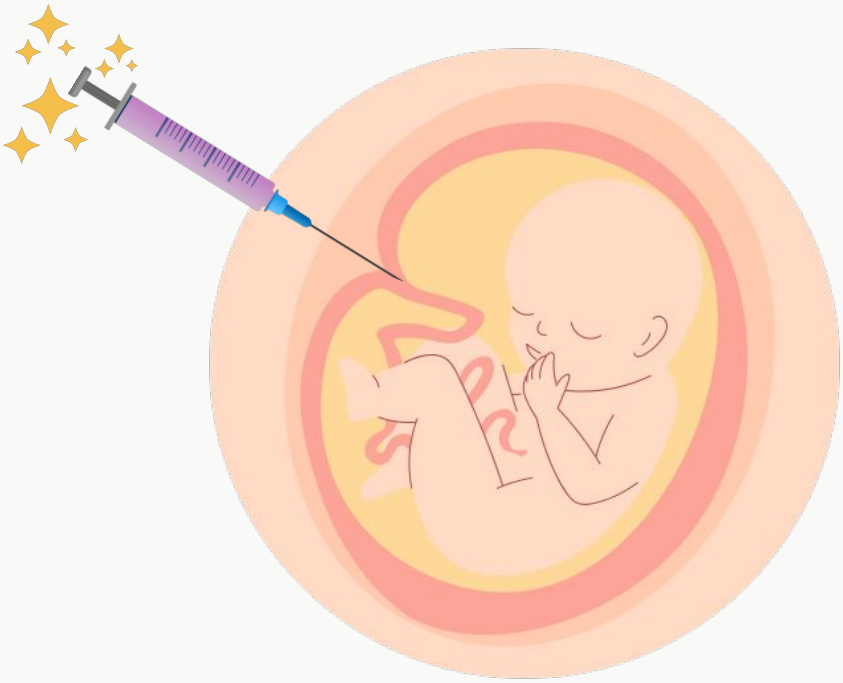
List of drugs



- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

L: Drug Inducing Ovulation

Drug	MOA	Uses	ADRs	P.K
Antiestrogens (SERMs)				
Clomiphene	**Compete with estrogen on the hypothalamus and anterior pituitary gland:** ○ ↓ the negative feedback of endogenous estrogen →↑ GnRH → ↑ production of FSH & LH → ***Ovulation.***	- Female infertility **not** due to ovarian or pituitary failure (=**Normogonadotropic**) - PCOS treatment: **PCOS is the most common cause of infertility and insulin resistance may play a role**→ use Metformin (first choice) , Clomiphene	• **Hyperstimulation of the ovaries & high** incidence of multiple birth(75% twins). • Hot Flushes & breast tenderness. • Gastric upset (nausea and vomiting). • Visual disturbances (reversible). • ↑ nervous tension & depression. • Skin rashes. • Fatigue. • Weight gain. • Hair loss (reversible).	-Given 50 mg/d for 5 days from **5th day of the cycle to the 10th day.** - If no response give 100 mg for 5 days again from 5th to10th day. -Each dose can be repeated **not more than 3 cycles**.
Tamoxifen		- Tamoxifen is alternative to clomiphene in women with PCOS and **clomiphene resistant cases** - Used in palliative treatment of estrogen receptor- positive breast cancer. (Tamoxifen has potent anti estrogen activity in breast cancer.)	–	Is similar & alternative to clomiphene.
GnRH Agonists				
Leuprorelin & Goserelin	GnRH Analogous with agonist activity.	For ovulation in patients with hypothalamic amenorrhea (GnRH deficient).	- GIT disturbances: abdominal pain, nausea. - Headache. - **Hypoestrogenism** → long term use (hot flashes , ↓ libido, osteoporosis, rarely ovarian hyperstimulation → ovaries swell & enlarge.)	• GnRH and agonists, given S.C. in a pulsatile (drip) to stimulate gonadotropin release (1 – 10 µg / 60 – 120 min), start from day 2-3 of cycle up to day 10. • Given continuously **(paradoxical opposite effect)**, when gonadal suppression is desirable e.g. precocious puberty and advanced breast cancer in women and prostatic cancer in men.
Gonadotropins				
Menotropin (hMG)	- Human **Menopausal** Gonadotropin (hMG) extracted from **postmenopausal** urine **contains LH & FSH.**	- Stimulation & induction of ovulation in infertility **secondary to gonadotropin deficiency (pituitary insufficiency)**	- **FSH** containing preparations: - Fever - Ovarian enlargement -Multiple pregnancy - **LH** containing preparation: Headache & Edema	- **hMG** is given I.M every day starting at day 2-3 of cycle for 10 days followed by **hCG** on (10th - 12th day) for ovum retrieval.
Pregnyl (hCG)	- Human **Chorionic** Gonadotropin (hCG) extracted from urine of **pregnant** women **contains mainly LH.**			
D2 Receptors Agonist				
Bromocriptine	- Is an ergot derivative (not a hormone). - D2 receptors agonists binds to dopamine receptors in the anterior pituitary gland & **Inhibit prolactin secretion**.	- Female infertility **secondary to hyperprolactinemia.**	- GIT disturbances: nausea, **vomiting**, constipation. - Headache dizziness - Orthostatic hypotension - Dry mouth - Nasal congestion - Insomnia	-

L:Drugs used in infertility

Drug	M.O.A.	Uses	ADRs
Testosterone			
Testosterone & Synthetic Androgens	- **Prostate and seminal vesicles:** Testosterone→ **DHT** by α-reductase. - **Bones and brain**: **Testosterone → estradiol by aromatase.** • **Bone**: estradiol accelerates maturation of cartilage into bone leading to **closure of the epiphysis.** • **Brain**: estradiol is a -ve feedback signal to hypothalamus.	- As **Testosterone Replacement Therapy**: • **Androgen deficiency** in adult male infertility • **In delayed puberty** with hypogonadism (given **slow and spaced** for fear of premature fusion of epiphyses) - DHT derivative: **Mesterolone** is **safer** , as it is: **1- Not aromatised into estrogens.** **2- Not Hepatotoxic.**	- Excess androgens: impotence, decreased spermatogenesis, gynecomastia. - ↓HDL & ↑ LDL → ↑ **risk of premature coronary heart disease**. - **Polycythemia**. - **Edema**. - **Hepatic dysfunction** & carcinoma. - **Behavioural changes, ↑aggressiveness.** - Premature closing of epiphysis. - Reduction of testicular size **#** : - Male patients w/ cancer of breast or prostate. - Severe renal & **cardiac disease.** - Psychiatric disorders. - Hypercoagulable states. - Polycythemia. **Drug interaction:** ○ Corticosteroids → edema. ○ Warfarin→ ↓ metabolism→ ↑ bleeding. ○ Insulin or oral hypoglycemics→ hypoglycemia. ○ Propranolol→ ↑ propranolol clearance→ ↓ efficacy.
Antiestrogen:			
1) SERMs			
Tamoxifen, Clomiphene	Increase GnRH & improves pituitary response *"they inhibit the negative feedback of estrogen on the hypothalamus"*	Inducing spermatogenesis when sperms count is low.	Can **induce libidio and bad temper in men**.
2) Aromatase inhibitors			
Anastrozole	Same as SERMs + **Blocks conversion of testosterone to estrogen within the hypothalamus**	Inducing spermatogenesis when sperms count is low.	-
GnRH + GnHs			
GnRH	**Pulsatile** administration	In hypothalamic dysfunction (Hypothalamic amenorrhea)	- Headache, depressions, generalized weakness, pain, gynecomastia, **osteoporosis**.
GnHs	-	- In secondary hypogonadism - GnH together with hCG→ treat pituitary failure	- Headache, local swelling (injection site), nausea, flushing, depression, gynecomastia, precocious puberty.
Non-Hormonal Therapy			
Antioxidants	Protect sperm from oxidative damage, e.g. (e.g. vitamin E,C)		
Folic Acid	Plays a role in **RNA & DNA synthesis in spermatogenesis** + has antioxidant properties.		
Zinc	Plays an important role in testicular development, sperm production & **sperm motility.**		
L-carnitine	Highly concentrated in the epididymis & is important for sperm maturation and motility.		

L:Medications affecting ED

Drug-induced erectile dysfunction

1-Centrally acting drugs

A) Antidepressants

Drugs	TCAs	SSRIs
Intro	●DA> NE promote arousal ● 5HT action on 5HT2 →↓DA release →↓arousal	
M.O.A.	• **Centrally:** ↓ 5HT uptake → ↑ 5HT in synapse act on $5HT_2$ Centrally→ ↓ DA release → ↓ arousal peripherally. • **Peripherally(especially SSRIs): Antagonize NO actions** → ↓genital sensation →Delay Ejaculation→Treat Premature Ejaculation	
	Non-selectively ↓ 5HT uptake.	Selectively ↓ 5HT uptake.

B) Antipsychotic Drugs (Dopamine Antagonists)

Drugs	Risperidone	Haloperidol
M.O.A.	• Dopamine (DA) antagonist → ↓ arousal → ↓ erection.	
ADRs	• Hyperprolactinemia.(↓ testosterone)	

C) Anti-Epileptic Drugs

Drugs	Phenytoin
M.O.A.	• Have GABA effect → antagonize excitatory amino acid → ↑ sedation → ↓ arousal.

D) Centrally-Acting Antihypertensives

Drugs	Methyldopa	Reserpine	Clonidine
M.O.A.	• ↓ arousal.		• Centrally: ↓ arousal. • Peripherally: vasoconstriction.

2- Peripherally acting drugs

A) Other Antihypertensives

Drug	β2 Blockers	Thiazide diuretics
M.O.A.	• -ve/block vasodilating β_2 → shifting NE to α_1 receptor & potentiate α_1 effect → vasoconstriction.	• ↓ spinal reflex controlling erection + ↓ arousal.

B) Anti-Androgens (↓ Desire)

Drugs	Cyproterone acetate	Cimetidine (high doses), Ketoconazole, Spironolactone	Estrogen-containing medications

3-Habituating factors induced ED

Cigarette smoking	Alcohol
vasoconstriction + penile venous leakage	• **Small amounts:** ↑ desire + ↓ anxiety + vasodilatation. • **Big amounts:** ↑ sedation → ↓ desire. • **Chronic:** hypogonadism + polyneuropathy→ED

L:Medications affecting ED

Drugs treating erectile dysfunction

Drug	MOA	Uses	P.K	ADRs	#
1-Centrally Acting Drugs					
Testosterone Replacement Therapy it's not an option if there's damage of nerve that innervate corpora cavernosa	-	**Indication:** Hypogonadism **Benefits:** -Correct secondary ED -Improve libido -Restore muscle strength & sexual drive	**Administration** -parenteral (effective and less hepatotoxic) -Oral -transdermal	- Na retention →weight gain & exacerbate HT,CHF,edema - Gynecomastia - Serum lipoproteins changes - Polycythemia - Exacerbate BPH and prostate cancer - Hepatotoxicity (monitor liver enzymes)	-Patients≥ 40 years should be screened for BPH & prostate cancer before initiating
2-Peripherally Acting Drugs					
Oral PDE5 Inhibitors [Sildenafil - Vardenafil - Tadalafil - Avanafil] All have same efficacy	-Inhibit PDE_5 → prevent breakdown of cGMP → pertain vasodilation and smooth muscle relaxation → erection - Do **not** affect libido (sexual Stimulation is essential)	Erectile dysfunction **1st line therapy** -Pulmonary hypertension. - BPH - Premature ejaculation. - Men who have ED, with HT, DM, spinal cord injury or other comorbid conditions.	metabolized by CYP3A4 dose should be reduced in patients receiving CYP450-3A4 inhibitors (cimetidine, erythromycin, clarithromycin, ketoconazole, ritonavir, squinavir) ↑ ADRs with inhibitors	**Common:** - Headache - Flushing - Dyspepsia - Nasal congestion - Visual disturbances -Back & muscle pain - Priapism **Rare but serious :** - Sudden loss of vision - Retinitis pigmentosa **Unique for Tadalafil:** - Back and muscle pain (due to its inhibition to PDE-11)	- Recent cardiovascular event Nitrates Because of ↑ risk of hypotension if combined - Hypotension - Anatomical deformity (Angulation, cavernosal fibrosis, Peyronie's) - Predisposition to prolonged erection (Sickle cell disease , Multiple myeloma ,Leukaemia)
Prostaglandin Analogues Alprostadil	•PGE_1 synthetic analogue (vasodilator) •Stimulate AC → ↑cAMP & enhance blood flow to corpora cavernosa	For patients who did not respond to PDE5Is	**Administration:** 5-10 mins before intercourse Intracavernosal Injection or Intraurethral	• **Cavernosa plaques** or fibrosis (2-12)% • **Penile pain** (10-44)% • **Priapism** (1-15)%, • Use with caution in patients at risk of priapism (sickle cell anemia, lymphoproliferative disorders)	
		Intracavernosal Injection: Effective in 70-90%			
		Can be combined with vacuum devices or (papaverine, phentolamine)	**Onset:** 5-15 mins **Duration:** less than one hour	High risk of **priapism if combined** with **PDE5Is** -priapism treatment→ phenylephrine	-
		Intraurethral (Muse suppository)			
		-	Patient should empty his bladder completely, Before administration	• pain (24-32)% • Female partner may experience vaginal burning, itching or pain	-

L:Medications affecting ED

Other pharmacological treatment vasoactive agents

Drug	MOA	Uses	P.K	ADRs	#
Papaverine	- PGE1 → ↑ cAMP+ cGMP - PDE2,3,4 Inhibitor	Used alone OR combined together OR with Alprostadil in severe cases	**Administration:** Intracavernosal Injection	–	
Phentolamine	α1 blocker				

Non-Pharmacological treatment

Lifestyle modifications	●Smoking cessation ●↓dietary fats, Weight, stress ●↑exercise, compliance with DM,CVD medications
Vacuum Constriction Device:	●**Results**: 80%-90% ● **Contraindications**: Bleeding disordersPenis placed in plastic tube ●Air evacuated from the tube ●Blood trapped in penis with constricting ring ●**Duration:** 30 minutes
Surgical interventions:	**Indications**: Severe penis tissue degeneration, no respond to pharmacological treatment. **Side effects:** ● infection,mechanical failure of the prosthesis

L:Hormonal replacement therapy

Drug	M.O.A	Admin	Uses	ADRs	#
Estradiol: **-Conjugated estrogen (equine)** **-Esterified estrogen**	It binds to estrogen receptors (ER): 1- ER α : mediates female hormonal functions. (Endometrium, breast, ovaries, hypothalamus) 2- ER β: mediates other hormonal functions (brain, bone, heart, lungs, kidney, bladder, intestinal mucosa, endothelial cells).	• **Oral:** Conjugated equine, Estradiol valerate, Estrial succinate. • **(estradiol):** 1. Transdermal Patches (24 hour twice weekly). 2. Subcutaneous implant: 6 monthly • **Subcutaneous implant (estradiol):** 6 monthly. • Intravaginal "topical" **:**Vaginal cream as such or as rings pessaries	In menopause: 1- **Alone** only after hysterectomy 2- **In presence of uterus combined with progestin to avoid cancer** (never exceed 5 years administration). 3-Increases bone density 4- Protects CVS **in short term use.** **Long-term use : thromboembolism & CVS problems**	• **Patients discontinue HRT** at early stages [non-compliance] : ○ Irregular vaginal bleeding ○ Breast tenderness • Nausea • Vaginal discharge (Increased vascularity) • Fluid retention, **Weight gain** • Spotting or darkening of skin on face	Absolute: Undiagnosed vaginal bleeding. - Severe liver disease. **-Thromboembolic manifestations** - Endometrial, **breast**, & ovarian cancers. **Interactions:** ○ With SERM: additive side effects for both drugs. ○ With Aromatase inhibitors: ↓efficacy. ○ With Corticosteroids: ↑ side effects.
Progestins	Binds to progesterone receptors(PR): PR-**α** & PR-**β**. Progesterone It can **only** be given **parenterally**. Thus, progestin preparations are synthesized to be taken orally.	• **Oral**: Micronized progesterone or progestins →see contraception • **IntraUterine (IU):** as Levonorgestrel or Progestasert • **Vaginal**: natural progesterone gel, pessary. • **Transdermal**: sequential (replaced daily), continuous patch	**- In menopause:** 1- Usually given in combination with estrogen **(protects against estrogen-induced endometrial cancer)** **-Other uses:** -Contraception -Dysmenorrhea	-Anxiety,irritability -headache -dizziness -nausea, vomiting & abdominal pain or bloating	-
Phytoestrogens	Supplements from plants containing **isoflavones** (soya beans, flaxseeds) or lignans (whole grains).	-	-Mimic the action of estrogen on estrogen **receptor- β** **-Alleviate symptoms related to hot flushes,** mood swings, cognitive functions & possess CVS protective actions. (data limited on their efficacy)	-	**Estrogen-dependent breast cancer**
Androgen Tibolone	Testosterone is responsible for sexual arousal in females, given only if there is **loss of libido** & orgasm.		• Testosterone is given as sole therapy to menopausal women in whom their menopausal symptoms are focused on lack of sexual arousal. • It is given as adjuvant to combined estrogen & progestin if all other menopausal symptom exist. • **Tibolone**, can be effective in some women has some androgen agonistic properties.		Androgen is not by FDA in women

L:Hormonal replacement therapy

Advantages and disadvantages of HRT

Advantages	Disadvantages
Definite benefit: -↓ *symptoms of* ***menopause*** *vasomotor genitourinary.* *-Improve* ***osteoporosis*** *(definite ↑ in bone mineral density → probable ↓ risk of fracture)*	*Endometrial cancer (estrogen only).*
	Venous thromboembolism (long term)
Uncertain benefit: ↑ ***cognitive*** *function.* ***Note: The risk of CVS problems and breast cancer with HRT is more than their benefits***	*breast cancer (long term 5 years)*

Non-hormonal therapy

Selective Estrogen Receptor Modulator (SERM)

	Raloxifene	Tamoxifen
M.O.A	• **Antagonist** in the breast and uterus • **Agonist** in bone	• **Antagonist** in the breast. • **Partial agonist** endometrium & bone
Effects	• Has no effect on hot flushes. • **Preventing vertebral bone fracture.** • **CVS problems are ↓ than Estrogen.** • For osteoporosis use of bisphosphonate is better than SERMs.	• Increase the risk of venous thrombosis. • Precipitates vaginal atrophy & **hot flushes.** • Not used for history of endometrial cancer

Non-hormonal Agents Used in management of menopausal symptoms

Fluoxetine	• Selective Serotonin Reuptake Inhibitor (SSRI)
Clonidine	• *Anti-adrenergic* Centrally acting antihypertensive
Gabapentin	• Anticonvulsant.
Physical activity	• Exercise, smoking cessation and relaxation of mind will improve symptoms of menopause (e.g.hot flushes) and fall prevention strategies prevents chances of fracture.

Note: **An ideal SERM for use as HRT should be agonistic in brain, bone, CVS, vagina & urinary system But antagonistic in breast & uterus.**

L:Oral and other forms of contraception

Estrogen preparations	Progesterone preparations
• **Ethinyl estradiol** or mestranol [a "prodrug" converted to ethinyl estradiol] • Concentration used is **very low to minimize estrogen hazards.**	•Norethindrone, Levonorgestrel(Norgestrel) & Medroxyprogesterone acetate (have systemic androgenic effects(acne, hirsutism & weight gain)) •Norgestimate, Desogestrel & Drospirenone **(Have no systemic androgenic effect (currently used)).**

Combined Oral Contraceptive (COC) Contains *(contain both **estrogen & progestin**)*

M.O.A.

-Inhibit ovulation by **suppressing the release of gonadotropins (FSH & LH)** → no action on the ovary → **ovulation is prevented**. *"-vefeedback"* (used in PCOS because it decreases LH)
-Inhibit implantation by causing **abnormal contraction** of the fallopian tubes & uterine musculature → ovum will be **expelled** rather than implanted.
-**Increase viscosity of the cervical mucus** making it so viscous → **no sperm pass**.
-**Abnormal transport time** through the fallopian tubes.*"due to the increased cervical viscosity"*

Admin.

Monthly pills:
For **21** days starting at day 5 to day 26, followed by **7** free days OR with placebo/ dummy pills to improve compliance **Formulation of 28 pills (mimic natural changes in hormones):**
-**Monophasic** (1 fixed dose)→ a **fixed** amount of estrogen & progestin. (E.g Loestrin)
-**Biphasic** (2 doses)→ a **fixed** amount of **estrogen**, while amount of **progestin** ↑ stepwise in the second half of the cycle (E.g jenest-28)
-**Triphasic** (3 doses)→ amount of **estrogen**; **fixed or variable** & amount of **progestin** ↑ stepwise in 3 phases. (E.g Triphasil)

Seasonal pills:
- 91 days (Long duration); taken for **84** days followed by **7** days free. (continuous/extended cycle)
- very low concentration of estrogen & progestins

Advantage: It **lessens menstrual periods** to 4 times a year (1 period every 3 months), useful in cases of endometriosis and migraines during period.
Disadvantages: ↑ incidence of breakthrough bleeding during early use.

ADRs

Estrogen related:
- **Breast tenderness**
- ↑ Skin Pigmentation
- ↑ Frequency of gallbladder disease
- ↑ Incidence of **breast, vaginal & cervical cancer.**
- **Thromboembolism** & HTN.
- Nausea
- Headache
- Impair glucose tolerance (hyperglycemia)

Progesteron related:
- Depression
- Menstrual irregularities.
- Weight gain
- Hirsutism
- Masculinization (**Norethindrone**).
- Ectopic pregnancy
- Nausea & Vomiting
- Fatigue, headache

#

- **Thromboembolic disorders** /thrombophlebitis.
- CHF or other causes of **edema**.
- **Vaginal bleeding** of **undiagnosed** etiology.
- Known or suspected **breast cancer** due to family history, or estrogen-dependent neoplasms.
- Known or suspected Estrogen-dependent neoplasms.
- Dyslipidemia, DM, HTN, migraine & impaired hepatic function.

-Lactating mothers (mini pills), Obese Females, Smokers and Females above 35 years → better given progestin only pills.

DDI

***-Medications that cause contraceptive failure*: (i.e impairing absorption & CYT P450 inducers)**
1. **Antibiotics** e.g. **Ampicillin** interfere with normal GI flora→ ↓absorption + enterohepatic recycling → ↓ its bioavailability
2. Enzyme Inducers: e.g. **Phenytoin, Phenobarbitone, Rifampin.**

-Medications that ↑ COC toxicity: (i.e. CYT P450 inhibitors)
Microsomal Enzyme Inhibitors; ↓ metabolism of OC → ↑ toxicity, (e.g. **Acetaminophen, Erythromycin,** SSRIs"used in depression").

-Medications of altered clearance (↓) by COC: ↑toxicity
e.g. **Warfarin, Cyclosporins, Theophylline**.

L:Oral and other forms of contraception

Mini Pills - progestin only Pills (POP)

Systemic androgenic effect: **Norethindrone, Levonorgestrel (Norgestrel), Medroxyprogesterone acetate,**
No systemic androgenic effect: **Norgestimate, Desogestrel & Drospirenone.**

M.O.A.	**Increase cervical mucus, so no sperm penetration** & therefore, no fertilization.
Indications	Are alternative **when estrogen is contraindicated** (e.g. **during breastfeeding, hypertension, cancers that induced by estrogen, smokers and female over the age of 35, obese females**).
Admin.	• Should be taken **every day, the same time, all year round.** • **I.M injection** e.g. Medroxyprogesterone acetate 150 mg every 3 months.

Morning-After Pills

Indications	• **Emergency or Post Coital Contraception.** (Coital=sexual intercourse) • When desirability for avoiding pregnancy is obvious: - Unsuccessful withdrawal before ejaculation. - Torn, leaking condom. - Missed pills. - Exposure to teratogen e.g. Live vaccine. - Rape.

Morning-after pills (Post Coital Contraception or Emergency Contraception) (1)

Composition	Method of Administration	Timing of 1st dose After Intercourse	Reported Efficacy
Ethinyl estadiol + Levonorgestrel	2 tablets BID with 12 hrs in between	0- 72hrs Not effective after that	75%
High-dose only Ethinyl estadiol	BID(2 times a day) for 5 days		75 - 85%
High dose only levonorgestrel			70 – 75%
Mifepristone (Antiprogestin) ± Misoprostol (Prostaglandin analogue)	A single dose *"Causes contractions→ expels ovum"*	0- 120 hrs	85 - 100% **Highest efficacy**

Other Methods of Contraception

Method	Info.
IntraUterine Device (IUD)	• **M.O.A:** ○ Changing the lining of the uterus making it unsuitable for a pregnancy. ○ Thickening the mucus of the cervix, preventing sperm from entering the uterus. ➔ **Hormonal IUD:** It is T-shaped, made of plastic and steadily **releases** small amounts of the **progestogen** directly into the uterus. ➔ **Copper T IUD:** Uses copper to prevent pregnancy *"kills sperm"*
Contraceptive Diaphragm	Covers the cervix, so sperm cannot get into the uterus.
Vaginal Ring	Releases a continuous dose of the hormones estrogen and progestin, the hormones are absorbed into the bloodstream: • Prevent ovulation. • Cause the cervical mucus to thicken and alter sperm movement
Condoms	• Internal female condoms. • External male condoms.

Drugs & Lactation

Drugs & Lactation

- Breastfeeding provides the baby with immunoglobulins (IgA, IgM) that are essential for protection against gastroenteritis.
- Monoclonal antibodies, pass very poorly into milk after the first 1st week postpartum.
- The epithelium of the breast alveolar cells is most permeable to drugs during the 1st week postpartum, drug transfer to milk may be greater during the 1st week of infant's life.
- Drugs ingested by the mother diffuse or are transported from the maternal plasma to the alveolar cells of the breast.
- The concentration of drugs achieved in breast milk is usually low (<1%).

Pharmacokinetics

Premature babies have very limited capacity for metabolism & excretion.
Compared to adults neonates have:

Higher	Lower
↑Gastric pH (↓Gastric acid output) ↑Gastric emptying time ↑Concentration of free drug ↑Percentage of body water	↓Serum albumin ↓Efficiency of renal clearance (↓ renal blood flow & GFR) ↓Rate of metabolism Due to immaturity of liver enzymes ↓Percentage of adipose tissue

Factors controlling passage of drugs into breast milk

Drug related factors	Metrenal factors	Infant factors
• Molecular weight • Lipid solubility • Degree of ionization • Drug pH • Protein binding • Half-life • Oral bioavailability	• Dose of drug • Route of administration • Time of breastfeeding (& drug administration) • Health status • Maternal concentration of drug	• Age • Body weight • Health status

A. factors related to the drug

Molecular weight	• **Very small molecules** (<200 daltons) such as alcohol, **equilibrate rapidly** between plasma & breast milk via the aqueous channels surrounding alveoli • **Large molecules drugs** (> 800 daltons) are **less likely to be transferred to breast** milk. ◦ Insulin: MW > 6,000 d ◦ Heparin: MW = 40,000 d
Plasma proteins binding	• Drugs circulate in maternal circulation in unbound (free) or bound forms to albumin. • **Only unbound** form gets into maternal milk. • definition of good plasma protein is > 90% binding (e.g. Warfarin).
Degree of ionization	• Ionized form of drugs are less likely to be transferred into breast milk. ◦ Heparins (Charged and ↑ MW) pass poorly into breast milk.
Volume of distribution	Transfer of drugs from maternal blood to milk is low with drugs that have large volume of distribution
Lipid solubility	Lipid-soluble drugs pass more freely into the breast milk than water-soluble drugs.
Drug PH	• pH of milk (7.2) is slightly more acidic than maternal blood (7.4). • **Weak basic drugs tend to concentrate in breast milk & become trapped secondary to ionization.** • Weak acidic drugs don't enter the milk to a significant extent and tend to be concentrated in plasma.
Half-life	• Avoid the use of drugs with long half-lives; short half-lives are preferable. • Oxazepam (short half-life) vs Diazepam (long half-life).

B. Factors related to the mother

Route of Administration *(topical > oral > injection)*	• Route of administration affects the concentration of the drug in maternal blood. • Maternal use of topical preparations (creams, nasal sprays, inhalers) is expected to carry less risk to a breastfed infant than systemically administered drugs.
Time of breastfeeding	• Lactating mother should take medication just **after nursing** and **3-4** hours before the next feeding (to allow time for drug to be cleared from the mother's blood–drug concentration in milk will be low *"after the ½ life"*).
Health status	**Breastfeeding is contraindicated in case of:** • HIV-positive women • Active, untreated TB in mother • Herpes on breast • Use of illegal drugs by mother • Certain medications used on chronic basis

Drugs & Lactation

C.factors related to the infant

Age	**Pediatric population is classified into:**
	• **Newborn:** less than 1 month
	  ○ **Preterm neonates** (more sensitive)**:** born before 38 weeks of pregnancy
	  ○ **Full-term neonates:** 38-42 weeks of gestational age
	• **Infants (babies)**: 1-12 months
	• **Children**: 1-12 years
	• **Adolescents**: 13-18 years

Health status	**Special caution is required in:** • Premature infants. • Infants with Impaired ability to metabolize/excrete drugs (e.g. hyperbilirubinemia) • Low birth weight. • Infants with G6PD deficiency

Neonatal Hyperbilirubinemia

Premature infants or **infants with inherited G6PD deficiency** are susceptible to oxidizing drugs that can cause → RBC hemolysis → ↑ bilirubin (hyperbilirubinemia) → kernicterus

Examples for oxidizing drugs: 1- Antimalarials: Primaquine
2- Antibiotics: Sulfonamides, Trimethoprim

Neonatal Methemoglobinemia

- **Infants under 6 months** of age are particularly prone to develop methemoglobinemia upon exposure to some oxidizing drugs.
- **Methemoglobin** is an oxidized form ferric [Fe3+] of hemoglobin that has decreased affinity for O2 → tissue hypoxia.

The amount of a drug to which the baby is exposed as a result of breastfeeding depends on:

- The **amount** of milk consumed.
- The **amount** of drug absorbed from the GIT.
- The **ability** of the baby to eliminate the drug.

Drugs **Contraindicated** in Lactation:

Only few drugs are totally contraindicated:

- **Anticancer drugs**: (cytotoxicity & neutropenia) Doxorubicin, Cyclophosphamide, Methotrexate.
- **Radiopharmaceuticals**: Radioactive Iodine.
- **CNS acting drugs** (due to their high lipid solubility) : Amphetamine, Heroin, Cocaine.
- **Ergotamine** (for migraine headaches; causes vomiting, diarrhea, convulsions in infants).
- **Tobacco smoke** (nicotine can cause vomiting, diarrhea & restlessness for the baby,
- decreased milk production and increase the incidence of respiratory & ear infections).
- **Immunosuppressants**: Cyclosporine.
- **Alcohol & Lithium** (high milk-to-plasma ratio).
- **Chloramphenicol** (bone marrow suppression).
- **Atenolol** (CVS drugs "risk of bradycardia & hypoglycemia").
- **Potassium iodide** (thyroid effect)

Drugs Affecting Milk Supply

Increase Lactation
Drugs that: ↑Prolactin.

Dopamine antagonists: **Stimulate prolactin secretion & galactorrhea.**

- **Metoclopramide** (antiemetic).
- **Domperidone** (antiemetic).
- **Theophylline** (used in asthma)
- **Haloperidol** (antipsychotic).
- **Methyldopa** (antihypertensive).

Suppress Lactation
Drugs that: ↓ Prolactin.

- **Levodopa** (dopamine precursor).
- **Estrogen & combined oral contraceptives** that contain high-dose of estrogen & progestin.
- **Bromocriptine** (dopamine agonist).
- **Androgens.**
- **Thiazide diuretics.**

Drugs of Choice in Lactation

Antibiotics	- Cephalosporins.	- Penicillins.	**Antithyroid**	**- Propylthiouracil** is preferable over others.	
Antidiabetes	- Insulin.	- Oral antidiabetics.	**Anticonvulsants**	- Carbamazepine	- Phenytoin
Anticoagulants	**- Heparin.**	**- Warfarin.**	**Oral contraceptives**	**Progestin-only pills (mini pills)** are preferred for birth control.	
Analgesics	Acetaminophen (Paracetamol).		**Antiasthmatics**	- Inhaled corticosteroids.	- Prednisone.

Drugs & Lactation

Group	Drugs that may be used ✓	Drugs that should be avoided ✕
Antibiotics Penicillins are the first choice.	• **Penicillins** (e.g. Ampicillin, Amoxicillin): no significant ADRs but mostly allergic reactions & diarrhea. • **Cephalosporins & Macrolides** (e.g Erythromycin, Clarithromycin): no significant ADRs but alterations to infant bowel flora.	• **Quinolones:** theoretical risk of arthropathies. • **Chloramphenicol:** grey baby syndrome. • **Sulfonamides** (Co-trimoxazole): hyperbilirubinemia - neonatal jaundice; should be avoided in premature infants or infants **with G6PD deficiency.** • **Tetracycline:** possible risk of teeth discoloration; absorption by the baby is probably prevented by chelation with milk calcium.

Sedatives (Hypnotics)	• **Benzodiazepines** (e.g Diazepam, Lorazepam):
	  ○ Single use of low dose → probably safe
	  ○ Prolonged use → lethargy & sedation in infants.
		• **Barbiturates** (e.g Phenobarbitone): lethargy, sedation, & poor suck reflexes with prolonged use.

Antidiabetics	• **Insulin:** safe. • **Oral antidiabetics:** compatible. ○ **Metformin:** use with caution	
Antidepressants	• **Selective Serotonin Reuptake Inhibitors (SSRIs):** Paroxetine is the preferred SSRI.	
Oral contraceptives	• **Progestin-only pills (mini pills):** preferred for birth control. • **Non-hormonal methods.**	• **Estrogens-containing pills:** ↓ milk quantity.
Antithyroid drugs	• **Propylthiouracil**: should be used rather than Carbimazole or Methimazole	• **Carbimazole, Methimazole, Potassium Iodide**: may suppress thyroid function in infants
Anticoagulants	• **Heparin:** safe; not present in breast milk. • **Warfarin:** can be used; very small quantities found in breast milk, **so monitor infant's prothrombin time during treatment.**	
Anticonvulsants	• **Carbamazepine:** preferable over others; compatible with breastfeeding • **Phenytoin:** amounts entering breast milk are not sufficient to produce ADRs	• **Valproic acid:** infants must be monitored for CNS depression, hepatotoxicity. • Lamotrigine: **avoid**
Antihistamines	• **Non-sedating antihistamines** 2nd & 3rd gen (e.g. Loratadine): safe at lower doses	• **Sedating antihistamines** 1st gen (e.g. Diphenhydramine)
Analgesics	• **Paracetamol:** safe. • **Ibuprofen:** compatible.	• Aspirin, theoretical risk of reye's syndrome

Teratogens and drugs of abuse in pregnancy

How Do Drugs Cross the Placenta?

- Most drugs can cross placenta through the placental membrane (semi-permeable).
- Drugs in the mother's blood can cross this membrane into fetal blood vessels in the villi and pass through the umbilical cord to the fetus.

Factors Controlling Placental Drug Transfer

Physicochemical Properties

1. Lipid Solubility or diffusion (Safe in pregnancy: ↓lipid solubility and ↑Polarity (ionized))

- **Lipophilic drugs** diffuse readily across the placenta and **enter fetal circulation**
  - Ex: **Thiopental**→ crosses placenta → **sedation and apnea** in newborn infants.
- **Ionized drugs** cross the placenta very slowly → very **low concentration in fetus.**
  - Ex: **Succinylcholine, & Pancuronium**

2. Molecular Size (Safe in pregnancy: ↑MW) | MW affects the rate of transfer:

- MW of 250-500 → cross the placenta easily.
- MW of 500-1000 → crosses the placenta with more difficulty.
- MW ↑ 1000 → can NOT cross the placenta. Ex: **Heparin**

3. protein binding (Safe in pregnancy: ↑Plasma protein binding)

- Protein binding in the maternal circulation hinders the passage of drugs. Ex: **Propylthiouracil, chloramphenicol**

Stage of Development

1. 1st trimester (1-12w)

A. **Blastocyst Formation First 2 weeks (1-16d) (pre-differentiated period, conceptus)**
- Drugs have **all-or-nothing effect** (None: no ADRs, All: abortion)
- Exposure to harmful drugs during this period → prenatal death → abortion

B. **Organogenesis (2-8 weeks) (17-60d)**
- The most sensitive period of pregnancy because major body organs & systems are formed.
- **Exposure to harmful drugs → major birth defects or major congenital malformation (teratogenesis)**

2. 2nd & 3rd trimester (13-28w) → Histogenesis and Functional Maturation (8 weeks onward)
- **Exposure to drugs → functional problems** rather than **gross malformations**,
- Exposure to drugs during 2nd and 3rd will not induce major structural malformation.
- Drugs during this period can produce minor morphological abnormalities, growth retardation, and functional defects

3. Near term (29-40w) →ADRs on neonates after delivery E.g NSAIDS

Duration of Exposure

- Once or for chronic use ? Some drugs ADRs won't appear immediately, but will appear after puberty.

Teratogenesis

What is it?

FDA classification system

	Characteristics	Examples
A	• **controlled human studies with no risk →Drugs can be used** in pregnancy.	**Folic acid | Thyroxine**
B	• Animal studies ok, No human data → **Drugs can be used** in pregnancy	**Paracetamol | Erythromycin**
C	• **Risk cannot be ruled out.** (Animal studies are not ok, No human data) • **Drug may be used in serious situation despite its potential risk.**	**Morphine**
D	• Positive evidence of human fetal risk based on adverse reaction data **from studies in humans**, investigational or marketing experience. (Benefits outweigh risks) • **May be used in serious diseases or life threatening situations**	**Antiepileptics** Phenytoin
X	• Proven fetal abnormalities in animal and human studies • risks in pregnant women clearly outweigh potential benefits • **Drugs are teratogens, contraindicated in pregnant women**+planning to conceive.	**Thalidomide** (sedative)

Proven Teratogens (category X)

Retinoids	A. Vitamin A (limited to 700 ug/day)	B. Isotretinoin : used in treatment of acne
Ionizing radiation	**Radioactive Iodine (I131)**	**ACEI**
Cytotoxic drugs	A. Folate antagonists (Methotrexate)	B. Alkylating agents (Cyclophosphamide)
Antibiotics	Tetracyclines, Quinolone	
Anticoagulants (Warfarin)	**Thalidomide (sedative/hypnotic)**	**Hormones**

Teratogens and drugs of abuse in pregnancy

Proven Teratogens

Thalidomide	**Phocomelia:** Shortened or absent long bones of the limbs.
Alcohol	**Fetal Alcohol Syndrome** • Microcephaly. • Craniofacial abnormalities. • CNS abnormalities (attention deficits, intellectual disability, mental retardation). • Intrauterine growth retardation. • CVS abnormalities.
Phenytoin	• **Fetal Hydantoin Syndrome:** ○ **Nail and digital hypoplasia** ○ Cardiac anomalies ○ **Oral cleft (cleft lip and palate)**
Valproic acid	• **Neural tube defect (spina bifida)** • **impaired folate absorption**
Corticosteroid	• Cleft lip and palate
Warfarin	• **Hypoplasia of nasal bridge.** (1st trimester) • **CNS malformation.** (1st trimester)
Tetracyclines	• Altered growth of teeth and bones. • Permanent teeth staining (yellow-brown discoloration of teeth). • Enamel hypoplasia
Lithium	**Ebstein's anomaly:** • CVS anomalies mainly **valvular heart defect involving tricuspid valve.** • fetal echocardiography should be considered for women.
ACEIs	Captopril, Enalapril • Renal damage: **ACEIs** disrupt fetal RAAS system which is essential for normal renal development. • Neonatal anuria. • Fetal **hypotension & Hypoperfusion.** • Growth retardation.
Hormones	• **Estrogens** → Testicular atrophy in **male** fetus • **Androgens**→Fetal masculinization in **female** fetus • **Diethylstilbestrol**→ Vaginal carcinoma of **female** offspring (Extended Teratogenic effect)

Adverse Effects of Drugs (2nd & 3rd trimesters)

Drug	Adverse Effect
Antibiotics	• **Tetracyclines** ○ Impaired teeth and bone development ◦ Yellow-brown discoloration of teeth
	• **Aminoglycosides ex: Streptomycin and Kanamycin** →Ototoxicity (8th cranial nerve damage)
	• **Chloramphenicol** → **Gray baby syndrome**
	• **Sulfonamides** → Displace bilirubin from albumin → neonatal hyperbilirubinemia, jaundice)
CNS depressants	• interference with suckling. + Respiratory depression • Reduced blood flow → Fetal distress ○ **Ex: Diazepam and Morphine**
	• **Benzodiazepines** ○ Chronic use → neonatal dependence and withdrawal symptoms **Ex: Diazepam**
Corticosteroids	• **Adrenal atrophy** • **Growth retardation**
Propranolol	• Bradycardia | Neonatal hypoglycemia • Placental insufficiency → reduced uterine blood flow → **fetal distress**
ACEIs	• Renal damage
Antithyroid	• Risk for neonatal hypothyroidism and goiter • **Ex: Methimazole, Carbimazole, Iodide & Propylthiouracil**
NSAIDs	• **Prostaglandin synthesis inhibitors** ○ Constriction of ductus arteriosus (close prematurely) → Pulmonary Hypertension in newborns ○ Increase in gestation time + Prolong labor, ○ neonatal bleeding and risk for postpartum hemorrhage. • **Ex: Aspirin-indomethacin**
Warfarin	• Risk of bleeding

Teratogens and drugs of abuse in pregnancy

Drugs of Choice During Pregnancy

Hypertension in Pregnancy

Probably safe	Contraindicated
• **α -Methyl dopa** • Labetalol (alpha- and beta blocker) • **Emergency: Labetalol** or Hydralazine	• ACE inhibitors • Angiotensin II receptor blockers • Ca2+ channel blockers in mild HTN • Thiazide diuretics • Propranolol

Coagulation Disorders in Pregnancy

Probably safe	Contraindicated
• **Heparin** (high molecular weight and polar) - It is polar → doesn't cross the placenta - There's an antidote **protamine sulphate.**	• **Warfarin in all trimesters** → Cross the placenta - **1st trimester:** teratogenicity. - **2nd/3rd trimesters:** risk of bleeding.

Antibiotics in Pregnancy

Probably safe	Contraindicated
• **Penicillins** (ampicillin, amoxicillin)First line • **Cephalosporins:** Ceftriaxone • **Macrolides (erythromycin, azithromycin):** **As an alternative in penicillin-sensitive patients** but **erythromycin estolate** avoided (risk of hepatic injury to mother). • Drug of choice: **Penicillins, Cephalosporins, erythromycin**	• **Tetracyclines → teeth and bones deformities** • **Quinolones (ciprofloxacin)**→ arthropathy: bone and cartilage damage. • **Aminoglycosides** → ototoxicity. • **Sulfonamides → neonatal jaundice and kernicterus.** • **Chloramphenicol → Gray baby syndrome.**

Antithyroid Drugs in Pregnancy

•**Are used in thyrotoxicosis or Grave's disease**
- ○ **Propylthiouracil:** preferable over others highly protein bound First line
- ○ Methylthiouracil (methimazole) (class D)
- ○ Carbimazole (class D)
- ○ Radioactive iodine (class X)

• All can cross the placenta, all have risk for congenital hypothyroidism and goiter → the **lowest dose** of antithyroid drugs should be used

Other Drugs

Antidiabetics	Analgesics	Anticonvulsants
• **Insulin** is the best choice • Avoid oral antidiabetics	• **Acetaminophen /** Paracetamol	• All antiepileptics have potential to cause malformations. • **Avoid valproic acid - highly teratogenic.** • **Folic acid supplementations** can prevent neural tube defects in women receiving antiepileptics

Drugs of Abuse During Pregnancy

Drug	Description
Alcohol	• The use of alcohol is contraindicated in all trimesters of pregnancy. • ***Chronic use of alcohol during early weeks*** of the 1st trimester leads to **Fetal Alcohol Syndrome (FAS)** which is characterized by: 1. **Microcephaly** 2. **Low birth weight** 3. CNS abnormalities: Attention deficits, Intellectual disability, Mental retardation 4. **Craniofacial abnormalities** 5. CVS abnormalities
Cocaine	• Cocaine has ***low MW***, so it can easily pass into fetus through the placenta. • Inhibits reuptake of sympathomimetics (***epinephrine, norepinephrine and dopamine)*** causing: 1. Vasoconstriction 2. Rapid heart rate 3. Hypertension -vascular disruption- • **Hypoxia**: It decreases blood flow to uterus and fetal oxygenation. • It increases uterine contractility. • *Fetal gross malformations include:* 1. **Microcephaly** 2. Prematurity 3. Growth retardation 4. Intrauterine growth retardation 5. Mental retardation 6. **Placental abruption**
Tobacco	• Tobacco contains ***nicotine & carbon monoxide*** that harm the fetus. No evidence that it causes birth defects but Tobacco increases the risk of: 1. Decreased blood flow to the placenta | Fetal hypoxia 2. Retarded fetal growth | **Low birth weight** 3. Spontaneous abortion 4. **Prematurity -preterm labor-** 5. Perinatal mortality

Tocolytics and oxytocin

Oxytocin (Syntocinon)

M.O.A

The interaction of endogenous or administered oxytocin with **myometrial cell membrane receptor promotes the influx of Ca^{2+}** from extracellular fluid and from sarcoplasmic reticulum into the cell: ↑ in cytoplasmic calcium → **stimulates uterine contraction**

Actions

1. Effect on uterus:
   - **Stimulates** both the **frequency** and **force** of uterine contractility particularly of the **fundus** segment of the uterus.
   - These contractions resemble the **normal** physiological contractions of uterus **(contractions followed by relaxation** "coordinated"**)**
   - **Immature** uterus is **resistant** to oxytocin.
   - Contract uterine smooth muscle **only at term**
     - Sensitivity **increases** to *8* fold **in last 9 weeks** and *30* times in **early labor** (term specific)
     - Clinically oxytocin is **given** only when uterine **cervix is soft and dilated** (ready for delivery)

2. Effect on Myoepithelial cells: Oxytocin contracts myoepithelial cells surrounding mammary alveoli in the breast & leads to milk ejection.

P.K.

- Not effective orally (destroyed in GIT)
- Administered **I.V. to augment labor** or as **nasal spray in impaired milk ejection**
- Not bound to plasma proteins
- Catabolized by liver & kidneys
- T ½ = 5 min very short (disadvantage)

Uses

Synthetic preparations of oxytocin (e.g. syntocinon) are preferred.

1. **Induction & augmentation of labor** (slow I.V infusion):
   - Mild preeclampsia near term
   - Uterine inertia (inefficient contractions)
   - Incomplete abortion
   - Post maturity (late delivery)
   - Maternal diabetes (can lead to preeclampsia)
2. **Postpartum uterine hemorrhage** (IV drip): but ergometrine is often used (1st line)
3. **Impaired milk ejection** (one puff in each nostril 2-3 min before nursing) **fast onset of action**

ADRs

- Maternal death **due to hypertension**
- Uterine rupture
- Fetal death **(ischemia)**
- **Water intoxication**: if oxytocin is given with relatively large volumes of electrolyte-free aqueous fluid intravenously

#

- Hypersensitivity
- Cephalopelvic disproportion
- Prematurity
- Incompletely dilated cervix
- Abnormal fetal position
- Evidence of fetal distress

Pre-cautions

- Multiple pregnancy
- previous C-section
- Hypertension

Ergot Alkaloids

Drug

Natural: Ergometrine (**Ergonovine**), I.M

Synthetic: Methylergometrine (**Methylergonovine**), I.M

M.O.A.

- Ergot alkaloids induce **Tetanic contraction** of uterus **without relaxation** in between (not like normal physiological contractions) tetanic = continuous
- It causes contractions of uterus as a whole i.e. **fundus and cervix** (tend to compress rather than to expel the fetus)

P.K.

- Extensively metabolized in liver (90% excreted in bile)

Preparations: **Syntometrine** (ergometrine + oxytocin)"for postpartum hemorrhage"

Uses

Postpartum hemorrhage (3rd stage of labor)

ADRs

- **NVD**
- Hypertension
- Vasoconstriction of peripheral blood vessels → Gangrene

#

Induction of labor:

a) **1st** and **2nd** stages of labor
b) vascular disease
c) Severe hepatic and renal impairment
d) Severe hypertension

Tocolytics and oxytocin

Prostaglandins

Drug	PGE2 Dinoprostone	PGF2α Dinoprost, Carboprost	Synthetic PGE1 Misoprostol
Administration	• Vaginal suppository • Extra-amniotic solution	Intra-amniotic injection	-
Uses	• Induction of abortion (*pathological*)	• Induction of labor (fetal death in utero)	• Postpartum hemorrhage
ADRs	• **NVD** (Nausea, Vomiting, Diarrhea) • Abdominal pain		
	Flushing	Bronchospasm	-
#	• Mechanical obstruction of delivery	• Predisposition to uterine rupture	• Fetal distress
caution	• Multiple pregnancy	• Glaucoma • Asthma	• Uterine rupture

Oxytocics Comparison

group	Oxytocin	Ergometrine	Prostaglandins
Contractions	• **Coordinated** contractions that resemble normal physiological contractions • Only at term	**Tetanic** contractions; doesn't resemble normal physiological contractions	• Coordinated contractions • Throughout pregnancy
Cervix	**Does not soften the cervix**	-	soften/relax the cervix
Onset & duration	• Rapid onset • Shorter duration of action	• Moderate onset • Longer duration of action (compared to oxytocin)	Longer duration of action (compared to oxytocin)
Uses	• To induce & augment labor • Postpartum hemorrhage	Only in postpartum hemorrhage	• Induce abortion in 2nd trimester • Used as vaginal suppository for labor induction

Tocolytics

Drugs Producing Uterine Relaxation

Drug	Ritodrine (IV) (β adrenoceptor agonists)	Nifedipine (Ca channel blockers)	Atosiban (IV) oxytocin antagonist (New tocolytic agent)
M.O.A.	**Selective β2 receptor agonist used specifically as a uterine relaxant** : bind to β-adrenoceptors, activate **enzyme Adenylate cyclase** → ↑ **cAMP** → ↓ intracellular calcium level → relaxation of uterine smooth muscle	• Causes relaxation of myometrium • Markedly **inhibits** the amplitude of spontaneous and **oxytocin-induced contractions**	Compete with **oxytocin** at its **receptors** on the uterus.
Uses	Relax the uterus and **arrest threatened abortion** or **delay premature labor.**		
ADRs	• Tachycardia (high dose) act on β1 • Flushing • Tremor • Nausea, vomiting • Sweating • Hypotension • Hyperglycemia • Hypokalemia	• Tachycardia • Hypotension • Flushing • Headache, dizziness • Constipation • **Ankle edema** • **Coughing** • **Wheezing**	-

Drugs used in treatment of syphilis

1) Natural Penicillins (first line)

drug	Penicillin G (Benzyl penicillin)	Procaine Penicillin G	Benzathine Penicillin G
MOA	Inhibits bacterial **cell wall** synthesis through inhibition of transpeptidase enzyme required for crosslinks of peptidoglycans. → **Bactericidal.**		
P.K.	- Given I.V, Short	- Given I.M Long	- Given I.M , Long
	All these penicillin preparations are: ○ Acid unstable ○ Not metabolized. ○ Penicillinase sensitive (β-lactamase sensitive). ○ Excreted unchanged in urine → Renal failure prolongs their DOA ○ procaine & benzathine make the combination long acting		
ADRs	• Hypersensitivity. • Super infections. • Convulsions with high doses or in renal failure.		

2) 3rd generation cephalosporins

drug	Ceftriaxone
MOA	• Inhibit bacterial **cell wall** synthesis. • **Bactericidal**
P.K.	• Given parenterally (I.V). • Eliminated via biliary excretion • Long Half-life. -
ADRs	• Hypersensitivity • Thrombophlebitis. • Superinfection. • GIT upset: Diarrhea.

Tetracycline

drug	Doxycycline
MOA	Inhibit bacterial **protein synthesis** by reversibly binding to **30S** bacterial ribosomal subunits. → Bacteriostatic.
P.K	• Given orally. • Long acting. • 100 mg twice daily for 14 days.
ADRs	• Nausea, vomiting ,diarrhea & epigastric pain (given with food). • Brown discoloration of teeth in children. • Deformity or growth inhibition of bones in children. • Hepatic toxicity). • Superinfections. • Vertigo.
C.I	• Pregnancy. • Breast feeding • Children (< 10 yrs)

Macrolides

drug	Azithromycin
MOA	Inhibits bacterial protein synthesis by binding to bacterial **50S** ribosomal subunits.
P.K	• Acid stable → Once daily oral dose (t1/2=2-4d) • Penetrates: most tissues except CSF. • No effect on cytochrome P450
ADRs	• **GIT upset:** Nausea, vomiting, abdominal pain and diarrhea. (given 1 hour before or 2 hours after meals). • **Allergic reactions:** Urticaria and mild skin rashes.
C.I	-

WHO Guidelines for the Treatment of Syphilis

1. Early Syphilis

Adults (Primary, secondary, early latent syphilis of not more than two years duration)	**Pregnant woman**
.**Benzathine penicillin G:** "First choice" 2.4 million units once I.M. , **Procaine penicillin G:** 1.2 million units I.M. for 10–14 days	
If penicillin is not allowed due to allergy, use: • **Doxycycline**: 100 mg twice daily orally for 14 days, or • **Ceftriaxone**: IM once daily 10–14 days, or **Azithromycin**: once orally.	• **If penicillin is not allowed due to allergy, use:** • **Erythromycin**: orally four times daily for 14 days • **Ceftriaxone**: IM once daily 10–14 days, or **Azithromycin**: once orally.

2. Late Syphilis

Adults *(infection of more than two years duration without evidence of treponemal infection)*	**Pregnant woman**
Benzathine penicillin G: 2.4 million units I.M. once weekly **for three** consecutive weeks, **Procaine penicillin G**: 1.2 million units I.M. for **20 days**.	
If penicillin is not allowed due to allergy, use: • **Doxycycline:** 100 mg twice daily orally for **30 days**.	**If penicillin is not allowed due to allergy, use:** • **Penicillin desensitization**. or **Erythromycin:** 500 mg orally four times daily for 30 days • **Ceftriaxone:** 1 g IM once daily for 10–14 days, or **Azithromycin:** 2 g once orally.

3. Congenital Syphilis

- In infants with confirmed congenital syphilis or infants who are clinically normal, but whose mothers had untreated syphilis

- **Aqueous crystalline penicillin G:** IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days, or
- **Procaine penicillin G**: 50,000 units/kg/dose IM in a single daily dose for 10 days, or **Benzathine penicillin G**: 50,000 units/kg/dose IM in a single dose.

Gonorrhea

1) Treatment of *uncomplicated* Gonorrhea CDC Recommended regimens at last slide

First line treatment:

3rd generation cephalosporins:
Ceftriaxone *(500 mg **I.M** single dose)* | **Cefixime** *(400 mg **orally** single dose)*

- To cover chlamydia: **typically given in combination with:**
- A single dose of **Azithromycin** (1gm orally) or **Doxycycline** (100 mg orally twice daily (BID) for 7 days)

Fluoroquinolones:
Ciprofloxacin *(500 mg)* | **Ofloxacin** *(400 mg)*

M.O.A	• **Single oral dose** **All Bactericidal: Inhibit DNA synthesis by inhibiting DNA gyrase enzyme (required for DNA supercoiling)**
ADRs	• GIT: Nausea ,vomiting & diarrhoea . • May damage growing cartilage & cause **Arthropathy** • CNS: Headache & dizziness. • **Phototoxicity**, avoid excessive sunlight
CIs	• **Pregnancy** & Nursing mothers • **Children (younger than 18 years)**

Alternative treatment: in patients that cannot tolerate or be treated with cephalosporins or quinolones

Spectinomycin

M.O.A	**Inhibits protein synthesis by binding to 30S ribosomal subunits** • **Given 2g I.M, once**
ADRs	• Pain at the site of injection. • Fever •Nephrotoxicity (not common).

2) Treatment of complicated Gonorrhea

Prophylaxis of neonatal conjunctivitis

- WHO guidelines suggest **one** of the following options for **topical** application to **both** eyes **immediately** after birth:
  - **Silver nitrate** 1% solution
  - **Erythromycin** 0.5% eye ointment
  - **Tetracycline hydrochloride** 1% eye ointment
  - **Povidone iodine** 2.5% solution (water-based)
  - **Chloramphenicol** 1% eye ointment

a. Silver nitrate	b. Erythromycin
• It has **germicidal effects** due to **precipitation of bacterial proteins** by liberated **silver** ions (NOT nitrate).	0.5% ointment For treatment & prevention of corneal and conjunctival infections

Put into conjunctival sac **immediately after birth** (no later than 1 hr after delivery)

CDC recommended regimens for *uncomplicated* gonococcal infections

Regimen for uncomplicated gonococcal infections of the cervix, urethra, or rectum:

- **Ceftriaxone**
  - 500 mg IM as a single dose for persons weighing <150 kg
  - For persons weighing ≥150 kg, 1 g of IM
- if ceftriaxone not available:
- **Cefixime** 800 mg orally as a single dose
- **Gentamicin** 240 mg IM as a single dose + **Azithromycin** 2 g orally as a single dose
- **If chlamydial infection has not been excluded when treating with cephalosporins**
  - Add doxycycline 100 mg orally twice daily for 7 days.
  - **During pregnancy**, azithromycin 1 g as a single dose is recommended to treat chlamydia.

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