregnancy
- Endometrium alterations → ↓ implantation success (by preventing endometrium from thickening)

Effectiveness

- Theoretical ≈ 99.7% VS Actual ≈ 92%
- Efficacy lowest in high-BMI women

- Reason: Hormones are fat soluble. So if you have a large amount of fat → ↓ blood concentration → ↓ efficacy + fat tissues can transform testosterone into estrogen – enough to replace LH surge inhibition)

Overall safety

- Currently prescribed OCs = much safer than older ones
- OCs mortality < Pregnancy/Delivery mortality
- Broadest range of adverse effects

Adverse effects

Overall: serious ADR risk is small → Watch out for contraindications

- Thromboembolic disorders
  - Relative risk = 2-3x increase BUT Absolute risk = 8-10/10 000 women-year (so ok)
  - Lower risk than pregnancy & delivery
  - Mitigation strategy:
    - Lowest effective dose
    - 2 types of progesterone to avoid in mixing: drosperidone & desogestrel
    - Avoid if 35+ smoker (risk+++)
    - Thromboembolic symptoms education
- Cancer
  - Promotion of EXISTING breast cancer development (doesn't trigger it if non-existent prior) – but if you had a tumor, it will accelerate the development of it
  - Only increase risk of cancer if you already have a genetic mutation (BRCA1 mutant)
  - There are protective benefits against endometrial & ovarian cancers
  - Has ZERO impact on cervical cancer → bcs it is HPV-caused
- Stroke risk ↑ in women with migraines
  - Absolute risk still low if under 35 and non-smoker
  - Contraindicated if visual changes (aura) migraines)
- Hypertension
  - Estrogen ↑ angiotensin & aldosterone levels
  - Low-dose estrogen OCs have minimal BP effects
- Abnormal uterine bleeding
  - Via endometrial alterations
  - Possible spotting with extended OCs
- Pregnancy
  - No therapeutic action → contraindicated!
  - If pregnancy occurs despite OCs → discontinue
  - No teratogenic action (simply no benefits)

- Benign hepatic adenoma
    - Rare & only with OCs containing mestranol
    - Tumor regression upon discontinuation
- Estrogen & progestin imbalances
    - Common but mild
    - INTERVENTION to mitigate: dosage at bedtime / adjusting estrogen dosage

<u>Noncontraceptive benefits</u>

- ↓ risk of: ovarian & endometrial cancers, ovarian cysts (PCOS), pelvic inflammatory disease (PIC), iron deficiency anemia & acne
- ↓ menstrual symptoms
    - ↓ cramps & blood volume + duration
    - Regulate cycles
    - ↓ menstruation-related migraines
- Surprising benefit: ↓ symptoms of rheumatoid arthritis

<u>Drug interactions</u>

- CYP450 inducers ↑ OCs metabolism (could decrease its efficacy)
    - Ex.: St-John's wort / Antiseizures drugs / Rifampin
- OCs ↑ clotting factors → if on warfaring, would ↓ Warfarin efficacy
- OCs ↑ blood glucose → ↓ Hypoglycemic Rx efficacy
- OCs ↑ hepatic metabolism → ↑ Drug Toxicity
    - Ex.: Diazepam / TCAs / Theophylline
- Antibiotics can also decrease the efficacy of contraceptive pill!!!

<u>Dosing schedule</u>

- 28 day cycle schedule
    - 21 days of active pills (with hormone) + 7 placebo/no pills day
        - Monophasic: constant estrogen-progestin dosage
        - Bi/Tri/Quadriphasic:dosage variations to mimic 'natural' ovarian cycle
            - Seems like there's no type of dosage is superior
    - Administration
        - Same time of day (meal or bedtime)
        - Start next cycle after 28 days even if spotting/bleeding
- Extended-cycles & continuous schedules

    - Extended cycle = 84 days of pills + 7 placebo pills
    - Continuous schedule = Ø interruption of active pill
    - Advantages over 28 day cycle: ↓ premenstrual sx, ↓ migraines, ↓ withdrawal bleeding
    - Drawback: breakthrough bleeding (more common)
    - Life-hack: if on monophasic 28 days cycle and you want to switch → buy 4 packs and use active pill for 84 days straight

What if you miss a dose?

- With 28 day schedule
    - 1 or more pills during 1st week → Take one ASAP + use extra contraception for 7 days
    - 1 or 2 pills on week 2 or 3 → Take one ASAP & skip the placebo days
    - 3+ pills on week 2 or 3 → Same as for 1 or 2 pills + extra contraception for 7 days
- With extended/continuous schedule
    - Up to 7 days can be skipped with minimal risk change if continuous intake 3 weeks prior

Progestin-only pill

- Advantage: slightly safer → ↓ migraines / nausea / thromboembolic event risks
- Disadvantage: less effective & frequent irregular bleeding
    - Efficacy: ↑ endometrium thickening → ↓ implantation success
    - Little effect on ovulation → ↑ bleeding
- Administration = continuous
    - If dose is missed → resume ASAP + extra contraception for 2 days
    - If 3+ doses missed + no bleeding = pregnancy test

Long-term contraceptives

<u>Novel delivery systems</u>

- Efficacy & toxicity ≈ OCs
- Transdermal patch (more constant delivery – steady amount of hormones)
    - 1 patch/week → ↑ admin convenience & adherence
    - 1 patch/week for 3 weeks + 1 week off (to mimic 28 days cycle)
    - ↑ risk of thromboembolism → debated data
    - IF patch detach partially or completely → replace ASAP + use extra contraception for 7 days
- Vaginal contraceptive ring
    - Insert 1 ring for 3 weeks → remove & skip one week

    - IF ring falls out → wash in warm water & reinsert + extra contraception for 7 days
- Subdermal etonogestrel
    - Implant placed between biceps & triceps of non-dominant arm
    - Effective for 3 years
    - Advantage: Very useful for remote location (living far from pharmacy)
    - Safe during breast-feeding
    - Main adverse effects: irregular bleeding
    - Kinetics: hepatic metabolism, same drug affecting OC metabolism can ↓ etonogestrel efficacy (ex: antiseizures, rifampin)
- Depot Medroxyprogesterone Acetate (DMPA)
    - MOA
        - Inhibits gonadotropin secretion (FSH & LH) for 3 months
        - Fertility returns 9 months after discontinuation
    - Main adverse effects
        - Irregular menses initially
        - No menses altogether within 6-12 months
        - Reversible bone density ↓ (slight)
    - Disregard black box warning of 2 years use limit
        - Large scale study after 1-2 years → serious BMD ↓ but BMD decrease stabilizes after 1-2 years
        - Returns to pre-treatment levels afterward (so black box warning is no longer valid – still appears even though we know it's not true anymore)
- Intrauterine devices (IUDs)
    - Very efficient, reliable & reversible
    - Only constitutes 5,5% of all contraceptives
        - Blame the old design (Dalkon Shield) that was associated with high rate of PID
    - Both options are spermicidal + do not prevent ovulation
    - Effective for 3-10 years
    - Main adverse effects: pelvic inflammatory disease (PID) secondary to STD, cramping upon insertion
    - Other uses: menses regulation, emergency contraception
    - 2 types:
        - Copper: physically blocks (blocks entry towards fallopian tubes)
        - Hormonal: thickens cervical mucus to prevent implantation (dual action)

Emergency contraception

- Plan B One-Step & Next Choice One Dose
    - Large levonogestrel (type of progestin) dose (no estrogen in this one!)
    - Available OTC / equivalent 10x regular extended-cycle OC pills

    - Efficacy ↓ exponentially post-intercourse → up to 5 days is recommended
    - Success = onset of menses within 21 days
    - Cannot harm the fetus or abort pregnancy if fertilization occurred (don't use for abortion)
    - ADRs: heavy menses, nausea, headaches
- Ulipristal acetate
    - Progestin agonist/antagonists (depending on concentration, can do one or the other → inhibit ovulation
    - Prescription-only despite similar toxicity
    - Efficacy remains high up to 5 days post-intercourse
- Mifepristone
    - 100% to prevent fertilization within 5 days post-intercourse
    - Causes abortion after 5 days (See next slide)
- Copper IUD
    - 99.9% effective within 5 days post-intercourse
    - Additional contraceptive benefits for next 10 years
    - MOA: inhibits implantation of fertilized egg in uterus

Medical abortions

- **Mifepristone + Misoprostol**
    - Mifepristone: progesterone inhibitor → promotes blastocysts detachment + ↑ prostaglandin contraction-promoting activity (boosts potential of prostaglandin to promote contraction)
    - Misoprostol: synthetic prostaglandin
        - Effectiveness: 95% of cases
        - Prescription by trained physicians only
        - Combining them makes sense (dual action)
- Adverse effects
    - Contraindications: ectopic pregnancies & hemorrhagic disorders
    - Unavoidable ADRs: abdominal pain + vaginal bleeding
    - Teratogenic effects → surgical abortions if failure

DRUG THERAPY FOR INFERTILITY

Pathophysiology review

- Fertility
    - Ovum is fertile only 12-24 hours
    - Sperms can survive 5-6 days in uterus

    - Fertile window = 5-6 days prior to ovulation
- Impaired fertility
    - Difficulty conceiving after 1+ years of unprotected sex (represents 15% of couples)
    - Responsibility falls on: male 20%, female 40%, mix 40%
        - Female reproductive system = more complex
        - Frequent ovulation disturbance
        - Uterine disorders → ↓ implantation
    - Age = major factor for women
    - Female fertility tests for:
        - Ovulation & endometrium accommodation
        - Reproductive tract diseases & lesions
    - Male infertility test for:
        - Sperm count & motility
        - Frequently hormonal disorders – more easily corrected
- PCOS: 2 out of the 3 → polycystic ovaries, anovulation, hyperandrogenism
    - ↑ Testosterone → ↑ follicular growth + ↑ follicular atresia
    - ↑ Insulin → abnormal HPG secretion pattern
    - Symptoms are related to anovulation & ↑ androgens

Infertility causes & strategies

Fertility requires proper functioning of: ovaries + uterus + hypothalamus pituitary axis

<u>5 main causes – Female Infertility</u>

1. Anovulation / follicular maturation failure
    - Caused by inadequate hormonal stimulation
    - Responds well to drugs (ex: Clomiphene, Menotropins ,hCG)
2. Unfavorable cervical mucus
    - Spontaneous or Drug-induced/Sticky or thick mucus = impaired sperm passage
    - Responds well to estrogen
3. Hyperprolactinemia
    - Caused by pituitary adenoma → unknown mechanism of infertility
    - Responds well to dopamine agonists (ex: Cabergoline)
4. Endometriosis → endometrial tissue outside of uterus
    - Impairs ovum transport in the fallopian tube
    - Surgery ↓ discomfort + ↑ fertility / NSAIDs & oral contraceptives only ↓ discomfort
5. Polycystic ovary syndrome
    - Therapy: lifestyle + drugs
    - Objective: restore menstruation, ovulation, insulin levels & ↓ androgen levels
        - Weight loss → improve insulin + androgen levels

- Clomiphene → ovulation induction
- Metformin → regulation of insulin & androgen levels
- Oral contraceptives → regulates menstrual cycle & ↓ acne & hirsutism
- Spironolactione → antiandrogen action → ↓ acne & hirsutism

Male infertility

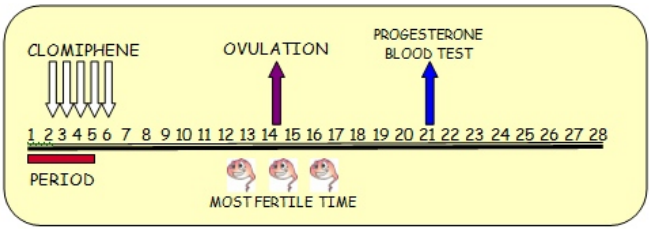
Not associated with endocrine dysfunctions → not very responsive to drug therapy

(so female infertility is slightly more common than men bcs only one ovary vs million of sperms, BUT females respond better to drugs)

1. Hypogonadotropic hypogonadism: low spermatogenesis d/t low LH/FSH levels
    - Mild spermatogenesis deficiency → Tx: hCG alone or hCG + menotropin → long (years!) & expensive
    - Severe spermatogenesis deficiency → Tx: androgen replacement therapy
2. Erectile dysfunction
    - Viagra
3. Idiopathic male infertility
    - No identifiable cause (≈ 25-40% of male infertilities
    - Trial and error therapy → hCG, androgens → success rate is very low

Drugs for controlled ovarian stimulation

- Drugs that promote follicular maturation
    - Clomiphene, Menotropins, Follitropins, Lutropin alpha
- Drugs that stimulate ovulation
    - hCG
- Drugs that prevent premature ovulation
    - Ganirelix, Cetrorelix



Clomiphene

- MOA: blocks estrogen receptors in the hypothalamus & pituitary, and thereby causes a compensatory increase in the release of LH and FSH (because no more feedback inhibition), which then act on the ovary to promote follicular maturation (and possibly ovulation)
- Therapeutic use: stimulate follicular maturation & ovulation
- Ineffective if pituitary or ovarian failure
- If follicular maturation without ovulation → add hCG (to stimulate ovulation)
- Monitor

    - Ultrasound → formation of corpus luteum (indicative to know best time for administration)
    - Confirms efficacy of treatment
- Adverse effects
    - Menopause-like vasomotor symptoms
    - Cervical mucus thickening
    - May impede conception (prevents sperm from reaching higher up in uterus)
        - Mitigate with Progestin

Menotropins

- MOA: 50:50 mixture of FSH and LH that acts on the ovary to promote follicular maturation. Treatment is ALWAYS combined with hCG to induce ovulation (unlike Clomiphene)
- Therapeutic use:
    - Anovulatory women → promote ovulation
    - Ovulatory women → pre-IVF program
    - Men → ↑ spermatogenesis
- Ineffective if ovaries are unresponsive
- Very expensive therapy
- Cannot induce ovulation → always followed by hCG
- Monitor
    - Ultrasound → ovarian follicle development
    - Determines the proper timing for hCG injection
    - Ovaries size → every other day during first 2 weeks
- Adverse effects:
    - Ovarian hyperstimulation syndrome
    - Most common during first 2 weeks
    - Multiple births: twins ≈ 15% / 3+ ≈ 5% (increased chance that multiple follicles develop at once)

Human Chorionic Gonadotropin (hCG)

- MOA: similar in structure and identical in action to LH. The drug acts on the ovary to induce ovulation
- Therapeutic use
    - Stimulation of ovulation → mimics LH surge (big loading dose)
    - Must be preceded by follicular maturation
    - Men → ↑ testosterone levels
- Main serious adverse effects

- Ovarian hyperstimulation syndrome
- Increased risk of ovarian cysts rupture
- Discontinue if either is observed

Drugs for hyperprolactinemia

Cabergoline

- Therapeutic use: correction of hyperprolactinemia-related amenorrhea & infertility
- Action: prolactin release inhibition (DA agonist – agonist of the inhibitory for release of prolactin)
- Better tolerated and convenient than Bromocriptine
- If cause is pituitary adenoma → tumor regression
- Kinetics: PO available / extensive hepatic metabolism
- Monitor: prolactin levels
  - Below 20ph/mL = treatment works
- Adverse effects
  - Most common: headaches and nausea
  - Rare: orthostatic hypotension & valvular heart diseases

DRUGS AFFECTING UTERINE FUNCTIONS

Drugs for preterm labor

- Only delays labor for 48h max!
- Buys time to
  - Treat infections or administer glucocorticoids
    - GCC will accelerate rapidly the development lung epithelial cells that will produce the surfactant – important for BABY
  - Accelerate lung development
- Drawback: fetal toxicity

Tocolytic drugs (uterine relaxation)

- Different classes
  - Beta2-adrenergic agonist (Terbutaline)
  - Calcium channel blocker (Nifedipine)
  - Cyclooxygenase inhibitor (Indomethacin)
  - Nitric oxide donor (Nitroglycerine)
- Toxicities: equivalent efficacy → selection based on toxicity profile (& on pt profile)
- All used off label for labor suppression

- Terbutaline: B2 agonist
    - ↓ contraction frequency & intensity
    - Admin: subcut
    - Stop after 48h or if mother's HR > 120 bpm
    - Serious toxicity: pulmonary edema & hypotension
- Nifedipine: Ca2+ channel blocker
    - Considered safer than Terbutaline
    - + admin: PO (so fav one for this usage)
    - Drawback: multiple dosing (q4-6h for 48h)
    - Serious toxicity: rare maternal side effects, possible ↓ fetal blood flow
- Indomethacin: COX inhibitor
    - More toxic than Nifedipine or Terbutaline
    - So it's reserved for very early labor
- Nitroglycerin: NO donor
    - Similar profile to Terbutaline
    - Admin: transdermal patch

Hydroprogesterone Caproate

- MOA: unknown (unknown why efficient in some women and not others)
- Only preterm labor prevention approved drug
    - Not the same as delaying labor = when you know preterm will happen so you want to prolong it as much as possible
    - Here, used when patient has a history of preterm labor in family → to decrease risk of preterm birth in this specific pregnancy
- Use: indicated with 'singleton' + history of preterm birth in family
    - Singleton: if mother is expecting a single baby (not twins or triplets)
- Adverse effects
    - Common: injection-site reactions
    - Rare: thromboembolic events
    - Possible: glucose intolerance
    - Fluid retention / clinical depression
- Contraindications
    - Multiple pregnancy
    - Suspected breast or liver cancer
    - Thrombosis history
    - Uncontrolled hypertension

Drugs for cervical ripening/Labor induction

- Induce labor when risk of pregnancy > induction risk itself
- Most common: pregnancy beyond 42 weeks
- Must ensure cervical ripening prior to induction
    - If cervix is not ready, can lead to significant maternal and fetal injuries!
- Prostaglandin analogs (fav drug here) because they both promote:
    - Cervix ripening + labor induction (dual action)
- If prostaglandin analog FAILS → add oxytocin (just promotes labor)

Oxytotic drugs

Applications of Selected Tocolytic and Oxytocic Drugs

Drug	Brand Name	Applications				
		Delay of Preterm Labor	Induction of Cervical Ripening	Induction of Labor	Control of Postpartum Hemorrhage	Induction of Abortion
OXYTOCIC (UTEROTONIC) DRUGS						
Prostaglandins						
Dinoprostone	Cervidil, Prepidil		✓*	✓		✓
Misoprostol	Cytotec		✓*	✓		✓
Carboprost	Hemabate				✓	✓
Oxytocin Receptor Agonist						
Oxytocin	Pitocin			✓	✓	

Prostaglandins

- Dinoprostone
    - Route: gel or vaginal insert (most common)
    - Drawbacks: must be stored in refrigerator & ++ expensive
    - Effects:
        - ↓ labor duration
        - ↓ oxytocin dosage needed to induce labor
        - ↓ need for C-sections
    - Main adverse effects: uterine tachysystole (excessive uterine contractions)
        - 5+ contractions/10 mins
        - Incidence: gel ≈ 1% VS vaginal ≈ 5%
        - Vaginal is cheaper & can be removed if tachysystole
- Misoprostol
    - Advantages over Dinoprostone: ↓ cost (1$ vs 500$/dose) & ↑ efficacy
    - Main adverse effects: more frequent uterine tachysystole

For both, you need to continuously MONITOR: Fetal HR + Uterine activity

Drugs for postpartum hemorrhage

Normally: following delivery → uterus contracts → blood vessels shut

Major cause of PPH = uterine atony → lack of uterine contraction = more bleeding

Drug options:

- Oxytocin: best option for PPH prevention (drug of choice for PPH)
    - Will boost the contractility of the uterus + closing down blood vessels = ↓ bleeding
- Misoprostol: also helps for uterine contractions
- Carboprost tromethamine
- Methylergonovine
    - Most toxic = last resort

Oxytocin

- 'Love/Bonding hormone' – released by posterior pituitary
- Physiological functions: ↑ uterine contractions + milk-ejection
- Uterus sensitivity ↑ during pregnancy → more efficient toward week 37+
- Pharmacological uses
    - Postpartum hemorrhage treatment
    - Uterine stimulation (↑ strength + frequency of uterine contractions)
    - Preinduction preparation: cervix ripening with Misoprostol or Dinoprostone
        - You need to promote cervix ripening before. If you give it without, you'll habe labor but high risk of injury for both mother and fetus because cervix not ready
    - Contraindicated in complicated pregnancies (ex: placental abnormalities)
- Dosage & administration
    - IV infusions / Choice between low-dose or high-dose regimen
        - Low dose: ↓ tachysystole
        - High dose: ↓ C-section, placental inflammation & ↑ efficacy
- Monitoring:
    - Mother: BP, HR, uterine contractions continuously
    - Fetus: HR
- Discontinue immediately if complications arise
- Adverse effects: water intoxication
    - Similar action to ADH
    - Very rare with labor induction doses

Carboprost tromethamine

- IM injectable prostaglandin analog
- Effect: produces powerful uterine contractions + vasoconstrictions
- Adverse effects:
    - Vomiting + diarrhea (60% of patients) → pre treat with antiemetic
    - Risk of fever, HTN or bronchoconstriction
- Precautions: asthma, HTN, diabetes
- Contraindications: active disease of heart, lung, kidney or liver

Very efficient but less practical than first 2 options

Drugs for menorrhagia

Excessive bleeding exceeding 7 days in duration or 80 mg in volume.

If untreated → risk of iron deficiency anemia

Tranexamic acid PO

- Up to 50% ↓ bleeding
- Adverse effects: very well tolerated… possible retinal artery thrombosis
- Interaction: with OCs → both increase thrombotic risks

NSAIDs (Naproxen / Diclofenac)

- Limit dosing to 5 days of bleeding
- Minmizes GI toxicity
- Bonus: menstrual pain relief

Combination oral contraceptives

- ↓ bleeding via endometrial atrophy
- Bonus: contraception

Levonorgestrel-releasing IUD

- Similar effect and efficacy as combination OCs