PEMAKAIAN OBAT PADA IBU HAMIL & MENYUSUI

FK-UM MALANG
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2020 / 2021

- Perubahan Parameter Farmakokinetik Ibu Hamil
- Obat Teratogenik
- Perubahan Parameter Farmakokinetik Ibu Menyusui

Pendahuluan

- Semua system mengalami perubahan selama kehamilan
- Terjadi perubahan farmakokinetik dan farmakodinamik obat selama kehamilan
- Informasi ttg perubahan farmakodinamik obat selama kehamilan masih terbatas

FARMAKOKINETIK OBAT SELAMA KEHAMILAN

♥ Absorbsi

- Awal hamil, sekresi asam lambung ↓ 30-40% ➔ absorbsi obat asam lemah ↓, obat basa lemah ↑
- Gastric emptying ↓ (lambat) krn progesterone tinggi
- Progesteron → motilin ↓→ Motilitas GIT ↓➔ absorbsi obat yg sukar larut (digoksin) ↑, absorbsi obat yg dimetab di dind usus (CPZ) ↓

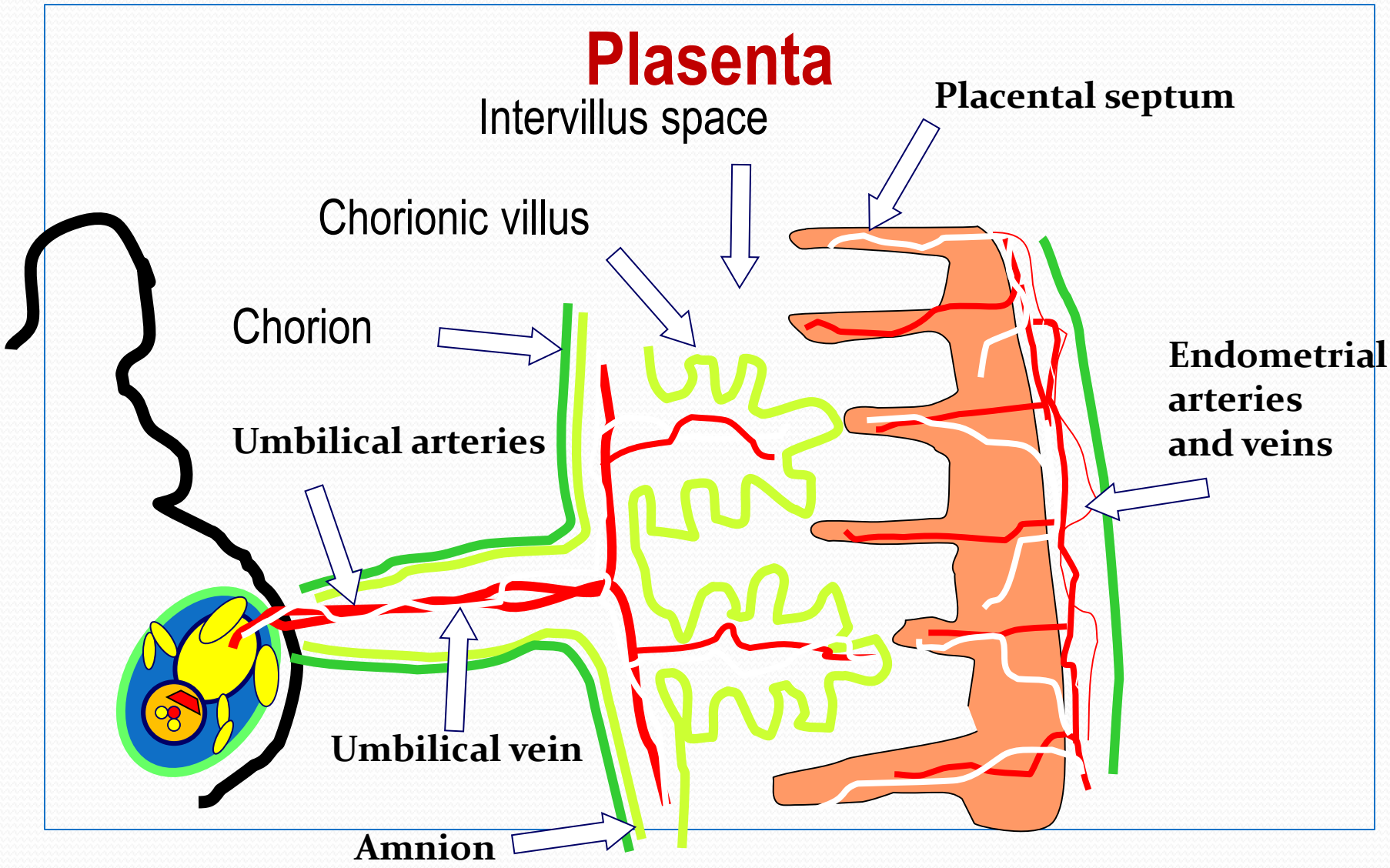
♥ Distribusi

- Vol plasma & CES ↑ (50%) ➔ kdr obat dg Vd kecil (ampicillin) dlm plasma <<
- Albumin serum ↓ 20%, glikoprotein ↑ 100% (t.u pd eklampsia) ➔ fraksi bebas obat asam ↑ (diazepam, fenitoin, as valproat), fraksi bebas obat basa ↓
- Body fat ↑ ➔ Obat lipofilik tersimpan di jar lemak ↑➔ durasi obat ↑(slow release).

♥ Eliminasi

- Trimest 2&3, progesteron me ↑ aktivitas enz metab hepar → kdr obat cpt ↓ (fenitoin, carbamazepin, fenobarbital)
- Awal hamil, renal blood flow dan GFR ↑ 2x → eliminasi obat yg eksresi lwt ginjal ↑(mis aminoglikosida)
- Akhir hamil, renal blood flow dan GFR ↓

Transplacental Drug Transfer



Faktor yang mempengaruhi

- Sifat fisikokimia obat
- Kecepatan melewati plasenta dan jumlah yang bisa mencapai fetus
- Lama paparan
- Karakteristik dostribusi obat pd berbagai jaringan bervariasi
- Tahap perkembangan plasenta dan fetus saat terpapar
- Efek obat dalam kombinasi

- Lipid solubility
  - Obat lipofilik lebih mudah dlm hidrofilik dlm melintasi sawar plasenta. Mis thiopenthal
- Molecular size & pH
- Placental transporter

➲ Though act as barrier to drug transfer

❖ Placenta is the organ of exchange for a number of substances, Including drugs

➲ Drug factors affecting placental transfer

✓ Lipid solubility ➔ **Lipophilic > hydrophilic** drugs (Opioids and antibiotics)

✓ Molecular weight →
- ✓ <500 Da ➔ readily cross the placenta
- ✓ 600 to 1,000 Da ➔ cross more slowly
- ✓ >1,000 Da ➔ do not cross the placenta in significant amounts.

✓ **Degree of protein binding** ➔ higher concentrations of certain protein-bound drugs in the fetus.

➲**Fetal pH is slightly more acidic than maternal pH** ➔ permitting weak bases to more easily cross the placenta.

❖Once in the fetal circulation, the molecule becomes more ionized ➔

➔ less likely to diffuse back into the maternal circulation.

➲Owing to fear of adverse effects on the developing fetus or newborn infant, a common solution is avoidance of therapy.

➲Studies conducted in the US have estimated that at least 2/3 of pregnant women take medications during pregnancy.

➲Moreover, since approximately **½ of pregnancies are unplanned** ➔ many women are **exposed to medications before being aware of their pregnancy.**

OBAT TERATOGENIK

PENGARUH OBAT PD JANIN

- TOKSIK → gangg fisiologik / biokimiawi janin → gejala terlihat stl lahir
- TERATOGENIK → malformasi anatomik pd pertumbuhan organ janin
- LETAL → kematian janin dlm kandungan

TGT SIFAT OBAT & UMUR KEHAMILAN SAAT TERPAPAR

Embriogenesis

- Perkembangan embrio-bayi
- Faktor yg berpengaruh :
  - genetik
  - mutasi genetik
  - fisiologi & faktor tak terklasifikasi
  - faktor lingkungan

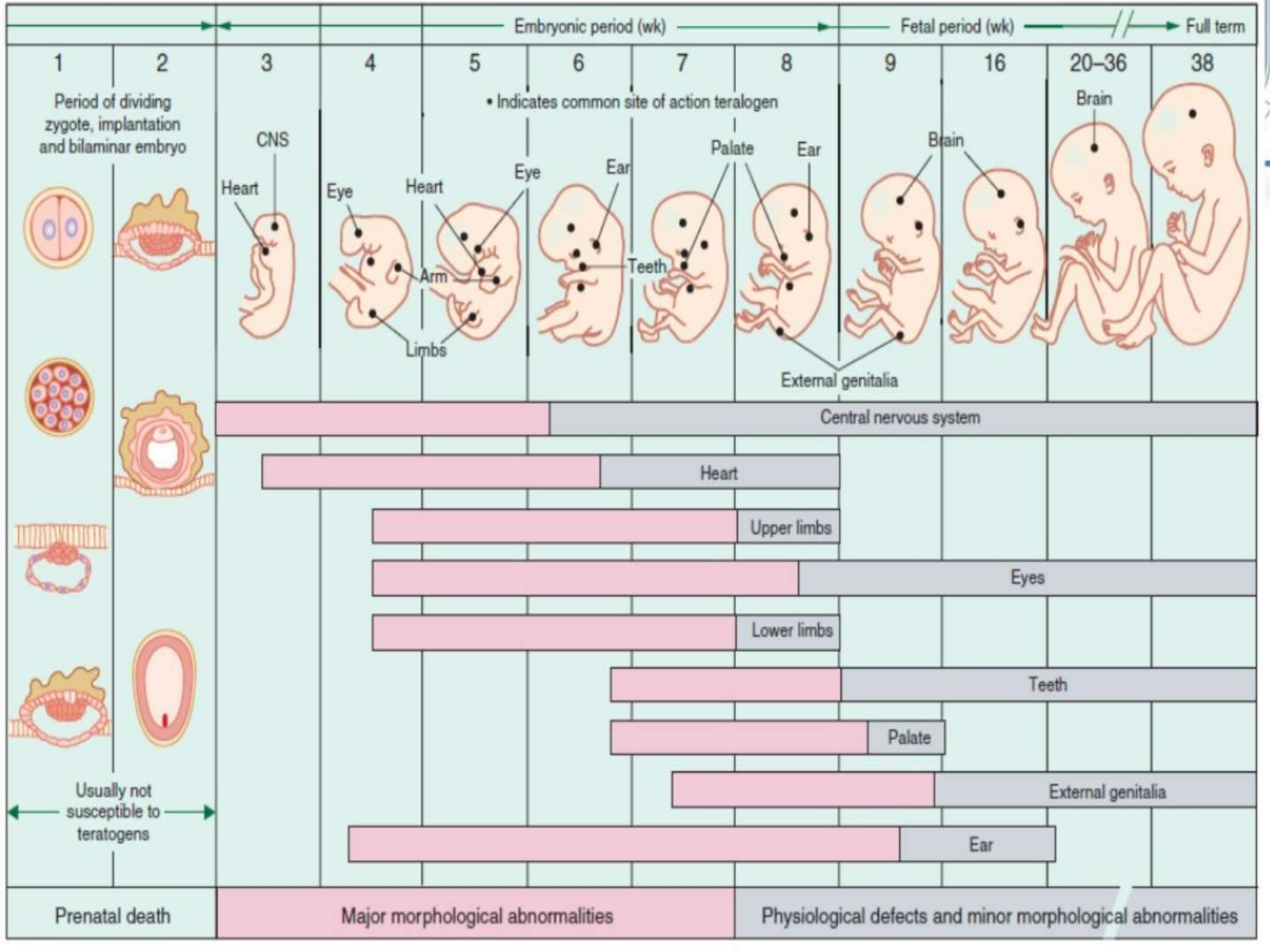
Embriogenesis

Hari/ minggu	Fase	Perkembangan
0-17 hari	Implantation & pre-differention /Preembrionik	Proliferasi
18-56 hari	Embrionik	Organogenesis
8-38 mgg	Janin/fetogenesis	Pematangan fungsi

➲The risk of birth defects is most often higher during organogenesis.

Phases of Embryonic and Fetal Development

Phase of Development	Stage of Pregnancy	What Happens During This Phase of Development	Potential Teratogenic Effect
Implantation and predifferentiation	0–14 days after conception (14–28 days after last menstrual period)	*All-or-none period* Very little contact between the blastocyst and the mother's blood Cells are pluripotent, capacity to repair a damage remains Cells are fragile at this moment. If too many are killed, a miscarriage will occur before the pregnancy is detected	Spontaneous abortion or miscarriage Even if stopped during this period, prolonged half-life drugs could cause organogenesis problems
Organogenesis (embryogenesis)	From day 14 until the 9th week after conception (From day 28 until the 11th week after last menstrual period)	Organs are formed; most critical period for structural anomalies Organs are formed at different times; period of sensitivity for a potential teratogen could be different for each organ	Major or minor structural anomalies
Fetogenesis	After the organogenesis and until birth	The fetus grows and organs begin to function (e.g., kidneys are formed during organogenesis, but glomerular filtration begins during fetogenesis) Active cell growth, proliferation, and migration (eg., CNS)	Fetal growth retardation Functional deficit (e.g., renal insufficiency, pulmonary hypertension, neurologic impairment)


Embryonic period (wk)
Fetal period (wk)
Full term
1
2
3
4
5
6
7
8
9
16
20–36
38
Period of dividing zygote, implantation and bilaminar embryo
• Indicates common site of action teralogen
CNS
Heart
Eye
Heart
Eye
Ear
Palate
Ear
Brain
Brain
Arm
Teeth
Limbs
External genitalia
Central nervous system
Heart
Upper limbs
Eyes
Lower limbs
Teeth
Palate
External genitalia
Ear
Usually not susceptible to teratogens
Prenatal death
Major morphological abnormalities
Physiological defects and minor morphological abnormalities

Contoh Pola Patogenesis Talidomid

Paparan pd usia hamil (hr)	Penyimpangan embriogenesis
21-22	Tdk ada telinga luar, paralisis syaraf kranial
24-27	Maksimal phocomelia(flipper limbs)
28-29	Reduksi berat pd pembentukan kaki
34-36	Hipoplastik thumbsand anorectal sterosis

KATEGORI KEAMANAN OBAT IBU HAMIL (FDA)

A	Data klinik dipercaya obat tidak ada resiko
B	B1 : pemakaian terbatas, pd hewan aman B2: penelitian hewan blm memadai, tp aman B3: pd hewan ada resiko, pd manusia tidak
C	Ada resiko (reversibel), tapi bukan malformasi
D	Resiko pada malformasi janin (irreversibel)
X	Terbukti malformasi, Kontraindikasi pada kehamilan

KATEGORI KEAMANAN OBAT IBU HAMIL (FDA)

A	parasetamol, penisilin, eritromisin, glikosida jantung, isoniazid, besi dan asam folat
B1	simetidin, dipiridamol, dan spektinomisin.
B2	ikarsilin, amfoterisin, dopamin, asetilsistein, alkaloid belladonna.
B3	karbamazepin, pirimetamin, griseofulvin, trimetoprim, dan mebendazol.
C	analgetik-narkotik, fenotiazin, rifampisin, aspirin, NSAID dan diuretika
D	androgen, fenitoin, primidon, fenobarbiton, kinin, klonazepam, valproat, steroid anabolik, dan antikoagulansia
X	isotretionin dan dietilstilbestrol.

Prinsip Pengobatan pd Ibu Hamil (MIMS, 1998)

- Tidak ada obat yang dianggap 100% aman bagi perkembangan janin.
- Obat diberikan jika manfaatnya > resikonya, baik bagi ibu maupun janin. Jika mungkin, semua obat dihindari pada trimester I, krn saat itu masa organogenesis
- Pengalaman penggunaan obat terhadap wanita hamil sangat terbatas, karena uji klinis obat saat hendak dipasarkan tidak boleh dilakukan pada wanita hamil.

OBAT TERATOGENIK

Trim I	Antineoplastik, Amfetamin, LSD, Klorpromazin, Barbiturat Fenitoin, Litium
Trim II	Aminoglikosida (streptomicin & kuinin) –tuli Tetrasiklin- gigi berwarna & pertumb tulang terhambat Novobiocin & sulfoamid- bilirubin ↑sewaktu bayi lahir Kloramfenikol-gray baby sindrom, OAD: hipoglikemia Obat hormonal : perubahan fisiologi pd fetus Androgen & progesteron : maskulinasi pd fetus perempuan Vitamin A >>>- menaikkan tekanan intrakanial
Trim III, sblm partus	Depresan CNS-depresi pernafasan saat bayi lahir: barbiturat, narkotik, tranquilizer, antikonvulsan, general anastetik Perdarahan pd bayi : salisilat, indometasin, prometasin, diazepam, CPZ AINS : perdarahan, kerusakan ginjal, penundaan proses kelahiran

Table 10–1 DRUGS THAT SHOULD BE AVOIDED DURING PREGNANCY BECAUSE OF PROVEN OR STRONGLY SUSPECTED TERATOGENICITY*

Drug	Teratogenic Effect
Anticancer/Immunosuppressant Drugs	
Cyclophosphamide	CNS malformation, secondary cancer
Methotrexate	CNS and limb malformations
Antiseizure Drugs	
Carbamazepine	Neural tube defects
Valproic acid	Neural tube defects
Phenytoin	Growth retardation, CNS defects
Sex Hormones	
Androgens (e.g., danazol)	Masculinization of the female fetus
Diethylstilbestrol	Vaginal carcinoma in female offspring
Other Drugs	
Alcohol (in high doses)	Fetal alcohol syndrome, stillbirth, spontaneous abortion, low birth weight, mental retardation
Angiotensin-converting enzyme inhibitors	Renal failure, renal tubular dysgenesis, skull hypoplasia (from exposure during the second and third trimesters)
Antithyroid drugs (propylthiouracil, methimazole)	Goiter and hypothyroidism
Nonsteroidal anti-inflammatory drugs	Premature closure of the ductus arteriosus
Lithium	Ebstein's anomaly (cardiac defects)
Sulfonylurea oral hypoglycemic drugs (e.g., tolbutamide)	Neonatal hypoglycemia
Vitamin A derivatives (isotretinoin, etretinate, megadoses of vitamin A)	Multiple defects (CNS, craniofacial, cardiovascular, others)
Tetracycline	Tooth and bone anomalies
Thalidomide	Shortened limbs, internal organ defects
Warfarin	Skeletal and CNS defects

CNS = central nervous system.

*The absence of a drug from this table does not mean that the drug is not a teratogen; it only means that teratogenicity has not been proved. For most proven teratogens, the risk of a congenital anomaly is only 10%.

Medications with Proven Teratogenic Effects in Humans

Drug or Drug Class	Teratogenic Effects	Critical Period
Alkylating agents	Malformations of many different organs	Organogenesis
Amiodarone	Transitory hypothyroidism (17%, goiter in 18% of these cases) or hyperthyroidism (3%)	From 10th week after conception
Androgens (danazol, testosterone)	Masculinization of genital organs in female fetus	Danazol: from 6th week after conception Testosterone: not defined
Angiotensin conversion enzyme inhibitors Angiotensin II receptor antagonists	Renal failure, anuria, oligohydramnios, pulmonary hypoplasia, intrauterine growth restriction, limbs contracture, skull hypoplasia	After the first trimester
Anticonvulsants • Carbamazepine • Phenytoin • Phenobarbital • Valproic acid	NTDs (for carbamazepine and valproic acid); oral cleft, skeletal, urogenital, craniofacial, digital, and cardiac malformations; microcephalia Risk of major malformations estimated at 5–10% depending on the agent used (about 5% for carbamazepine, 10–14% for valproic acid). Valproic acid: abnormal neurologic development	7–14 weeks (gestational age); higher risk between 8 and 11 weeks. Neurologic development: not established
Systemic corticosteroids	Oral cleft (risk of 3–4/1,000 versus 1/1,000 in general population)	Organogenesis
Diethylstilbestrol	Girls: Cervical or vaginal adenocarcinoma, incidence of less than 1.4/1,000 exposures. Structural genital anomalies (e.g., of cervix, vagina) in 25% of cases Boys: Genital anomalies, spermatogenesis anomalies	First and second trimesters
Fluconazole high doses	Skeletal and craniofacial malformations, cleft palate (with chronic dose more than 400 mg/day; not reported with 150 mg single dose)	Not defined, but cases are reported where exposure was for most parts of pregnancy
Radioactive iodine (I^{131})	Thyroid suppression (goiter)	From 10th week after conception (consider the dosage and time to eliminate the product on a case-by-case basis)

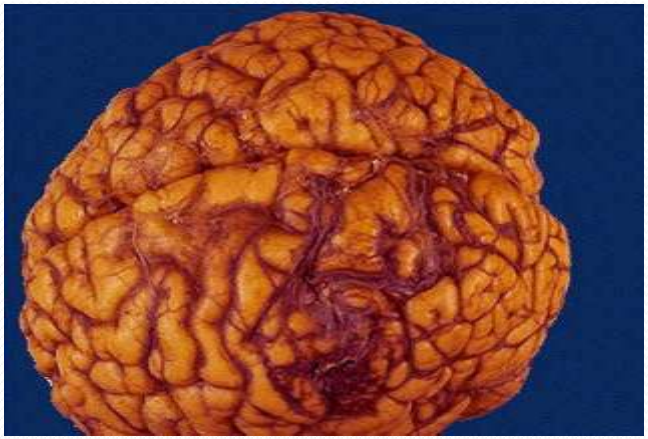
Isotretinoin, acitretin, etretinate, and vitamin A (more than 10,000 IU/day)	CNS, skull, eyes and ears malformations, micrognathia, oral cleft, cardiac malformations, thymus anomalies, mental retardation: estimated at 25–30% (may be higher for neurologic development impairment) Contraindicated throughout pregnancy Isotretinoin: discontinue 1 month before pregnancy, prescribed under a special program called iPLEDGE Acitretin, etretinate: discontinue 2–3 years before pregnancy (alcohol consumption decreases elimination)	Organogenesis (risk of teratogenic effect after organogenesis not excluded)
Lithium	Cardiac malformations: risk of 0.9–6.8% (higher risks from small studies that included also minor cardiac anomalies) (general population risk: approximately 1%) Includes Ebstein's anomaly: risk estimated at 0.05–0.1%	Cardiac organogenesis
Methimazole/ propylthiouracil	Methimazole: aplasia cutis, syndrome including choanal atresia, esophageal atresia, facial anomalies, developmental delay; risk probably low Methimazole/propylthiouracil: fetal hypothyroidism in 2–10% of infants whose mothers were treated for Graves disease or goiter	Organogenesis Second and third trimesters
Methotrexate	CNS and cranial malformations, oral cleft, skeletal and limb malformations It is recommended to stop the medication 3 months before pregnancy	Organogenesis
Misoprostol	Moebius syndrome ± limb anomalies ± CNS anomalies	Organogenesis
Mycophenolate mofetil	Ear anomalies, oral cleft, other anomalies (causality to be confirmed)	Uncertain
Nonsteroidal anti-inflammatory drugs	In utero closure of ductus arteriosus (constriction is rare before 25 weeks, 50–70% at 30 weeks and 100% at 32 weeks (gestational age) and pulmonary hypertension	Third trimester
Penicillamine	Cutis laxa	Not defined
Tetracyclines	Teeth discoloration	14 weeks postconceptional
Thalidomide	Limb anomalies Cardiac, urogenital, GI, and ear malformations Prescribed under a special program called STEPS (System for Thalidomide Education and Prescribing Safety)	20–36 days after conception
Trimethoprim	Cardiac and urogenital malformations, neural tube defects, oral cleft	Organogenesis
Warfarin/ acenocoumarol	Warfarin embryopathy including nasal hypoplasia, epiphysis dysplasia, vertebral malformations	Between 4th and 7th week postconception

Ox sitostatika=Kategori X

METHOTREXATE

Indications: moderate to severe active rheumatoid arthritis; Crohn's disease; malignant disease; psoriasis

CLP-Limb malformation

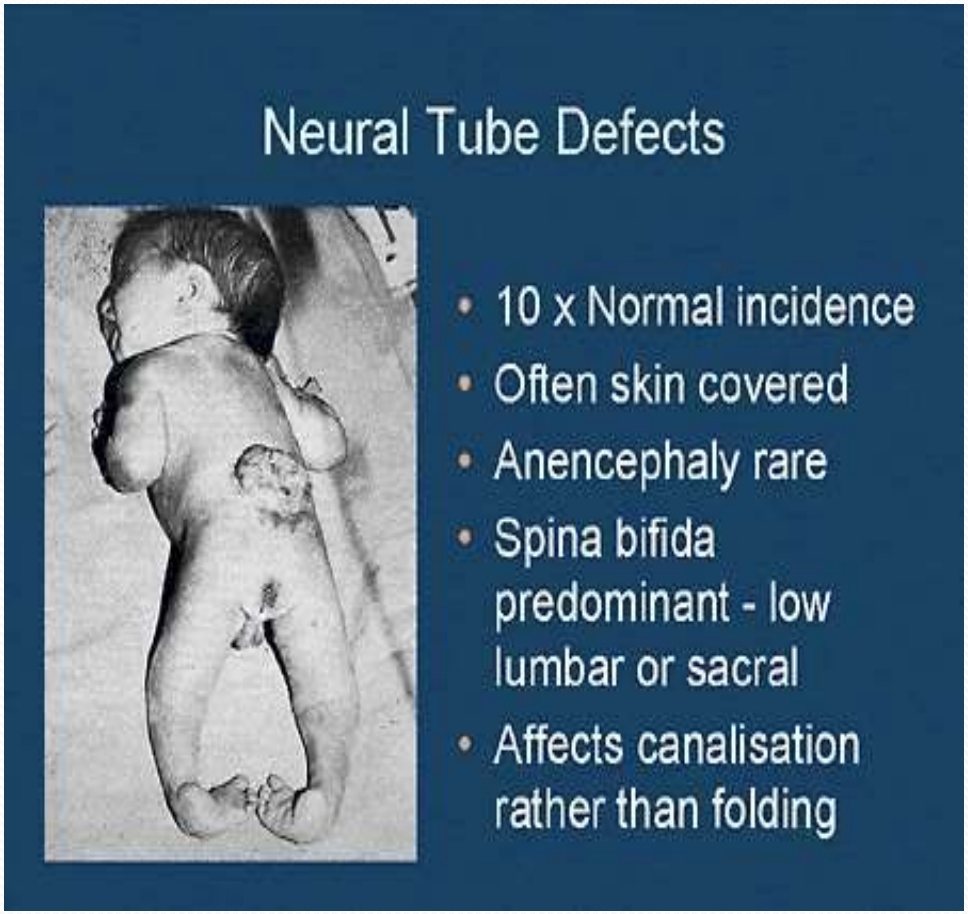


CNS malformation

Ox Antikonvulsi = Kategori X

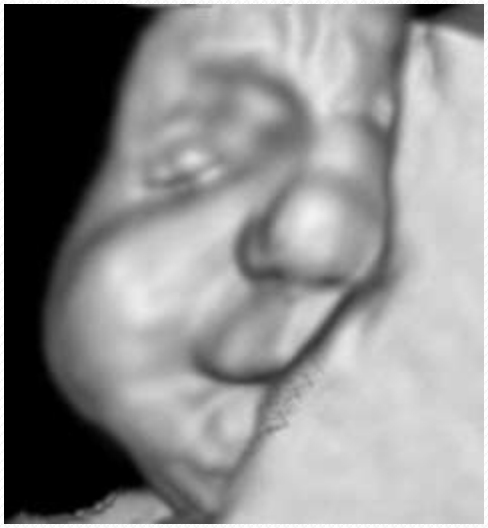
CARBAMAZEPINE

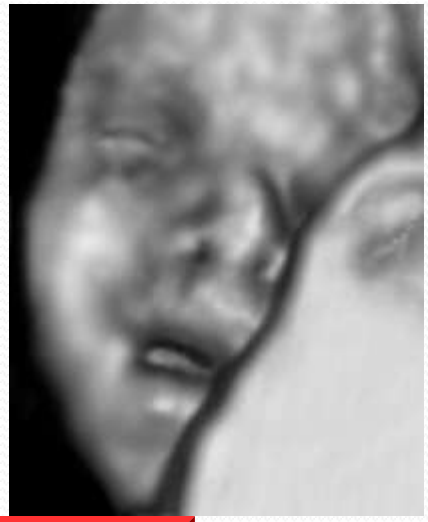
Indications: partial and secondary generalised tonic-clonic seizures, some primary generalised seizures; trigeminal neuralgia; prophylaxis of bipolar disorder unresponsive to lithium



Neural tube defect

Ox Antikonvulsi=Kategori X





Growth retardation

PHENYTOIN

Indications: all forms of epilepsy except absence seizures; trigeminal neuralgia if carbamazepine inappropriate

Cautions: hepatic impairment (reduce dose), pregnancy, breast-feeding; avoid sudden withdrawal; manufacturer recommends blood counts; avoid in porphyria

Sex Hormon=Kategori X

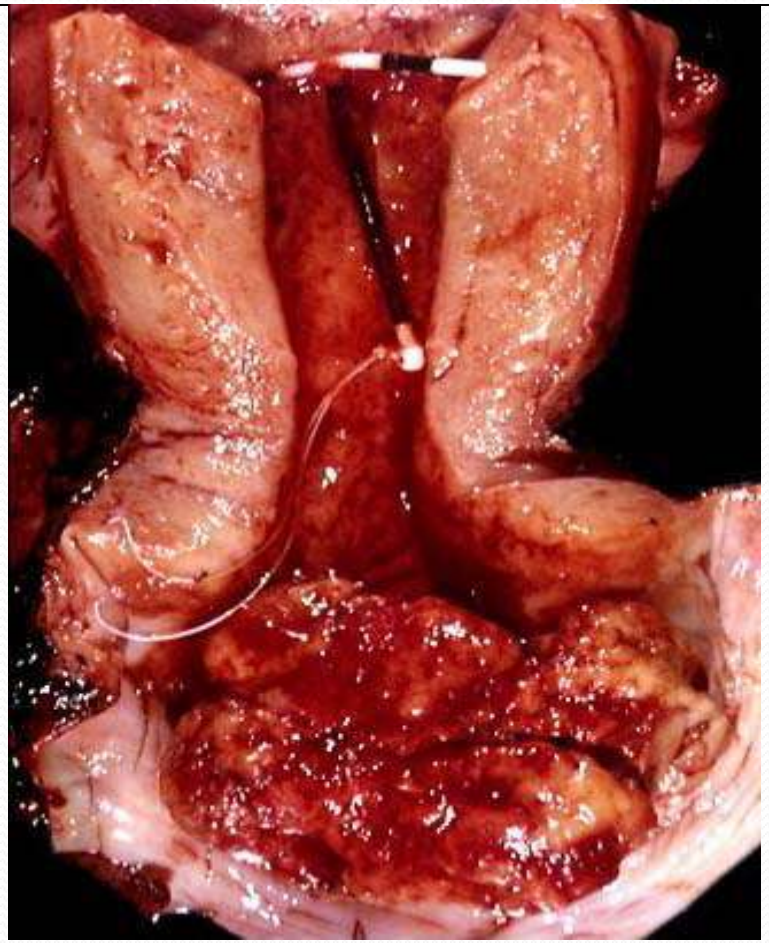
DIETHYLSTILBESTROL

Cautions: cardiovascular disease

Contra-indications: pregnancy, hepatic impairment

Side-effects: sodium retention with oedema, thromboembolism, jaundice, feminising effects in men;

Dose: breast cancer, 10–20 mg daily
Prostate cancer, 1–3 mg daily



Cervix carcinoma

Sex hormon=Kategori X

DANAZOL

Contra-indications: pregnancy, ensure that patients with amenorrhoea are not pregnant; breast-feeding, severe hepatic, renal or cardiac impairment; thromboembolic disease; undiagnosed genital bleeding; androgen-dependent tumours; porphyria

Masculinization of female fetus

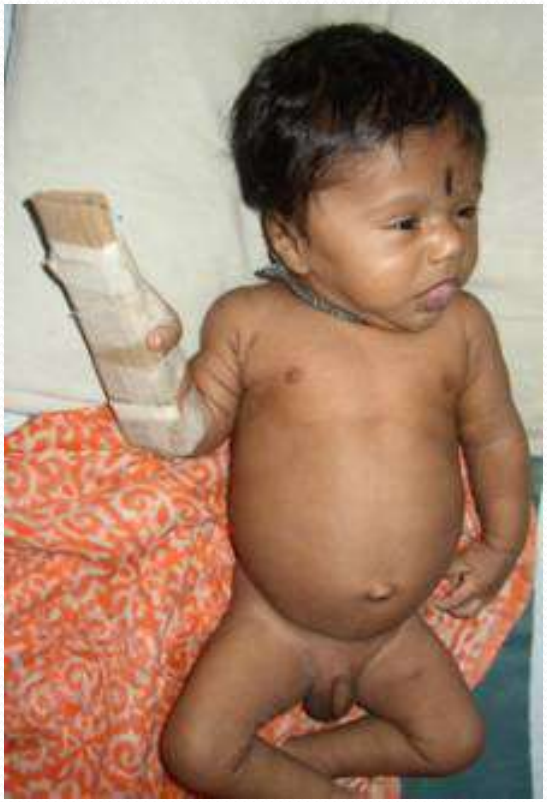
Indication:

Endometriosis

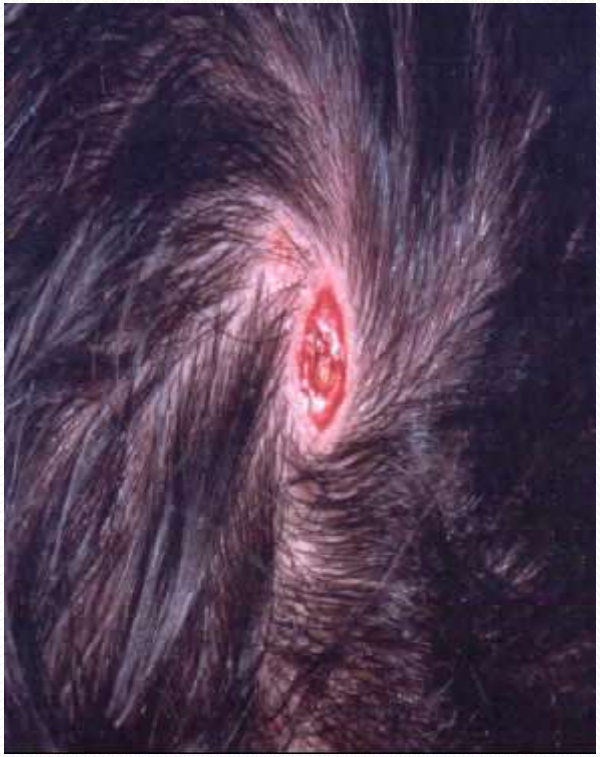
Severe pain and tenderness in benign fibrocystic breast disease not responding to other treatment

Hereditary angioedema [unlicensed indication]

OxAntiroid=Kategori X



ANTITHYROID DRUGS: propilthiouracyl & methimazol



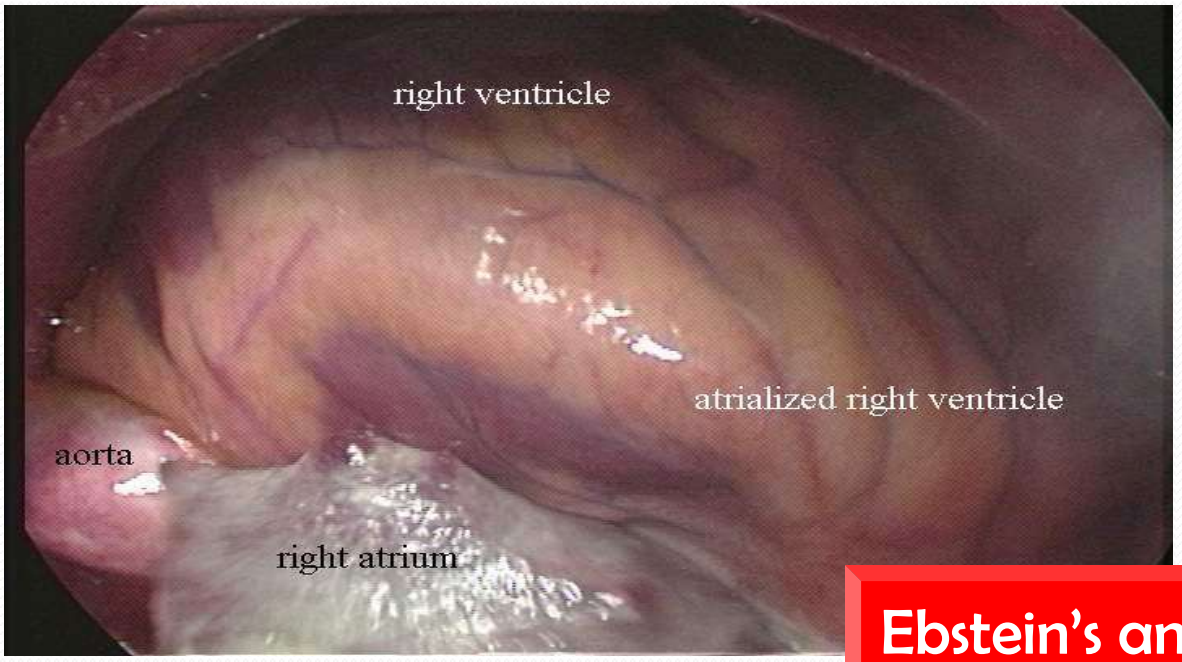
Neonatal goiter

Aplasia cutis

Antipsychotic=Kategori X

Lithium

Lithium salts are used in the prophylaxis and treatment of mania, in the prophylaxis of bipolar disorder (manic-depressive disorder) and in the prophylaxis of recurrent depression (unipolar illness or unipolar depression). Lithium is unsuitable for children.



Ebstein's anomaly

Antikoagulan =Kategori X

WARFARIN SODIUM

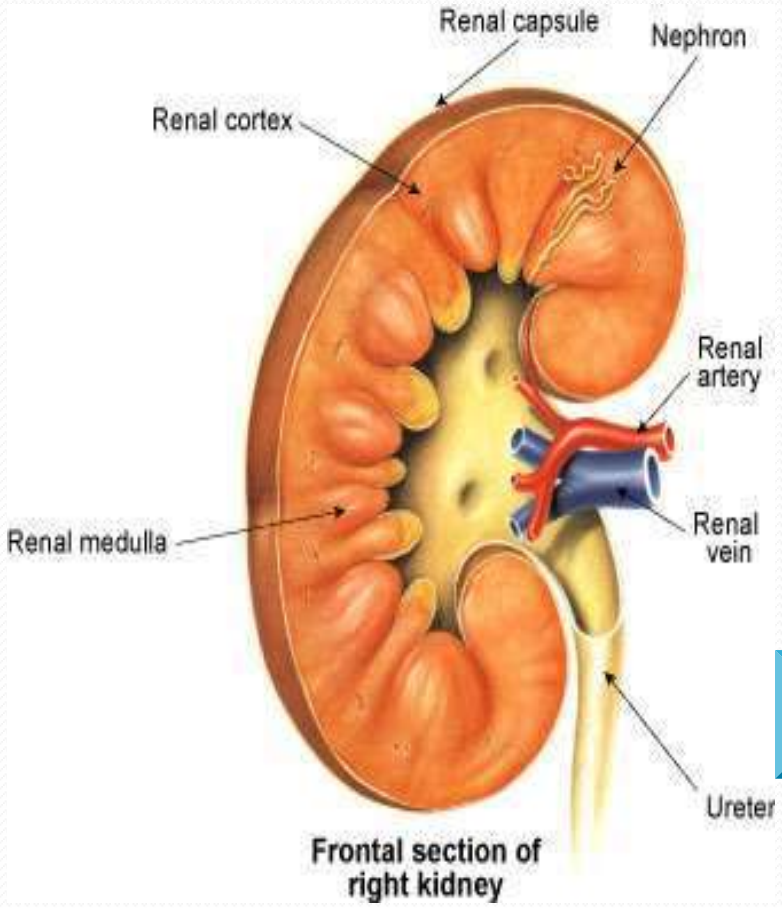
=Antikoagulan oral

Indications: prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation; prophylaxis after insertion of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism; transient ischaemic attacks

Contra-indications: peptic ulcer, severe hypertension, bacterial endocarditis; pregnancy

Dandy Walker syndrome

Ox Antihipertensi=Kategori X



ACE INHIBITOR

Indications: Hipertensi

- Ramipril
- Lisinopril
- Captopril

Prolonged renal failure in neonates

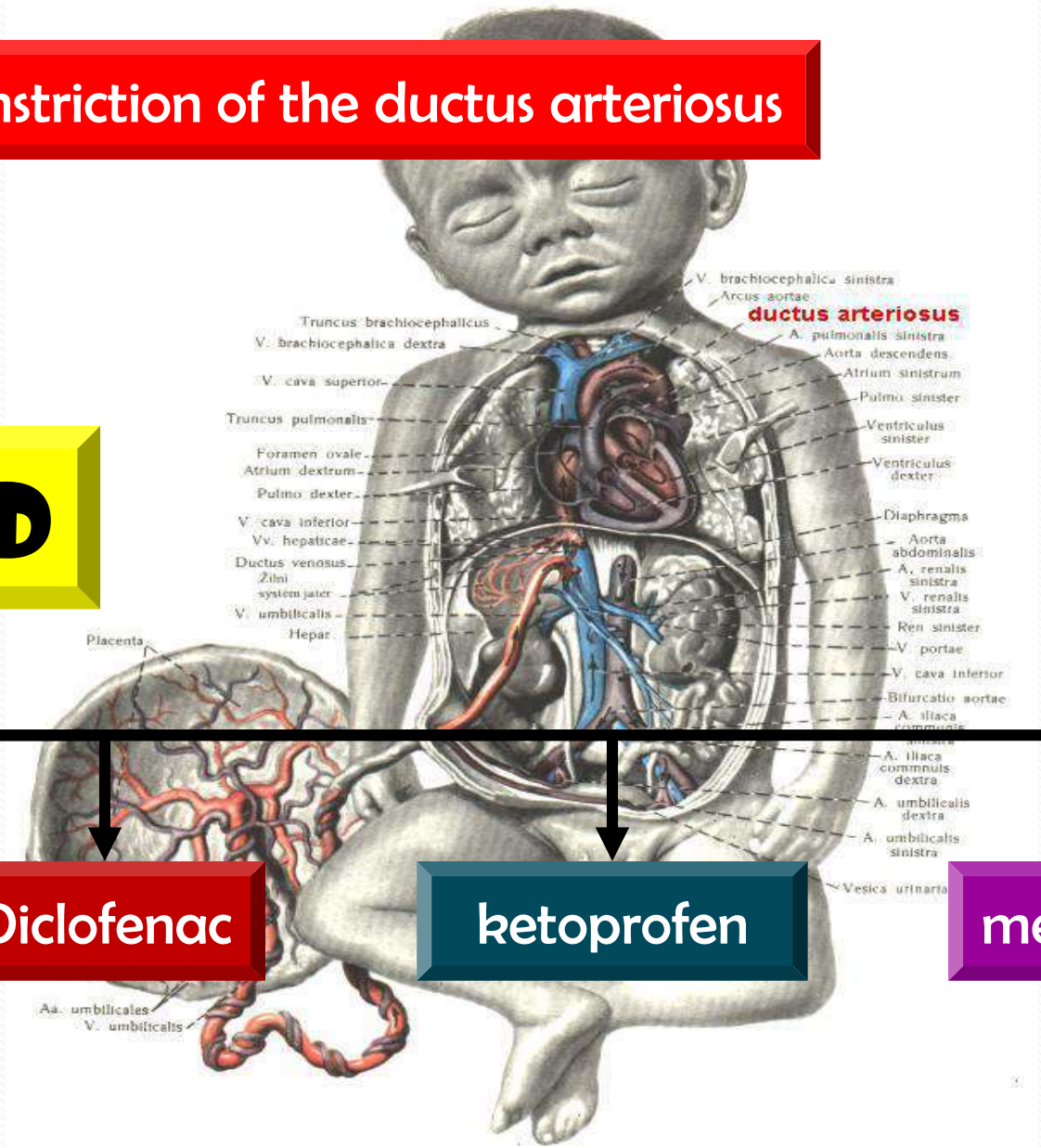
Preconception Risk Factor	Potential Adverse Pregnancy Outcomes	Management or Prevention Options
Use of known teratogens		
• Antiepileptic drugs	• Known teratogens; causes craniofacial, cardiac, and limb defects[e] • NTD • Fetal hydantoin syndrome	• Use lowest possible dose to maintain control • Folic acid 4 mg daily
• Isotretinoins	• Miscarriage • Known teratogen; causes CNS, craniofacial, and cardiac defects[e]	• Use effective pregnancy prevention
• Oral anticoagulants	• Fetal warfarin syndrome	• Switch to nonteratogenic anticoagulant (e.g., LMWH) before becoming pregnant
Lifestyle factors		
• Alcohol misuse	• Fetal alcohol syndrome	• Cease alcohol intake before conception
• Obesity	• NTD • Preterm delivery • Diabetes, HTN, VTE • Cesarean section	• Weight loss with appropriate nutritional intake before pregnancy

• Tobacco use	• Preterm birth
	• Low birth weight
	• Spontaneous abortion
	• Increased perinatal mortality
		• Ideally, cease tobacco use before conception
		• Nonpharmacologic therapies (e.g., CBT, counseling, hypnosis)
		• No consensus for NRT product, dosing, or frequency:
		  • Intermittent forms (e.g., gum)
		  • Transdermal patch (limit to 16 hours/day)
		• Bupropion risk may be less than risk posed by smoking; efficacy unclear
		• Varenicline safety unknown

CBT, cognitive behavioral therapy; HTN, hypertension; LMWH, low-molecular weight heparin; NRT, nicotine replacement therapy; NTD, neural tube defect; VTE, venous thromboembolism.

Kategori X

Constriction of the ductus arteriosus



NSAID

Diclofenac

ketoprofen

meloxicam

PEMAKAIAN OBAT PADA IBU HAMIL

ANTIBIOTIK

- Tetrasiklin : sebaiknya dihindari
  - Trim I ; deposisi tulang ini utero → gangg pertumb tulang, tu pd bayi prematur (reversibel)
  - Trim II-III : perubahan warna gigi (kekuningan) (irreversibel) dan Hipoplasia enamel
- Aminoglikosida ; teratogenik
  - Nefdrotoksik & otottoksik utk ibu
  - Trim I : Kerusakan ginjal tk saeluler pd janin, kerusakan saraf kranial VIII

PEMAKAIAN OBAT PADA IBU HAMIL

ANTIBIOTIKA

- Kloramfenikol :
  - Trim II –III : sindroma Grey pd bayi saat lahir
  - Saat menyusui
- Sulfonamid :
  - Trim III : kern icterus (s.d 7 hr stl lahir)
- Eritromisin : aman selama kehamilan
- Trimetoprim ; teratogen pd dosis besar
- Nitrofurantoin : trim III anemia hemolitik pd janin

OBAT ANTI FUNGAL

Nama Obat	ADE-FDA	ES
Nystatin (topical)	A-C	-
Ketokonazole, Itrakonazole, Griseofulvin	B3-C	Risk limb malformation
Flukonazole	D-C	Repeated dose→birth defect
Topikal Ketokonazol	A	

OBAT YANG MEMPENGARUHI MOTILITAS UTERUS

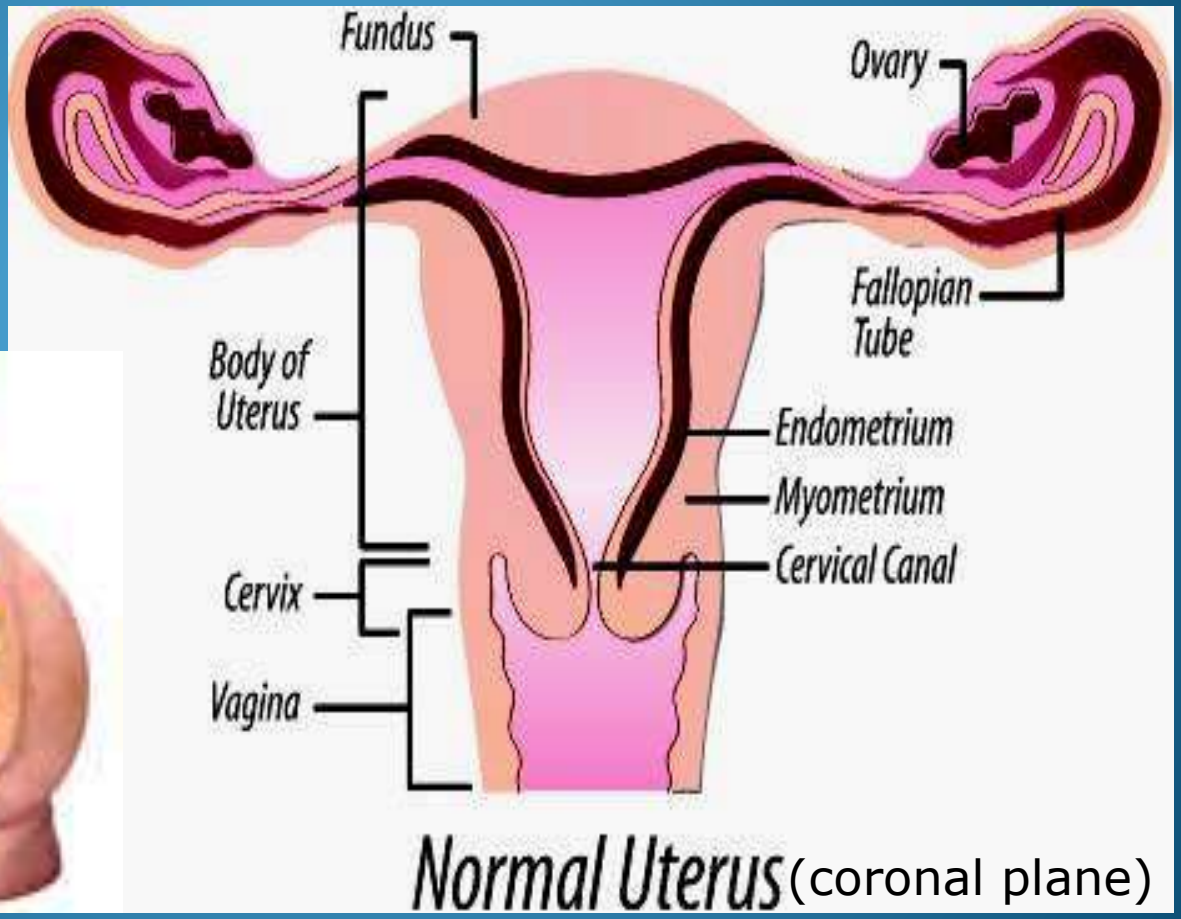
OBAT MENINGKATKAN KONTRAKSI (UTEROTONIC AGENT)

OBAT MENURUNKAN KONTRAKSI (TOCOLYTIC AGENT)

Drugs acting on the uterine smooth muscle

Drugs

(sagittal plane)



Normal Uterus (coronal plane)

Stimulants/
Uterotonik

★**for birth or abortion**

e.g. oxytocin

dinoprostone (PGE_2)

dinoprost ($PGF_{2\alpha}$)

★ **for hemostasia & uterus restoration after labor**

e.g. oxytocin

ergonovine methlergometrine

Inhibitors/
Tokolitik

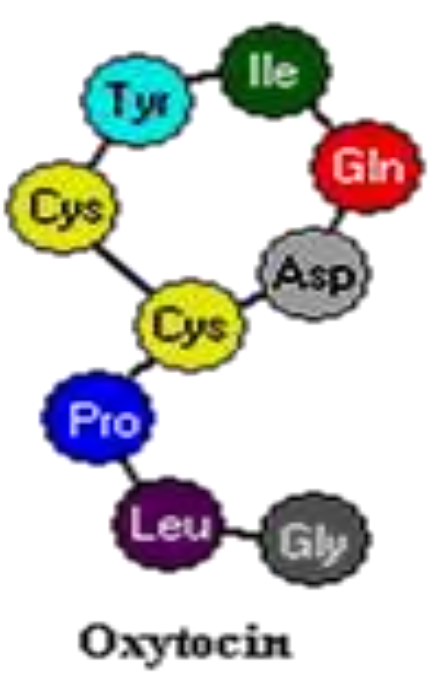
- **for guard against miscarriage or alleviation of dysmenorrhea**

salbutamol, nifedipine, $MgSO_4$

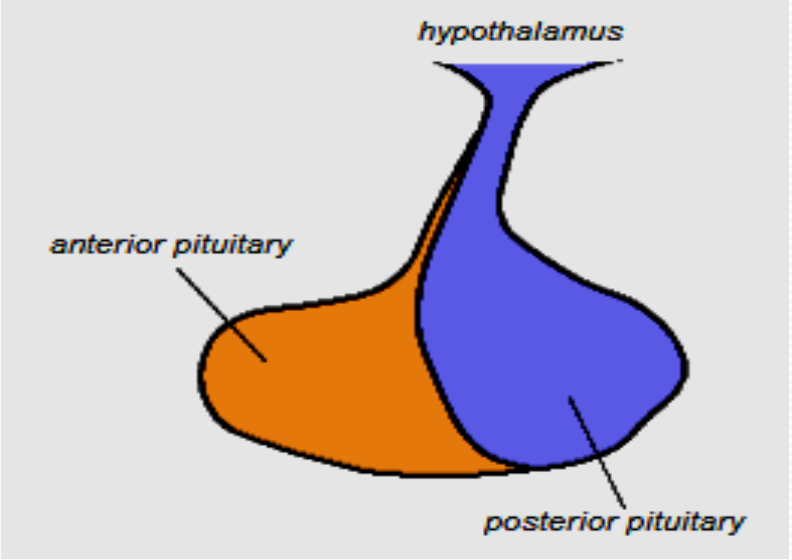
OBAT UTEROTONIK

Oksitosin

- Sintesis: nukleus paraventricular dan supraoptic di hypothalamus
- *storage* dan *release*: lobus posterior kelenjar pituitary

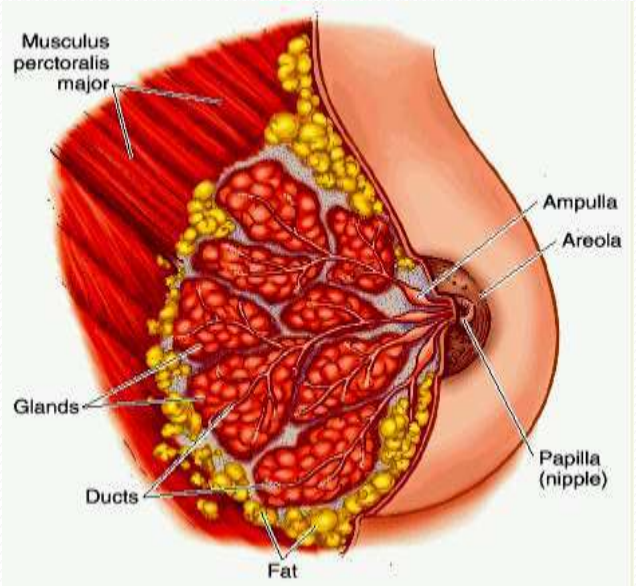


Brain, ovaries and testes also release little

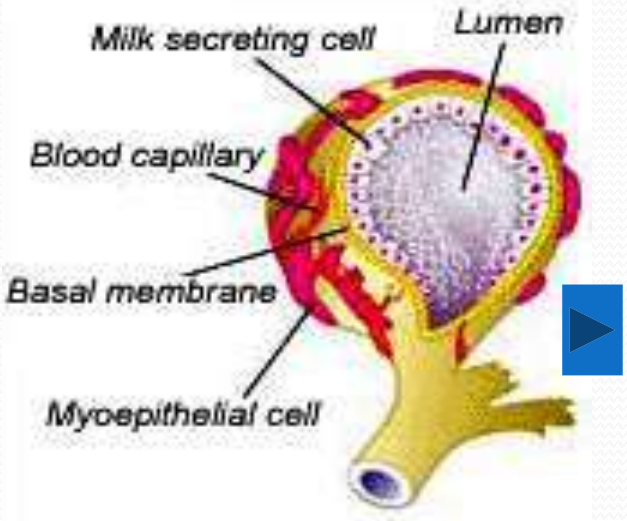


Efek Fisiologi

★ Stimulasi *milk ejection (milk letdown)*



mammary alveoli

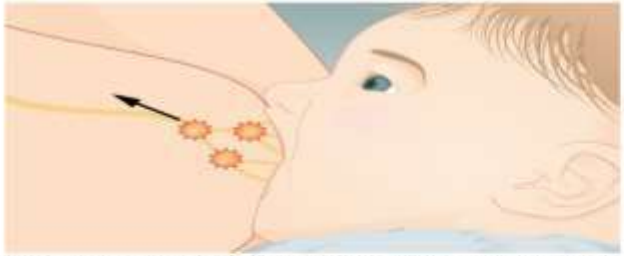


★ Stimulasi kontraksi otot polos uterus selama proses kelahiran

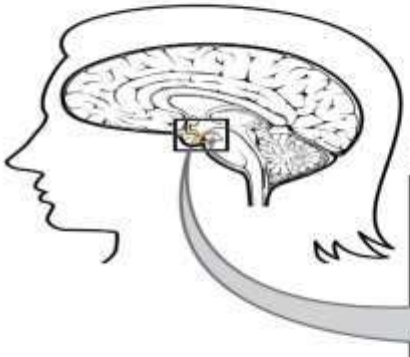
★ Membentuk prilaku maternal behavior

Increased milk production triggers increased suckling by infant (positive feedback loop)

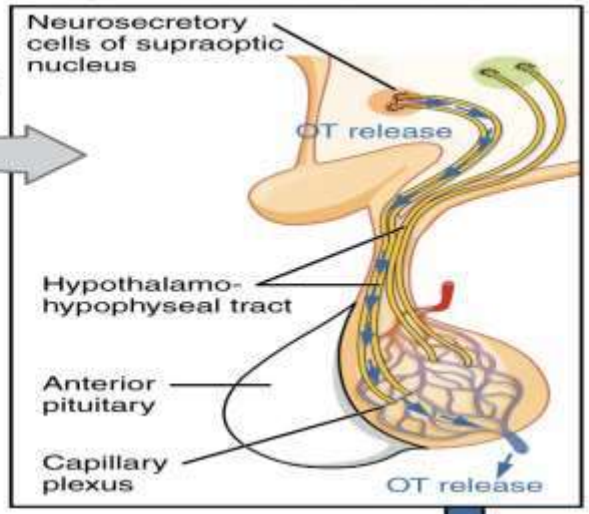
+



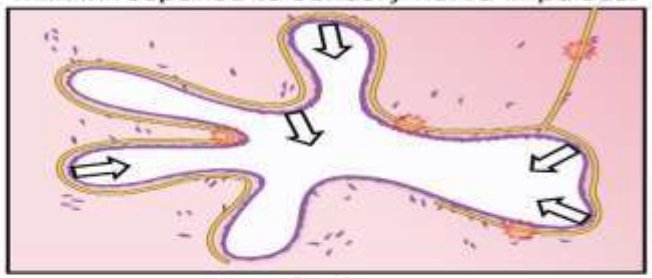
Suckling triggers sensory nerve impulses in the areola.



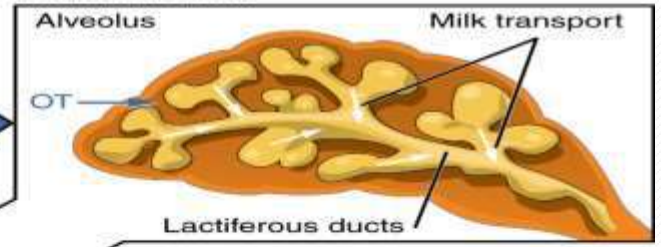
Brain receives sensory impulses from the areola and releases oxytocin (OT) from the hypothalamus and posterior pituitary.

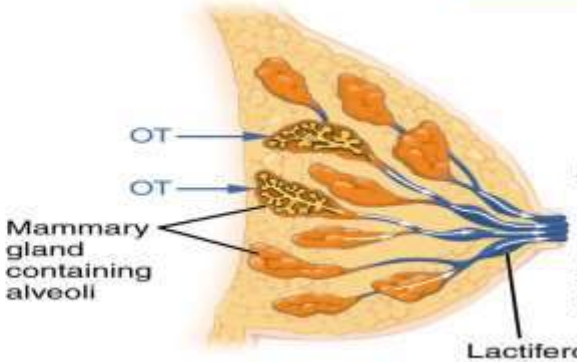


Lactocytes in mammary alveoli produce milk in response to sensory nerve impulses.



Oxytocin (OT) triggers myoepithelial cells to squeeze milk from alveoli so it drains into lactiferous ducts.





Milk is pooled in lactiferous sinus before being discharged through nipple pores.

Efek Farmakologi

★ **Stimulasi kontraksi uterius**

Karakteristik

① Frequency and force all enhanced

②Affected by sexual hormone levels in blood plasma:

estrogen sensitizes, and progesterone oppresses it

③Different dosages lead to different contractions

low dosage: rhythmic contraction

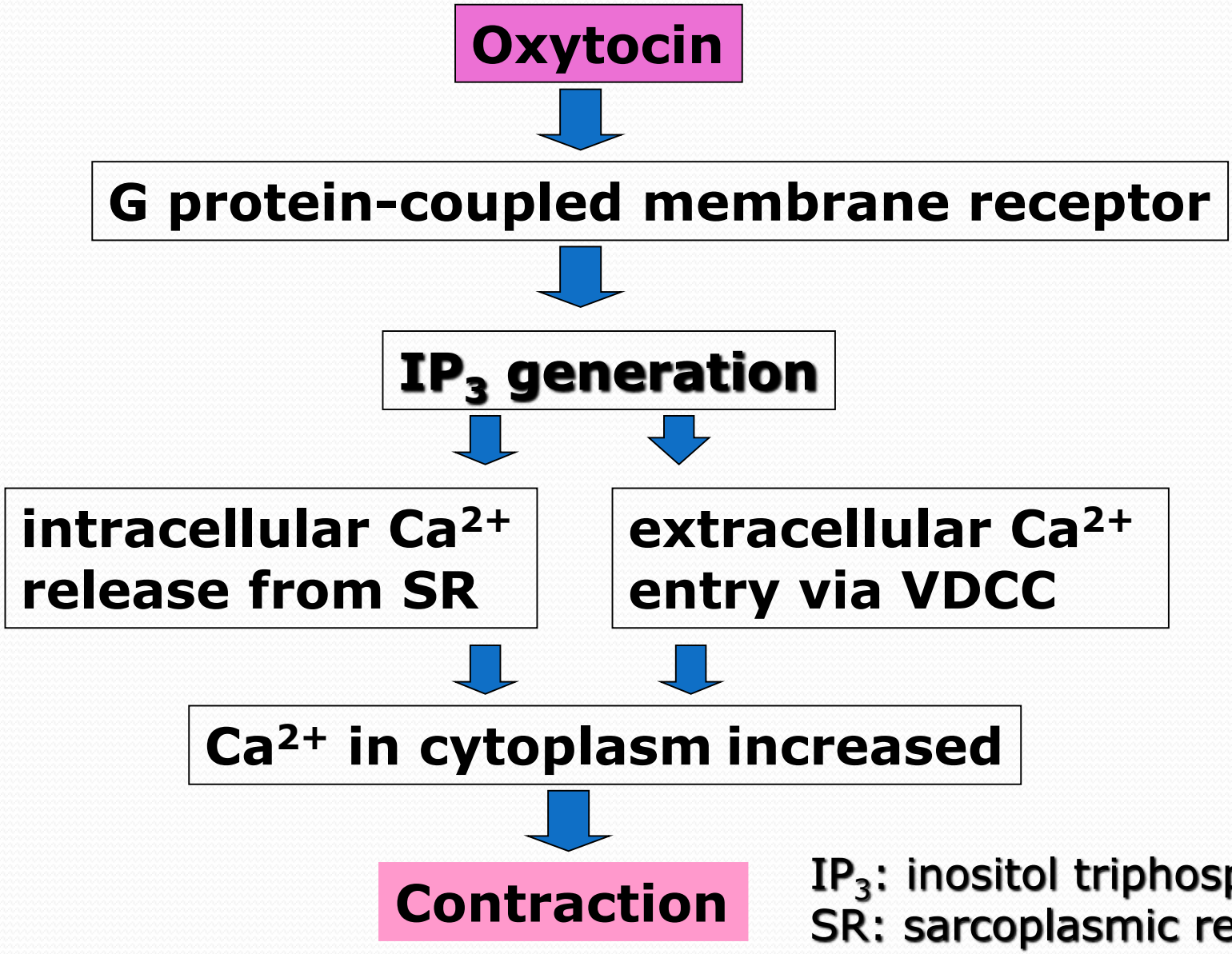
uterine fundus contracts while cervix relaxes

high dosage: sustained contraction in whole uterus

★ **Milk letdown effect & weak antidiuretic effect**

★ Dilation of vessels at High dosage

Mechanism of stimulation of uterine smooth muscle contraction



IP_3: inositol triphosphate
SR: sarcoplasmic reticulum

pharmacokinetics

- Null swallowed
- im or iv usually used, iv for parturition
- Not bound to plasma protein
- Catabolized by kidney & liver
- $T_{1/2}$: 5 min

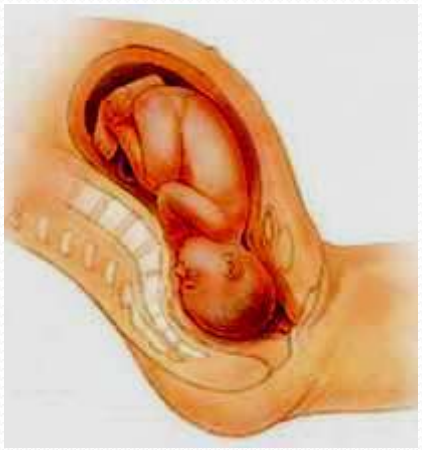
Clinical use

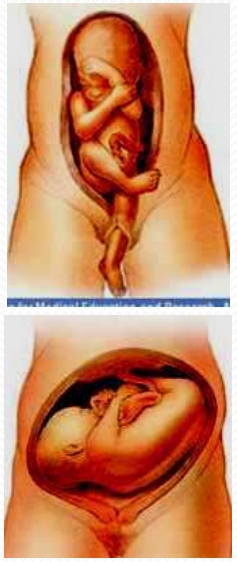
- Induction (abortion) or Augmentation (birth)

ivd 1mU/min initially and increased to 5-20 mU/min gradually

<u>contraindications</u>:

* malposition
* cephalopelvic disproportion
* birth canal abnormality





- postpartum hemostasia &uterus

Restoration *im 5-10 U each time*

II. Ergot alkaloids

- Ergot: an epiphyte parasitizes in rye (gandum hitam)
- Drugs

  Ergotamine ergotoxine

  Ergometrine (ergonovine)

Pharmacodynamics

- stimulation of uterus smooth muscle contraction

Characteristics

①pregnant uterus more sensitive to them

②fiercer and more sustained than oxytocin

- stimulation of blood vessel constriction by stimulation of α-adrenoceptor and serotonin receptor , and inhibition of EDRF

  Drug- and vessel-dependent

  In a predictable, prolonged, and potent manner

Clinical use

★uterus hemorrhage

★postpartum uterus restoration

ergometrine po 0.2-0.5 mg, im or iv 0.1-0.3 mg, 1-2/d

★migraine

ergotamine po 1-2 mg, im 0.25-0.5 mg, <10 mg/w

Ⅲ. Prostaglandins analog

- Drugs : dinoprostone (PGE_2) dinoprost ($PGF_{2\alpha}$)
- Effects : Stimulation of rhythmic uterine contraction
- Clinical use : For inducing abortion
- contraindications
  * Similar to oxytocin
  * $PGF_{2\alpha}$ is banned for patient with asthma
  * PGE_2 is banned for patient with glaucoma

Brief summary

1. Oxytocin

low dosage: rhythmic contraction of uterus;
fundus contracts while cervix relaxes;
used via iv for induction or augmentation.

high dosage: sustained contraction in whole uterus;
used via i.m or i.v for hemostasia or restoration of postpartum uterus.

2. Ergot alkaloids

stimulation of sustained contraction in whole uterus,
ergometrine used via po, im or iv for hemostasia or restoration of postpartum uterus;
stimulation of blood vessel constriction,
ergotamine used via p.o or i.m for migraine.

3. Prostaglandins

PGE_2 & $PGF_{2\alpha}$ stimulation of rhythmic uterine contraction,
used via ivd for induction (abortion)

Tocolytic Agent

= anti-contraction medications = labour repressants

Tujuan :

- menunda persalinan beresiko, diberikan slm perjlnan menuju RS dg fasilitas lengkap
- memberi kesempatan pemberian glukokortikoid 2x 24j u/ maturitas paru janin

Golongan obat Tokolitik :

- β2 Agonis (Terbutalin, Ritodrine)
- Ca antagonis (nifedipin) (best benefit-to-risk-ratio)
- Antagonis R/ Oksitosin (Atosiban)
- NSAID (Indometasin, Sulindac)
- MgSO4

Hindari pemberian kombinasi, memperpanjang / pemakaian berulang-----beresiko pd janin

TOCOLYTIC AGENT

Agent	Regime	Side effects		Contraindications
		Maternal	Fetal	
Nifedipine	Initial dosage :- sublingual 10mg, repeat every 15 minutes until contractions cease total maximum dosage 40mg - Maintenance dosage: Oral 20mg start 6 hrs after the initial sublingual dose q8h for 2 days Titrate against response and side-effects Can increase dosage, firstly to 20mg q6h then up to 40 mg q6h on the first day	- Flushing or headache - Significant hypotension, maternal tachycardia,	Foetal tachycardia	Hypotension Preload-dependent cardiac lesions (e.g. aortic insufficiency)

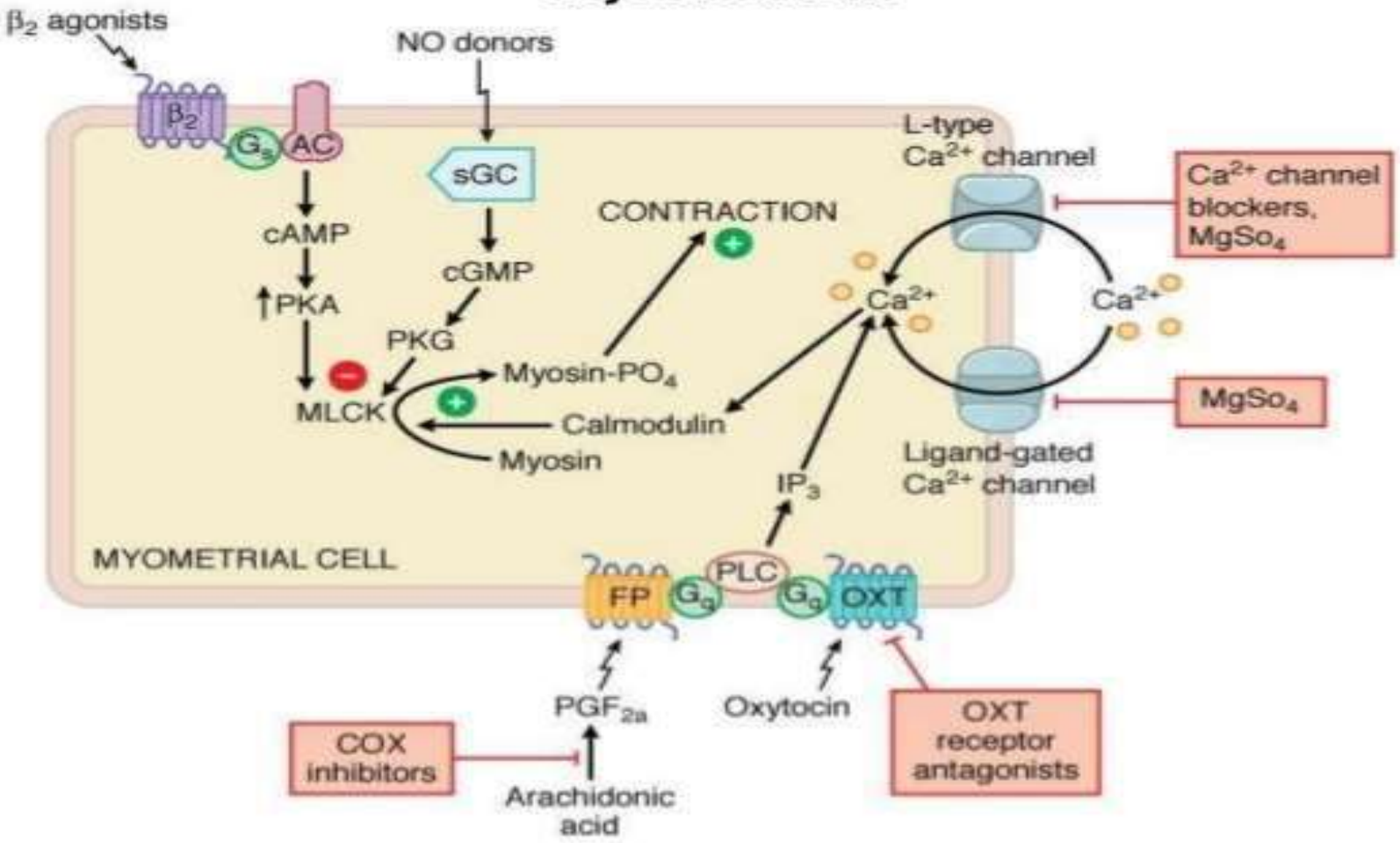
TOCOLYTIC AGENT

Agent	Regime	Side effects		Contraindications
		Maternal	Fetal	
Atosiban	Loading dose: - 6.75mg ivi over 1 minute - Then start high dose loading infusion: 75mg in 100ml. Infusion rate 24ml/hour (18mg/hour or 300mcg/min) for 3 hours - Then start low dose Maintenance infusion: (75mg/100ml) Infusion rate to 8ml/hour (6mg/hour or 100mcg/min) for 21 hours (Maximum duration: 45 hours)	- Nausea and vomiting - Dizziness and hot flushes - Tachycardia and hypotension - Hyperglycaemia - Injection site reaction		Allergy to Atosiban

TOCOLYTIC AGENT

Agent	Regime	Side effects		Contraindications
		Maternal	Fetal	
Indomethacin Sulindac	50 to 100mg rectal suppository Then 15mg 4-6 hrs for 48 hours 200mg po Q12H for 4 doses	GI upset (Nausea, heartburn) Drug rash, bleeding disorders	Transient constriction foetal ductus arteriosus, oligohydramnios	Asthma Drug allergy Renal, cardiac, hepatic impairment Peptic ulcer Thrombocytopenia
Ritodrine	Start IV infusion using syringe pump (150mg in 50ml 5%-dextrose) with 50ug/min or 1ml/hr Increment at 15 minute-interval by 50ug/min until uterine contractions are suppressed, or maximum dosage attained (350ug/min), or complications arise Maintain infusion rate for at least 6 hours after contractions have ceased, and up to 24 hours for steroid to work	Tachycardia and hypotension Palpitation Shortness of breath chest discomfort Hypokalaemia Hyperglycaemia ECG changes (ST depression, prolonged QT interval), pulmonary edema	Foetal tachycardia Increased intraventricular haemorrhage	- Severe cardiac diseases and arrhythmia - Poorly controlled hyperthyroidism or taking beta-blocker for control of tachycardia - Poorly controlled diabetes mellitus

Sites of action of tocolytic drugs in the uterine myometrium



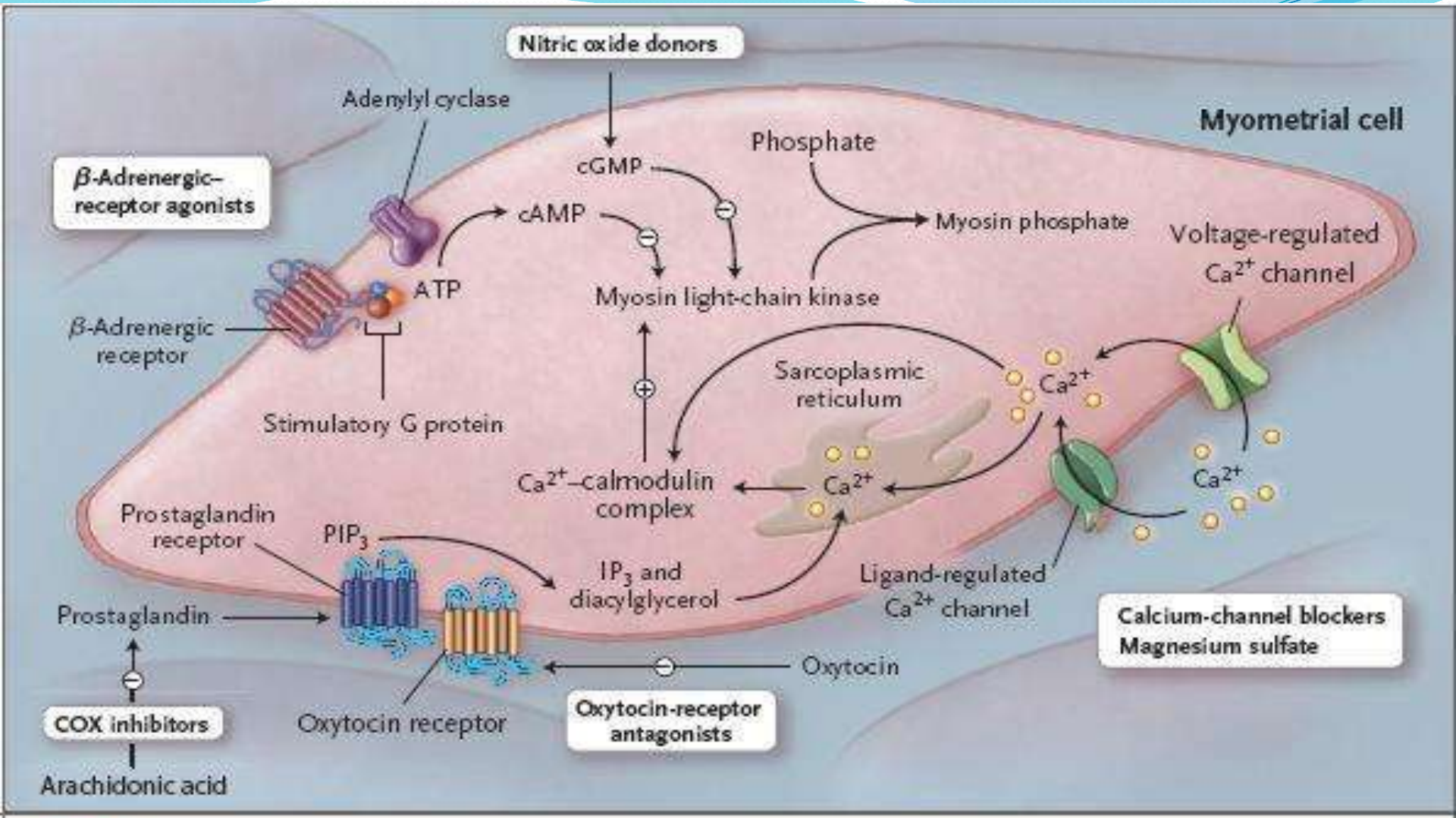


Figure 1. Sites of Action of Commonly Used Tocolytic Drugs.

COX denotes cyclooxygenase, PIP_3 phosphatidylinositol triphosphate, IP_3 inositol triphosphate, cAMP cyclic AMP, and cGMP cyclic guanosine monophosphate.

OBAT PADA IBU MENYUSUI

BREAST-FEEDING COMPATIBILITY

Category (+)	Generally compatible with breast-feeding.
Category (-)	Avoid with breast-feeding. Toxicity can be seen.
Category (CI)	Contraindicated.

Transfer of Drugs into Milk

- Semua obat terdistribusi ke dalam ASI, difusi psf;
- Yg penting → perkiraan jml obat yg msk dlm ASI
- Faktor yg pengaruhi laju difusi: Farmakokinetika ibu, Sifat fisiologis ASI, Sifat fisikokimiawi obat;
- ASI berbeda dg plasma ibu: pH lebih rendah, kapasitas ikatan PP lebih rendah, kandg. lipid yg tinggi
- Obat basa lemah → "terjebak" dlm ASI;
- Obat dg ikatan PP tinggi → "trjebak" dlm Plasma
- Obat lipofilik → kadar dlm ASI tinggi

Estimating Infant Exposure

- Obat masuk ke ASI dg mekanisme difusi transeluler (mll membran biologis)→ derajat ionisasi
- **"Fraksi obat tak-terionisasi dan bersifat lipofilik dapat berdifusi melewati membran biologis"**
- Dg mengetahui derajat ionisasi obat (pKa) dan per bedaan pH antara plasma ibu dan ASI,maka Rasio M/P (Milk-Plasma) scr teoritis dpt dihitung
- Nilai pH plasma ± 7,4 dan pH susu ± 7,0

Estimating Infant Exposure

- Jika Rasio M/P dpt diketahui or dihitung teoritis, maka dpt dihitung dosis obat yg diminum bayi:
  - Dosis bayi: $D_{inf} = Cp_{mat} \times M/P \times$ Vol.susu diminum dimana Cp_{mat} adl rata2 konstr.obat plasma ibu, bila Vol.susu yg diminum bayi tak diketahui gunakan ang ka 150 ml/kgBB/hari
- Level Aman Expos Obat kpd bayi yg sdg menyu sui dilihat "% dosis", cara menghitung:
  - ✓ % dosis = $\dfrac{D_{inf}\ (mg/kgBB/hari) \times 100\ \%}{D_{mat}\ (mg/kgBB/hari}$
- Level aman bila "% dosis" dibawah 10 %

Pendekatan utk Meminimalisasi Expos bayi

1. **Tidak Minum Obat**; bbrp jenis obat spt: sakit kepala, obat flu, dpt dihindari dg kerjasama ibu.
2. **Tunda Pemberian Obat**; jika ibu ada rencana utk menyapih ASI, maka penggunaan obat/pembedah-an elektif dapat ditunda terlebih dahulu.
3. **Pilih obat yg sedikit diekskresikan dlm ASI**; utk klas terapi yg sama dpt dipilih yg paling sedikit melewati ASI.
4. **Pilih alternatif rute pemberian lainnya**; utk ku-rangi konst.obat dlm darah ibu maka digunakan sediaan lokal (mis. Kortikosteroid inhalasi, dll)

Pendekatan utk Meminimalisasi Expos bayi

5. Tidak menyusui bayi pd saat konstr. obat dlm ASI maksimal; scr umum konstr.obat dlm ASI capai maks.: 1-3 jam setelah dosis oral sang ibu, menyusui tepat sebelum minum obat dpt kurangi expos obat thd bayi,hanya u/ obat dg waktu paruh pendek, tdk utk obat ***slow release***. Juga, jadwal bayi minum ASI sulit utk diatur scr tetap.
6. Minum obat sebelum bayi tidur lama; berguna utk obat ***long acting*** yg diminum sekali sehari.
7. Berhenti menyusui; bila demi kesehatan ibu & utk obat yg sangat toksis (khemoterapi kanker).

Pendekatan utk Meminimalisasi Expos bayi

8. **Tidak menyusui bayi utk sementara waktu**; bila digunakan obat jangka pendek stl prosedur operasi/prwtn gigi, sblm tind.medis-ASI dipompa utk dpt diberikan pd bayi. Memompa ASI (tapi tdk diberikan kpd bayi) selama terapi obat tetap dilakukan utk menjaga aliran ASI. ASI dpt diberi kan lagi segera setelah 1-2 x t½ eliminasi obat (50-75% tereliminasi). Utk obat yg sangat toksis meski dlm dosis kecil, pemberian kembali ASI setelah 4-5 kali t½ eliminasi obat (94-97% obat telah tereliminasi

Drugs Contraindicated during Breastfeeding

- Amiodarone
- Amphetamine
- Bromocriptine
- Coccaine
- Cyclophosphamide
- Cyclosporine
- Doxorubicin
- Ergotamine
- Heroin
- Isotretinoin
- Lithium
- Marijuana
- Methotrexate
- Nicotine (smooking)
- Phenylcyclidine

Drugs to be Use with Caution during Breastfeeding

- Acebutolol
- Alcohol (large amounts)
- Alluminium antacids
- Amantadine
- Antidepresant:amytriptilin, amoxapine,desipramine, domipramin, doxapin,fluoxetin,fluvoxamin, imipramin trazodone
- Antipsychotic:chlorpromazine,haloperidol,mezoridhazine,perphenazine
- Atenolol
- Chloramphenicol
- Benzodiazepin: diazepam,lorazepam,midazolam,prazepam, quazepam,temazepam
- Clemastine
- Gold Salts
- Indomethacin
- Methadone (>20 mg/day)
- Metoclopramide
- Methimazole
- Metronidazol
- Nalidixic acid
- Nitrofurantoin
- Phenobarbital
- Primidone
- Phenytoin
- Salicylates
- Sulfonamide
- Sulfasalazine

KI untuk IBU MENYUSUI

OBAT / GOL. OBAT	EFEK PADA BAYI
Amfetamin	Terakumulasi dalam ASI dan dapat menyebabkan iritasi, dan pola tidur yang jelek
Antineoplastik	Potensial menekan sistem imun, efek sitotoksik obat pada bayi belum diketahui
Bromokriptin	Menekan laktasi
Cocain	Diekskresikan lewat ASI, kontraindikasi karena CNS stimulan dan intoksikasi
Ergotamin	Potensial menekan laktasi, muntah, diare, dan kejang telah dilaporkan
Etanol	Kontraindikasi masih kontroversial, intake yang tinggi pada ibu dapat menyebabkan bayi yang disusui : sedasi, diaforesis, *deep sleep*, lemah,menghambat pertumbuhan danberat badan abnormal. Paparan yang kronik juga menimbulkan keterlambatan perkembangan psikomotor. Bayi dari ibu alkoholik menyebabkan risiko yang potensial hipoprotombin berat,perdarahan, dan *pseudo cushing sindrome*. AAP mengklasifikasikan compatible (dapat diterima), tapi harus dipertimbangkan kontraindikasinya. Satu review menyarankan untuk menunggu 1-2 hari setelah minum sebelum menyusui
Heroin	Kemungkinan adiksi jika jumlahnya mencukupi
Immunosupresan	Potensial menekan sistem imun
Lithium	Konsentrasi dalam serum dan ASI rata-rata 40 % dari konsentrasi serum plasma ibu menyebabkan reaksi toksik yang potensial, kontraindikasi
Asam lisergat dietilamida (LSD)	Kemungkinan diereksikan dalam ASI
Mariyuana	Diekskresikan dalam ASI
Misoprostol	Ekskresi dalam ASI belum jelas, tapi kontraindikasi karena potensial terjadi diare berat pada bayi
Nicotin	Kontraindikasi masih kontroversial, absorpsi melalui perokok pasif lebih tinggi dari pada melalui ASI. Merokok secara umum tidak direkomendasikan selama menyusui, menurunkan produksi ASI
Pensiklidin	Potensial bersifat halusinogenik

"Compatible" utk Ibu Menyusui

OBAT / GOL. OBAT	EFEK PADA BAYI
Acetaminophen	Compatible, malulopapular rash pada bayi bagian atas dan wajah pada bayi telah dilaporkan
Acyclovir	Compatible, terkonsentrasi dalam ASI
Alprazolam	Withdrawal nyata setelah 9 bulan terpapar melalui ASI. Penggunaan obat lain yang termasuk golongan ini selama menyusui dipertimbangkan
Amiodaron	Diekskresikan lewat ASI, tidak direkomendasikan karena waktu paruh eliminasi panjang
Amitriptilin	Tidak ada efek samping yang dilaporka, tapi AAP mempertimbangkan penggunaannya
Aminoglikosida	Potensial mengganggu flora normal saluran cerna bayi
Aspartam	Dieksresikan lewat ASI, penggunaannya hati-hati pada bayi dengan fenilketonuria
Aspirin	Satu kasus terjadi keracunan salisilat berat (asidosis metabolik), potensial terjadi gangguan fungsi platelet dan rash, AAP merekomendasikan penggunaannya dengan perhatian.
Beta - blocker	Amati pada bayi tanda-tanda blokade seperti hipotensi , bradikardi, asebutolol, atenolol dan nadolol terkonsentrasi dalam ASI
Bromfeniramin	Amati gejala pada bayi: iritasi, gangguan pola tidur. Compatible

"Compatible" utk Ibu Menyusui

Bupropion	Terakumulasi dalam ASI, penggunaan dengan hati-hati
Caffein	Akumulasi dapat terjadi jika ibu pengkonsumsi berat, compatible dalam jumlah biasa. Amati iritasi dan gangguan tidur
Carbamazepin	Compatible
Cephalosporin	Potensial mengganggu flora normal usus, considered compatible
Chloramfenikol	Dieksresikan lewat ASI, potensial menekan sumsum tulang. AAP merekomendasikan penggunaannya dengan hati-hati
Chlorpromazin	Diekskresikan lewat ASI, ngantuk dan lemas teramati pada bayi. AAP mempertimbnagkan penggunaannya karena efek dan potensial galaktore
Cimetidin	Dapat terakumulasi dalam ASI, potensial menekan asam lambung, menghambat metabolisme obat, dan CNS stimulan. Compatible
Clindamisin	Considered compatible
Codein	Compatible
Diazepam	Letargin dan kehilangan berat badan dilaporkan, amati akumulasi pada bayi, pertimbangkan penggunaannya
Digoxin	Eksresi lewat ASI, compatible
Difenhidramin	Eksresi lewat ASI, tidak ada efek yang dilaporkan

Drugs that Affect Milk Production

- Bromokriptin
- Cabergoline
- Thiazide diuretic
- Combined Oral Contra septive → use progestin
- Ergotamine

Should be avoided in the breast-feeding

IBU Menyusui..(*key point*)

- Sdpt mungkin hindari gunakan obat pd wanita menyusui atau hentikan pmberian ASI bila obat akan lanjut
- Pilih obat dg ESO teraman terutama obat yg telah direkomendasikan aman utk ibu menyusui
- Bila minum obat→ pantau ESO
- Waktu minum obat segera setelah menyusui

Drug Safety & Selection

Drug Class	During Pregnancy	During Lactation
Analgesic	Acetaminophen	Acetaminophen
Anticoagulant	Heparin, LMWH	Heparin, Warfarin
Anticonvulsant	Phenobarbital	Carbamazepin/Etho-suximide/Valproic
Antidiabetic	Insulin	Insulin,Tolbutamide
Antihypertensi	Methyldopa	ACEI/Ca-antagonist
Anti-infection	Penicillin/Cephalo-sporin	Penicillin/Cephalo-sporin

LMWH = low molecular weight heparin; ACEI = Angiotensin Conver-ting Enzyme Inhibitor

Drug Safety & Selection

Drug Class	During Pregnancy	During Lactation
Corticosteroids	Prednisone	Prednisolone
Decongestan	Oxymetholazide drop/spray	Oxymetholazide drop/spray
GI protection	MgOH, AlOH,Ca-carbonat,ranitidin, sucralfate	Sucralfate,famotidin
Laxative/Stool Softener	Psyllium/docusate	Psyllium/docusate

MgOH= Magnesium Hydroxida; AlOH= Aluminium Hydroxida

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TERIMA KASIH ATAS PERHATIANNYA

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