

Final Reproductive Pharmacology

REVISION



Done by:

OMAR ALRAHBEENI, KHALID ALDURAIBI, REEMA ALNASSER, NOUF ALMASOUD and MAHA ALRABIAH

Lecture 2: oral and other forms of contraception

Combined Pills (COC) Contains both Estrogen & Progestin Norgestimate, Desogestrel and Drospirenone

MOA	ADRs	C.I.	Interactions	Type	Comments
<ul style="list-style-type: none"> - Inhibit ovulation by ↓ (FSH & LH) ⇒ no action on the ovary ⇒ ovulation is prevented. - Inhibit <i>implantation</i>. - Increase <i>viscosity</i> of the cervical mucus. - Abnormal <i>transport time</i> through the fallopian tubes. 	<p>Related to Estrogen:</p> <ul style="list-style-type: none"> - Impair glucose tolerance (hyperglycemia). - ↑ Incidence of breast, vaginal & cervical cancer. - Cardiovascular: <ul style="list-style-type: none"> A. Thromboembolism. B. Hypertension. <p>Related to Progestin:</p> <ul style="list-style-type: none"> - Fatigue, depression of mood. - Weight gain. - Hirsutism. - Masculinization (Norethindrone). - Ectopic pregnancy. 	<ul style="list-style-type: none"> - Thrombophlebitis / thromboembolic disorders - CHF or other causes of edema. - Vaginal bleeding. - Known or suspected pregnancy. - Known or suspected breast cancer, or estrogen-dependent neoplasms. - Impaired hepatic functions. - Dyslipidemia, diabetes, hypertension, migraine. <hr/> <ul style="list-style-type: none"> - Lactating mothers* - Obese* - Smoker* - Females > 35 years* <p>*(better given progestin only pills "minipills")</p>	<p>Medications that cause contraceptive failure:</p> <ol style="list-style-type: none"> 1. Impairing absorption: <ul style="list-style-type: none"> Antibiotics 2. CYT P450 Inducers: <ul style="list-style-type: none"> Phenytoin, Phenobarbitone, & Rifampin <p>Medications that ↑ COC toxicity:</p> <ol style="list-style-type: none"> 1. CYT P450 Inhibitors: <ul style="list-style-type: none"> Acetaminophen, Erythromycin. <p>Medications altered in clearance ↓ by COC:</p> <ol style="list-style-type: none"> 1. ↑ In their toxicity: <ul style="list-style-type: none"> Warfarin, Cyclosporine, Theophylline 	<p>M O N T H L Y</p>	<p>Methods of administration:</p> <ol style="list-style-type: none"> 1. Taken same time of day. 2. For 21 days (start on day 5 → end on day 26). 3. 7 days pill free period. <p><i>To improve compliance: a formulation of 28 pills</i></p> <ol style="list-style-type: none"> 1. The first 21 pills are of multiphasic formulation. 2. Followed by the last 7 pills are actually placebo.
				<p>S E A S O N A L</p>	<ul style="list-style-type: none"> • Cover 91 days Schedule (84 days breaking by 7 days). • Low doses of both estrogens and progestins are known as Continuous / Extended cycle <p>Benefits:</p> <ul style="list-style-type: none"> - Periods only 4 times a year. - Useful in: pre-menstrual or menstrual disorder and perimenopausal women with vasomotor symptoms. <p>Disadvantages:</p> <ul style="list-style-type: none"> - Higher incidence of breakthrough bleeding & spotting during early use.

cont.: oral and other forms of contraception

Morning-After Pill / Post Coital Contraception Contraception on instantaneous demand, 2 nd ry to unprotected sexual intercourse.			Mini Pills / Progestin-Only Pills (POP) Norethindrone, Levonorgestrel (Norgestrel), Medroxyprogesterone acetate		
Composition	Administration	Indications	MOA	Indications	Instructions
Ethinyl estadiol + Levonorgestrel	2 tablets twice with 12 hrs in between.	When desirability for avoiding pregnancy is obvious: - Unsuccessful withdrawal. before ejaculation. - Torn, leaking condom. - Missed pills. - Exposure to teratogen. e.g. Live vaccine. - Rape.	Increase cervical mucus, so no sperm penetration & therefore, no fertilization.	Are alternative when oestrogen is contraindicated: - During breast feeding - Hypertension - Cancer - Smokers over the age of 30	- Should be taken every day, the same time, all year round. - I.M injection e.g. medroxyprogesterone
High-dose only Ethinyl estadiol	Twice daily for 5 days.				
High dose only levonorgestrel	Twice daily for 5 days.				
Mifepristone ± Misoprostol	A single dose .				

Lecture 3: DRUGS INDUCING OVULATION

Class	Drug	MOA / Composition	Indications	Administration	ADRs
Antiestrogens SERMs	Clomiphene	↑ <i>Negative feedback</i> of endogenous estrogen on hypothalamus and anterior pituitary ⇒ ↑ GnRH ⇒ ↑ FSH & LH ⇒ OVULATION!	-Female infertility <i>(Normogonadotropic)</i> .	-Given from 5 th to 10 th day of the cycle. -Can not be repeated more than 3 cycles.	- Hot Flashes & breast tenderness. - Visual disturbances (<i>reversible</i>). - ↑ Nervous tension & depression. - Weight gain. - Hair loss (<i>reversible</i>). - High incidence of multiple birth.
	Tamoxifen	Similar to Clomiphene <i>But Non-steroidal.</i>	-Women with PCOS and clomiphene-resistant cases. <i>-Estrogen receptor- positive breast cancer.</i>	-	-
GnRH agonists	Leuprolin & Goserelin	-	-Female infertility due to hypothalamic amenorrhea <i>(GnRH deficient)</i> .	-Given S.C. in a pulsatile drip to stimulate gonadotropin. -Release Start from day 2-3 of cycle up to day 10. - Given continuously , when gonadal suppression is desirable e.g.: • Precocious puberty. • Breast cancer in women. • Prostatic cancer in men.	- Headache. - Hypoestrogenism <i>on long term use</i> : ○ Hot flashes. ○ ↓ Libido. ○ Osteoporosis. ○ Rarely ovarian hyperstimulation. (ovaries swell & enlarge)
Gonadotrophins	Menotropin (hMG)	Extracted from postmenopausal urine (<i>contains LH & FSH</i>).	-Female infertility <i>2ndry to gonadotropin deficiency (pituitary insufficiency)</i> .	I.M. daily starting at day 2-3 of cycle for 10 days.	• <u>FSH containing preparations</u> : - Fever. - Ovarian enlargement (hyperstimulation). - Multiple Pregnancy. • <u>LH containing preparations</u> : - Headache and Edema.
	Pregnyl (hCG)	Extracted from pregnant women urine (<i>contains mainly LH</i>).		Given on 10 th - 12 th day for Ovum retrieval.	
D2 R Agonists	Bromocriptine Ergot derivative (Not a hormone)	D2R agonists binds to dopamine receptors in the AP gland ⇒ <i>inhibits prolactin secretion.</i>	-Female infertility <i>2ndary to hyperprolactinemia.</i>	-	

Lecture 4: OXYTOCICS AND TOCOLYTICS

Oxytocics							
Class	Drugs	MOA	Indications	ADRs	C.I	Kinetics	
Synthetic Oxytocin	Syntocinon	<ul style="list-style-type: none"> Interaction of oxytocin with myometrial receptor → influx of Ca^{++} from ECF and from S.R. → stimulates uterine contraction particularly in the fundus. Resemble normal physiological contraction Milk ejection. 	<ol style="list-style-type: none"> Induction & augmentation of labor: <ul style="list-style-type: none"> Mild preeclampsia near term. Uterine inertia. Incomplete abortion. Post maturity. Maternal diabetes. Postpartum uterine hemorrhage (I.V drip). Impaired milk ejection. 	<ul style="list-style-type: none"> Maternal death due to hypertension Uterine rupture. Fetal death (ischemia). Water intoxication (if given with large volumes of electrolyte-free aqueous fluid intravenously). 	<ul style="list-style-type: none"> Hypersensitivity. Prematurity. Abnormal fetal position. Fetal distress. Cephalopelvic disproportion. Incompletely dilated cervix. Precautions: Multiple pregnancy. Previous c- section. Hypertension 	<ul style="list-style-type: none"> Given when uterine cervix is soft and dilated. Not effective orally. I.V. (augment labor) Nasal spray (impaired milk ejection). 	
Ergot Alkaloids	Natural: Ergometrine (Ergonovine)	<p>Tetanic Contraction of the whole uterus <u>without relaxation in between</u> (tend to compress rather than to expel the fetus).</p>	<p>Only in Postpartum hemorrhage (3rd stage of labor)</p>	<ul style="list-style-type: none"> Nausea, vomiting, diarrhea. HTN: Vasoconstriction of peripheral blood vessels. Gangrene. 	<ul style="list-style-type: none"> Induction of labour: (1st and 2nd stage of labor). Vascular disease Severe hepatic and renal impairment. Severe hypertension. 	<ul style="list-style-type: none"> I.M Metabolized in liver. Excreted in bile. Preparations: Syntometrine: is a combination of oxytocin and ergometrine(I.M) 	
	Synthetic Methyl ergometrine (Methylegonovine)						
Prosta-glandins	PGE2 Dinoprostone	<ul style="list-style-type: none"> Contract uterine smooth muscle throughout pregnancy. Soften the cervix. 	<ul style="list-style-type: none"> Induce abortion in 2nd trimester of pregnancy. Induction of labor (fetal death in utero). Postpartum hemorrhage. 	<ul style="list-style-type: none"> Nausea , vomiting.. Abdominal pain. Diarrhea. Flushing (PGE2) 	<ul style="list-style-type: none"> Mechanical obstruction of delivery. Fetal distress Predisposition to uterine rupture. Precautions: Asthma. Multiple pregnancy. Glaucoma. Uterine rupture. 	<ul style="list-style-type: none"> Vaginal suppository. Extra- amniotic solution. Longer duration of action than oxytocin. 	
	PGE2 α Dinoprost Carboprost			<ul style="list-style-type: none"> Bronchospasm. 			<ul style="list-style-type: none"> Intra-amniotic injection.
	PGE1 Misoprostol						

CONT.: OXYTOCICS AND TOCOLYTICS

Tocolytics					
Class	Drugs	MOA	Indication	ADRs	Kinetics
Selective β_2 adrenoceptor agonist	Ritodrine	<ul style="list-style-type: none"> - Bind to β-adrenoceptors → activate enzyme Adenylate cyclase → ↑ cAMP → ↓ intracellular calcium level. - Specific as uterine relaxant 	<ul style="list-style-type: none"> - Relax the uterus. - Arrest threatened abortion. - Delay premature labour. 	<ul style="list-style-type: none"> - Tremor, Nausea, vomiting. - Flushing, Sweating. - Tachycardia (high dose). - Hypotension, Hyperglycemia. - Hypokalaemia. 	I.V Drip
Calcium channel Blockers	Nifedipine	<ul style="list-style-type: none"> - Inhibits the amplitude of spontaneous and <u>oxytocin-induced contractions</u>. - Cause relaxation of myometrium. 		<ul style="list-style-type: none"> - Headache, Dizziness, Hypotension. - Flushing. - Constipation. - Ankle edema. - Coughing, Wheezing. - Tachycardia. 	-
Atosiban	Atosiban	Compete with oxytocin at its receptors on the uterus.		-	IV infusion for 48 hrs

Lecture 5: Teratogens & Drugs of Abuse in Pregnancy

Physio-chemical properties of the drugs

Lipid solubility	<ol style="list-style-type: none"> Lipophilic drugs: Thiopental → crosses placenta & causes sedation, apnea in newborn infants. Ionized drugs: cross the placenta very slowly e.g Succinylcholine & pancuronium.
Molecular Weight	Heparin: High molecular weight → cannot cross placenta.
Protein Binding	High protein binding prevents the drug to go to placenta: propylthiouracil and chloramphenicol .

FDA Classification System

Categories	In animals	In humans	Use in pregnancy	Examples
Category A	-	NO risk	✓	Folic acid, Thyroxine
Category B	NO risk	NO data	✓	Paracetamol, Erythromycin
Category C	Adverse effect	NO data	Used in serious situation despite its potential risk	Morphine
Category D	-	Adverse effect	Used in serious diseases or life threatening situations	Antiepileptics
Category X	Fetal abnormalities	Fetal abnormalities	Teratogenic and contraindicated.	<ul style="list-style-type: none"> - Retinoids: vitamin A (700 µg/day) & isotretinoin. - Cytotoxic drugs: Folate antagonists (methotrexate) & Alkylating agents (cyclophosphamide). - Anticonvulsant drugs (valproic acid, phenytoin, carbamazepines). - Anticoagulants (warfarin). - Antibiotics (tetracyclines, quinolones). - Thalidomide, Lithium, Alcohols, ACEIs, Ionizing radiation, Radioactive iodine (I131), Corticosteroids, Hormones.

CONT.: TERATOGENS & DRUGS OF ABUSE IN PREGNANCY

Category X "Proven teratogens"					
Agent		Teratogenesis (During 1 st trimesters)	Agent		Adverse effects (During 2 nd & 3 rd trimesters)
Thalidomide		Phocomelia: shortened/absent long bones of limbs.	Antibiotics	Aminoglycosides Streptomycin Kanamycin	Ototoxicity = 8th Cranial nerve damage.
Phenytoin		Fetal Hydantoin Syndrome: digital hypoplasia.	Chloramphenicol		Gray baby syndrome.
Valproic acid		Spina bifida & impairs folate absorption.	Sulfonamides		Neonatal hyperbilirubinemia (jaundice).
Lithium		Ebstein's anomaly: CVS anomalies.	β - Blockers: Propranolol		- Placental insufficiency → ↓ uterine blood flow → fetal distress. - Neonatal hypoglycemia,
Tetracyclines		Altered growth of teeth and bones, teeth staining and enamel hypoplasia.	Tetracyclines		Impaired teeth and bone development, discoloration of teeth.
Warfarin		Hypoplasia of nasal bridge & CNS malformation.	Warfarin		Risk of bleeding.
Corticosteroids		Cleft lip and Palate.	Corticosteroids		Adrenal atrophy → growth retardation.
Hormones	Estrogens	Testicular atrophy in male fetus.	Antithyroid	Iodide. Methimazole Carbimazole Propylthiouracil	Risk of neonatal hypothyroidism and goiter.
	Androgens	Fetal masculinization in female fetus.	NSAIDs	Aspirin. Indomethacin	- PG synthesis inhibitors: Constriction of ductus arteriosus, pulmonary HTN. - ↑ Gestation time and prolonged labor. - Postpartum hemorrhage (aspirin).
	Diethylstilbestrol	Vaginal carcinoma of female offspring.	Benzodiazepines	Diazepam	- Chronic use → neonatal dependence & withdrawal. - Respiratory depression ↓ blood flow.
ACE inhibitors	Captopril	Renal damage, anuria and hypotension.	Morphine, Diazepam		Respiratory depression ↓ blood flow.
	Enalapril		ACE inhibitors		Renal damage.

CONT.: TERATOGENS & DRUGS OF ABUSE IN PREGNANCY

Drugs in pregnancy			
Drug	Probably safe	Contraindicated	Drugs of choice
Hypertension	<ul style="list-style-type: none"> - α- methyl dopa. - Labetalol. <p>Emergency:</p> <ul style="list-style-type: none"> - Hydralazine - Labetalol 	<ul style="list-style-type: none"> - ACE inhibitors. - Angiotensin II receptor blockers. - Thiazide diuretics. - Propranolol (not selective). - Ca channel blockers. 	<ul style="list-style-type: none"> - α-methyl dopa. - Labetalol. - Hydralazine
Anticoagulants	<ul style="list-style-type: none"> - Heparin. - Antidote: Protamine sulphate 	<p>Warfarin:</p> <ul style="list-style-type: none"> - 1st trimester: Chondroplasia. - 2nd and 3rd: risk of bleeding. 	Heparin.
Antibiotics	<ul style="list-style-type: none"> - Penicillins: (ampicillin, amoxicillin). - Cephalosporins. - Erythromycin & azithromycin (in case of penicillin-hypersensitivity). 	<ul style="list-style-type: none"> - Tetracyclines. - Quinolones (ciprofloxacin): arthropathy. - Aminoglycosides - Sulfonamides. - Chloramphenicol. - Erythromycin estolate (risk of hepatic injury) 	<ul style="list-style-type: none"> - Penicillin. - Cephalosporins. - Erythromycin
Antithyroidism	Propylthiouracil (protein-bound)	<ul style="list-style-type: none"> - Methylthiouracil (Methimazole). - Carbimazole. - Radioactive Iodine (I^{131}). 	Propylthiouracil (protein-bound)
Antidiabetics	-	Antidiabetics	Insulin.
NSAIDs	-	-	Acetaminophen.
Anticonvulsants	-	Valproic acid (highly teratogenic)	Folic acid supplementation (prevents neural tube defects in women receiving AEDs).

Drugs of Abuse in pregnancy	Alcohols	Fetal Alcohol Syndrome (FAS): Microcephaly – Low weight birth – Craniofacial abnormalities – CNS and CVS abnormalities.
	Cocaine	Inhibits reuptake of sympathomimetics, Hypoxia, Microcephaly, Retardation, Placental abruption.
	Tobacco	No evidence it causes birth defects: Spontaneous abortion, Preterm labor, ↓ blood flow to placenta, hypoxia, Retarded fetal growth, Low birth weight, Perinatal mortality.

Lecture 6: Hormonal replacement therapy

	Drugs	MOA	Indications	ADRs	Other	
Estrogen	Estradiol	<u>Binds to its receptors:</u> ERα: mediates female hormonal functions Endometrium, breast, ovaries... ERβ: mediates other hormonal functions on other organs.	A- In menopause (Not given unless presence of symptoms). - Hot flushes & night sweats. - Sleep disturbance & mood swings. - Urethral & urinary symptoms. - Vaginal dryness. - Increases bone density. - Protects CVS (enhance vasodilatation via \uparrow NO production, \uparrow HDL & \downarrow LDL). - Improves Insulin resistance. - Improves cognitive function - Delays parkinsonism B- Contraception. C- Primary ovarian failure. D- Amenorrhea & Hirsutism caused by excess androgens.	- Long term HRT increases CVS problems. - Irregular vaginal bleeding. - Vaginal discharge. - Fluid retention, Weight gain. - Breast tenderness. - Spotting or darkening of skin. If given with: - <u>SERMs</u> : additive side effects. - <u>Aromatase inhibitors</u> : \downarrow efficacy - <u>Corticosteroids</u> : \uparrow side effects	- Never exceed 5 yrs administration. - Alone after hysterectomy or with progestin as HRT. - Oral: Conjugated equine, Estradiol valerate, Estrial succinate. (<u>Oral bioavailability is low</u>). - Transdermal “estradiol” (Patches ,Gel) . - Subcutaneous “estradiol” (implant). - Intra-Vaginal (cream or rings pessaries). - Intramuscular (depot) Contraindications: # Undiagnosed vaginal bleeding. # Severe liver disease. # Thromboembolic manifestations. # Cancer: endometrial, breast (hormone sensitive), ovarian.	
	Conjugated Estrogens					
	Esterified estrogens					
Progestins	Progesterone	Binds to its receptors PR-A & PR-B	Protects against breast cancer	- Mood changes, as anxiety, irritability. - Headache, dizziness or drowsiness. - Nausea, vomiting, abdominal pain or bloating (distention). - Hirsutism , masculinization (Not with new preparations)	Administration	Degraded in GIT, so can be given only <u>parentally</u>
	Progestins		- Protects against estrogen induced endometrial cancer. - Confers neuroprotection. - Controls insomnia & depression. - Counteract osteoporosis.		-Oral; Micronized progesterone or progestins -IU; as Levonorgestrel or Progestasert	Not degraded by GIT
	Progestin preparations		- Contraception (Estradiol + Progestins). - Dysmenorrhea. - Menopausal symptoms (Estradiol + Progestins).		-Vaginal - natural progesterone gel / pessary. -Transdermal - sequential / continuous patch.	

CONT.: Hormonal replacement therapy

	Drugs	MOA	Indications	ADRs	Others
SERMs	Raloxifen	Antagonist in breast and uterus and <u>agonist in bone</u>	Preventing vertebral bone fracture and CVs problems less compared to Estrogen.	No effect on hot flushes.	Osteoporosis use of bisphosphonate is better than SERMs
	Tamoxifen	Antagonist in breast and partial <u>agonist in bone and endometrium</u> .	--	- Risk of venous thrombosis - Vaginal atrophy. - Hot flushes.	
Phytoestrogens	Isoflavones	- Mimic action of estrogen on ER-b.	- Alleviate symptoms related to menopause. - Possess CVS protective actions.	Avoid in estrogen dependent breast cancer.	In soybeans, flaxseeds
	Lignans	- Block actions mediated by ER-a in some target tissues	- Lower risks of developing endometrial & breast cancer (ER-a).		In whole grains
Androgens	Testosterone	Sexual arousal in females.	- Lack of sexual arousal. - Adjuvant to combined estrogen & progestin if all other menopausal symptom exist.	--	Not approved by FDA in women

Non-hormonal agents used in management of menopausal symptoms

Fluoxetine (SSRI)	Clonidine (centrally acting antihypertensive, alpha 2 agonist)	Gabapentin (anti-convulsant)
Reduces vasomotor symptoms.		Reduces severity and frequency of hot flushes.

Lecture 7: DRUGS AFFECTING BREAST MILK & LACTATION

Factors controlling passage of drugs into breast milk

Factors related to drugs	Factors related to Mother	Factors related to Neonates	
<ol style="list-style-type: none"> Molecular Weight: alcohol < Insulin < Heparin. The epithelium of the breast alveolar cells is most permeable to drugs during the 1st week postpartum Lipid Solubility of the drug “pass more freely. Degree of Ionization: Heparin pass poorly. PH Of Drug: Weak basic drugs concentrate in breast milk. Weak acidic drugs concentrated in plasma Weak Acidic Drugs: concentrate in plasma. Plasma Protein Binding of drugs: Only unbound form gets into maternal milk (Warfarin). Half life of the drug: Oxazepam (short) vs diazepam (long) Volume of Distribution: Large VOD = low transfer to milk. 	<ol style="list-style-type: none"> Dose of the drug. Route of Administration: topical preparations carry less risk. (creams, nasal sprays or inhalers) Time of Breastfeeding: mother should take medication just after nursing and 3-4 hours before the next feeding. Health Status: Breastfeeding is contraindicated in: <ul style="list-style-type: none"> HIV-positive. Active, untreated TB. Herpes on breast. Use of illegal drugs. Certain medications used chronically. Maternal Drug Concentration 	Amount of a drug Depends on <ul style="list-style-type: none"> - Amount of milk consumed. - Amount of drug absorbed from GI. - Ability of baby to eliminate drug. 	
		Factors <ul style="list-style-type: none"> - Age. - Body weight. - Health status 	
		special cautions <ul style="list-style-type: none"> - Premature infants. - Low birth weight. - Infants with G6PD deficiency. - Infants with impaired ability to metabolize/excrete drugs: eg. hyperbilirubinemia. 	

Neonatal hyperbilirubinemia	Neonatal Methemoglobinemia
<p>Premature infants or infants with inherited G6PD deficiency: oxidizing drugs (Antibiotics: sulfonamides, trimethoprim, Antimalarials: Primaquine) → hemolysis of RBCS → bilirubin (hyperbilirubinemia) → Kernicterus,</p>	<p>Infants < 6m are prone to develop methemoglobinemia upon exposure to some oxidizing drugs. Methemoglobin: oxidized Hb that has ↓ affinity for O₂ → hypoxia</p>

Drugs contraindicated during lactation	<ol style="list-style-type: none"> Anti-cancer: Doxorubicin, cyclophosphamide, methotrexate. Radiopharmaceuticals: radioactive iodine. CNS acting drugs: amphetamine, heroin, cocaine. Others: Lithium, Chloramphenicol, Atenolol, Potassium iodide.
Drugs that can suppress lactation (↓ prolactin)	Levodopa (dopamine precursor), Bromocriptine (dopamine agonist). Estrogen (oral contraceptives), Androgens , Thiazide diuretics .
Drugs that can augment lactation (Dopamine antagonists: stimulate prolactin → galactorrhoea)	Metoclopramide (antiemetic), Domperidone (antiemetic), Haloperidol (antipsychotic). Methyl dopa (antihypertensive drug), Theophylline (used in asthma).

CONT.: DRUGS AFFECTING BREAST MILK & LACTATION

Using drugs during lactation			
Class	✓	compatible	✗
Antibiotics	<ul style="list-style-type: none"> ● Penicillins: Ampicillin, amoxicillin ● Cephalosporins ● Macrolides: erythromycin, clarithromycin 	-	Quinolones, Chloramphenicol, Tetracyclines, Sulfonamides (co-trimoxazole)
Sedative/ hypnotics	-	<ul style="list-style-type: none"> ● Benzodiazepines: Diazepam, Lorazepam (<i>only single dose</i>). ● Barbiturates (phenobarbitone) (<i>NO prolonged use</i>). 	-
Antidiabetics	Insulin	Oral antidiabetics	Metformin (lactic Acidosis)
Analgesics	Acetaminophen (paracetamol)	Ibuprofen	Aspirin (Reye's syndrome)
Antithyroid	Propylthiouracil	-	Carbimazole, Methimazole, potassium iodide
Anticoagulants	Heparin	Warfarin (monitor infant's prothrombin time during treatment).	-
Antidepressants (SSRI)	Paroxetine	-	-
CVS drugs	-	-	Atenolol
Anticonvulsants	Carbamazepine, phenytoin	Valproic acid (Infants must be monitored for CNS Depression).	Lamotrigine
Oral contraceptive	<ul style="list-style-type: none"> ● Progestin only pills or minipills. ● Non hormonal method. 	-	Estrogens containing pills
Antiasthmatics	Inhaled corticosteroids - prednisone	-	-
Other	-	-	Cytotoxic drugs, Iodine (radioactive), Lithium

Lecture 8: DRUGS TREATING GONORRHOEA & SYPHILIS

Syphilis							
Class	Drugs	Type	MOA	Pharmacokinetic	Adverse effects	Note	
Penicillins 1st Choice If Allergic to it use the others	Penicillin G	B A C T E R I C I D A L	Inhibits bacterial cell wall synthesis through inhibition of transpeptidase enzyme required for .crosslinks	<ul style="list-style-type: none"> - Acid unstable. - Penicillinase sensitive. - Not metabolized. - Excreted in urine through acid tubular secretion. - Renal failure prolonged the duration of action. 	<ul style="list-style-type: none"> - Hypersensitivity. - Convulsions. - Super infections. 	<ul style="list-style-type: none"> - Narrow spectrum. - Active against: <ul style="list-style-type: none"> o Gram +ve. o Gram -ve cocci. o Non β-lactamase producing anaerobes. - β-lactamase sensitive 	Short, i.v.
	Procaine penicillin G						Long acting, i.m & Delayed absorption
	Benzathine penicillin G						
3rd Generation Cephalosporins	Ceftriaxone	B A C T E R I C I D A L	Inhibit bacterial cell wall synthesis.	-	<ul style="list-style-type: none"> - Hypersensitivity reactions. - Thrombophlebitis. - Superinfections. - Diarrhea. 	<ul style="list-style-type: none"> - Given parenterally - Eliminated via biliary excretion - Long Half-life 	
	Cefixime						<ul style="list-style-type: none"> - Given orally. - More effective against gram -ve. - Excreted in urine.
Tetracyclines	Doxycycline	B A C T E R I O S T A T I C	Inhibit bacterial protein synthesis by reversibly binding to 30S bacterial ribosomal subunits.	<ul style="list-style-type: none"> - Given orally - Well absorbed orally - Long acting - Twice daily for 14 days. 	<ul style="list-style-type: none"> - Nausea, vomiting ,diarrhea, Vertigo & epigastric pain. - Brown discoloration of teeth in children. - Deformity or growth inhibition of bones in children. - Hepatic toxicity (prolonged therapy with high dose). - Superinfections. 	<ul style="list-style-type: none"> - Not effective for treatment of gonorrhoea. - Contraindication: <ul style="list-style-type: none"> o Pregnancy. o Breast feeding. o Children (below 10 yrs). 	
Macrolides	Azithromycin	B A C T E R I O S T A T I C	Inhibits bacterial protein synthesis by binding to bacterial 50S ribosomal subunits.	<ul style="list-style-type: none"> - Acid stable. - Don't penetrate CSF. - Half life : 2-4 days. - Once daily,oral dose. - Given 1- 2 h after meals. - No effect on cyt P450. 	<ul style="list-style-type: none"> - GIT upset: Nausea, vomiting, abdominal pain & diarrhea. - Allergic reactions: urticaria, mild skin rashes. 	-	

CONT.: DRUGS TREATING GONORRHOEA & SYPHILIS

Gonorrhoea					
Class	Drugs	MOA	PK	Adverse effects	Note
3rd Generation Cephalosporins 1st Choice	Ceftriaxone Cefixime	-	500mg ceftriaxone, I.M or 400 mg of cefixime, po	-	- Typically given with a single dose of ○ Azithromycin(1gm, po) or ○ Doxycycline(100 mg BD, po)
Fluoroquinolone 2nd Choice	Ciprofloxacin Ofloxacin	All are bactericidal Inhibit DNA synthesis by inhibiting DNA gyrase enzyme (required for DNA supercoiling).	Single oral.	- GIT: NVD. - CNS: Headache & dizziness. - May damage growing cartilage and cause arthropathy. - Phototoxicity, avoid excessive sunlight.	CONTRAINDICATIONS - Pregnancy. - Nursing mothers. - Children under 18 years.
Spectinomycin	-	Inhibits protein synthesis by binding to 30 S ribosomal subunits.	Is given 2 g, i.m, once.	- Pain at site of injection. - Fever. - Nephrotoxicity (not common).	-
Silver nitrate	-	It has germicidal effects due to precipitation of bacterial proteins by liberated silver ions.	Put into conjunctival sac once immediately after birth (no later than 1 h after birth).	-	- Treatment of Complicated infections With conjunctivitis ○ Corneal (Erythromycin) in New born.
Erythromycin	-	-			

LECTURE 9: DRUGS USED IN MALE INFERTILITY

Category	Drug	MOA	Indications	Kinetics	ADRs	Note
Testosterone	-		-	- Ineffective orally. - <u>I.M or S.C.</u> - Inactivated in the liver. Disadvantages: Short duration of action.	- Excess androgens (> 6 wks) → impotence, ↓ spermatogenesis & gynecomastia. - ↓ HDL & ↑ LDL → ↑ risk CHD.	Testosterone 1\Contraindication: - Male patients with cancer of breast or prostate. - Severe renal & cardiac disease. - Psychiatric disorders. - Hypercoagulable states. - Polycythemia.
Synthetic Androgens	-	- Virilizing (eg. spermatogenesis).	-	-	- Edema. - Hepatic dysfunction.	-
Derived from Testosterone (ester)	Propionate	- Anabolic effects (eg. ↑ bone density).	- Androgen deficiency in adult male infertility. - Delayed puberty with hypogonadism (give androgen slow & spaced)	- Oil for IM; every 2-3 weeks - Long duration of action	- Hepatic carcinoma (long term use) - Behavioral changes: aggressiveness. - Polycythemia → ↑ risk of clotting.	2\Interaction: + corticosteroids → oedema + warfarin → ↑ bleeding + insulin or oral hypoglycemics → hypoglycemia + propranolol → ↓ propranolol efficacy
	Enanthate					
	Cypionate					
Derived from Testosterone (Other)	Fluoxymesterone			- Orally; daily. - Long duration of action.	- Premature closing of epiphysis. - ↓ Testicular size.	
	Methyltestosterone					
	Danazol					
Derived from DHT	<u>Mesterolone</u>	Not aromatized into estrogens → no -ve of GnHs → encourages natural testosterone production spermatogenesis is enhanced.	- ↓ Testosterone. - 2ndry hypogonadism.	- Orally; daily. - Long duration of action.	-	Not hepatotoxic.
Antiandrogens SERMs	Clomifen	- ↑ GnRH & improve its pituitary response. - Induce libido.	-	-	Bad temper in men	
	Tamoxifen					
Antiandrogens Aromatase inhibitors	Anastrozole	- ↑ GnRH & improve its response. - Blocks conversion of testosterone to estrogen within the hypothalamus. - Inducing spermatogenesis.	Best to improve sperm count & motility with good pregnancy rates.	Given as daily dose over a period of 1–6 months.	-	

CONT.: DRUGS USED IN MALE INFERTILITY

Category	Drug	MOA	Indications	Kinetics	ADRs
GnRH	-	Androgenization & spermatogenesis.	hypothalamic dysfunction.	Given as Pulsatile GnRH therapy using a portable pump.	- Exogenous excess → ↓ LH responsiveness. - Depression, generalized weakness, pain. - Gynecomastia. - Osteoporosis.
GnHs	-	Spermatogenesis	2ndry hypogonadism	GnHs replacement must be combined : + hCG (IM. 2 ms.) followed by hCG + hMG (IM. 6-12 ms).	- Local swelling (injection site). - Flushing, - Gynecomastia. - Precocious puberty.
Non- hormonal therapy	Antioxidants	Protect sperm from oxidative damage (e.g. vit E,C).	-	-	-
	Kallikrein	Proteolytic activity, cleaving kininogen to kinins → <u>important for sperm motility.</u>	-	-	-
	Folic acid	RNA and DNA synthesis during spermatogenesis & has antioxidant properties.	-	-	-
	Zinc Supplements	Testicular development, sperm production & sperm motility.	-	-	-
	L-Carnitine	important for Sperm maturation.	-	-	-