Drug Use During Pregnancy

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Drug use during Pregnancy

- Every system in the body is affected by pregnancy
- Pharmacokenetics & pharmacodynamics of drugs is affected by pregnancy
- At present these pharmacokinetic factors are beginning to be understood whereas pharmacodynamics information is still incomplete

Pharmacokenetics Of Drugs During Pregnancy

- 1. Absorption: ↑ed
- Gastric emptying time is delayed & gut motility reduced because of ↑ed progesterone
- Vasodilation , tissue perfusion ↑ed
- 2. Distribution: ↑ed
- Total body water increases i.e. hemodilution
- Plasma albumin conc. ↓ed so ↑ed free drug conc.
- Increased body fat, reservoir of lipid soluble drug

Pharmacokenetics Of Drugs During Pregnancy

- 3. Metabolism:

➢ hepatic metabolism increases but no altered hepatic blood flow

- 4. Elimination:

➢ Renal blood flow doubles, so rapid elimination of drugs excreted by kidney (e.g.Aminoglycosides)

➢ Dose should be increased in such cases

Factors Affecting Placental Drug Transfer & Subsequent Effect On Fetus

1. Physiochemical properties of the drug
2. Rate at which drug crosses placenta & amount reaching the fetus
3. Duration of exposure to drug
4. Distribution characteristics of drug in different fetal tissues
5. Stage of placental & fetal development at the time of exposure
6. Effects of drugs used in combination

A. Lipid solubility

Lipophilic drugs crosses placenta more

e.g.thiopental may cause apnoea in fetus,

salicylate is ionised but very lipid soluble

B. Molecular size & pH

250-500 easily

500-1000 with difficulty

>1000 poorly

maternal blood pH 7.4 & fetal 7.3 , may lead to ion trapping in c/o pKa >7.4

C. Placental transporters

e.g. P glycoprotein transporter encoded by MDR1 gene pumps back some drugs like cancer drugs (doxorubicin)

and viral protease inhibitors

D. Protein binding

more protein bound drug crosses less

doesn't affect lipid soluble drug that much

differential protein binding – Glyburide

E. Placental & fetal drug metabolism

1) Placenta: aromatic oxidation reactions occur e.g. Phenobarbital

may also lead to toxic metabolite e.g. ethanol, benzpyrenes

2) Fetus: 40-60% blood enters fetal liver

a proportion of blood is shunted back through placenta

Pharmacodynamics

A. Maternal Drug Actions

- Effect on reproductive tissue may be altered by endocrinal environment due to pregnancy
- Effect on other tissues not changed much
- Altered physiologic context may require treatment

  e.g. cardiac glycosides & diuretics for heart failure , insulin for pregnancy induced diabetes

Pharmacodynamics

B. Therapeutic Drug Actions In The Fetus

emerging area ‘ Fetal Therapeutics’

i. Corticosteroids: e.g. dexamethasone for lung maturation in premature labour
ii. Phenobarbitone: for neonatal jaundice or decrease intra cranial bleeding
iii. Zidovudine or nevirapine: alone or in combination to prevent vertical transmission

Toxic Effects Of Drugs On The Embryo, Fetus, Or Neonate

May vary

- No effect.
- Little
- Serious- fetal toxicity
- Spontaneous abortion
- Death
- Fetal malfunction
- Fetal malformations.

Pharmacodynamics

C. Predictable Toxic Effects

i. Opioids : dependance , neonatal withdrawal syndrome, respiration depression

ii. ACE inhibitors : renal damage

iii. Diethylstilbestrol: adenocarcinoma of vagina after puberty

Pharmacodynamics

D. Teratogenic Drug Actions:

Birth Defects

- Incidence of major structural defects(abnormalities) is about 6% of all pregnancies.
- 3% are caused by drugs or environmental factors/exposure
- 3% have a genetic or unknown causes

- 1/2 of the birth defects are obvious at birth.
- 1/2 of the birth defects aren't discovered until later in life or discovered during an autopsy
- Incidence of minor structural anomalies is not known.
- Incidence of functional abnormalities is not known-growth restrictions, mental retardation, and learning disabilities
- Some abnormalities have multiple causes-genetic factors, environmental factors, chemicals or drugs.

Teratogenic
Teratogenesis

- Teras-”monster”
- Gensis-”producing”
- Birth defects/distortion of gross anatomy.
- Examples- cleft lip/palate, clubfoot, neural tubal defects, missing or malformed limbs/fingers.
- Now also- behavioral and/ or biochemical and/or physiological abnormalities.
- Death of fetus & carcinogenic effect

Mechanism of Teratogenesis

- Direct effect on maternal tissue with secondary effect on fetus
- Indirect-such as interfering with o2 or nutrients.
- Teratogenesis maybe direct-malformations of structures. e.g.

i. Vitamin A analogs (isotretinoin,etretinate)
ii. Deficiency of a critical substance (folic acid causing neural tube defects)
iii. Continues exposure to teratogen may produce cumulative effect (Fetal Alcohol Syndrome)

Proving A Drug Is A Teratogen

3 Criteria must be met:

- 1. Drug must cause a characteristic set of malformations with selectivity for certain organs
- 2. It must act only during a specific window of vulnerability (organogenesis of target organ)
- 3. The incidence of malformations should increase with increased dosage & duration of exposure.

Fetal Effects From Drugs Depend On Several Factors

- Time- when drug is taken in pregnancy.
- Preimplantation/presomite period- conception to 2 week
- High dose- maybe lethal/death/abortions.
- Low dose-maybe nothing.

As per time …..

① 0-2 weeks-period of dividing zygote , implantation

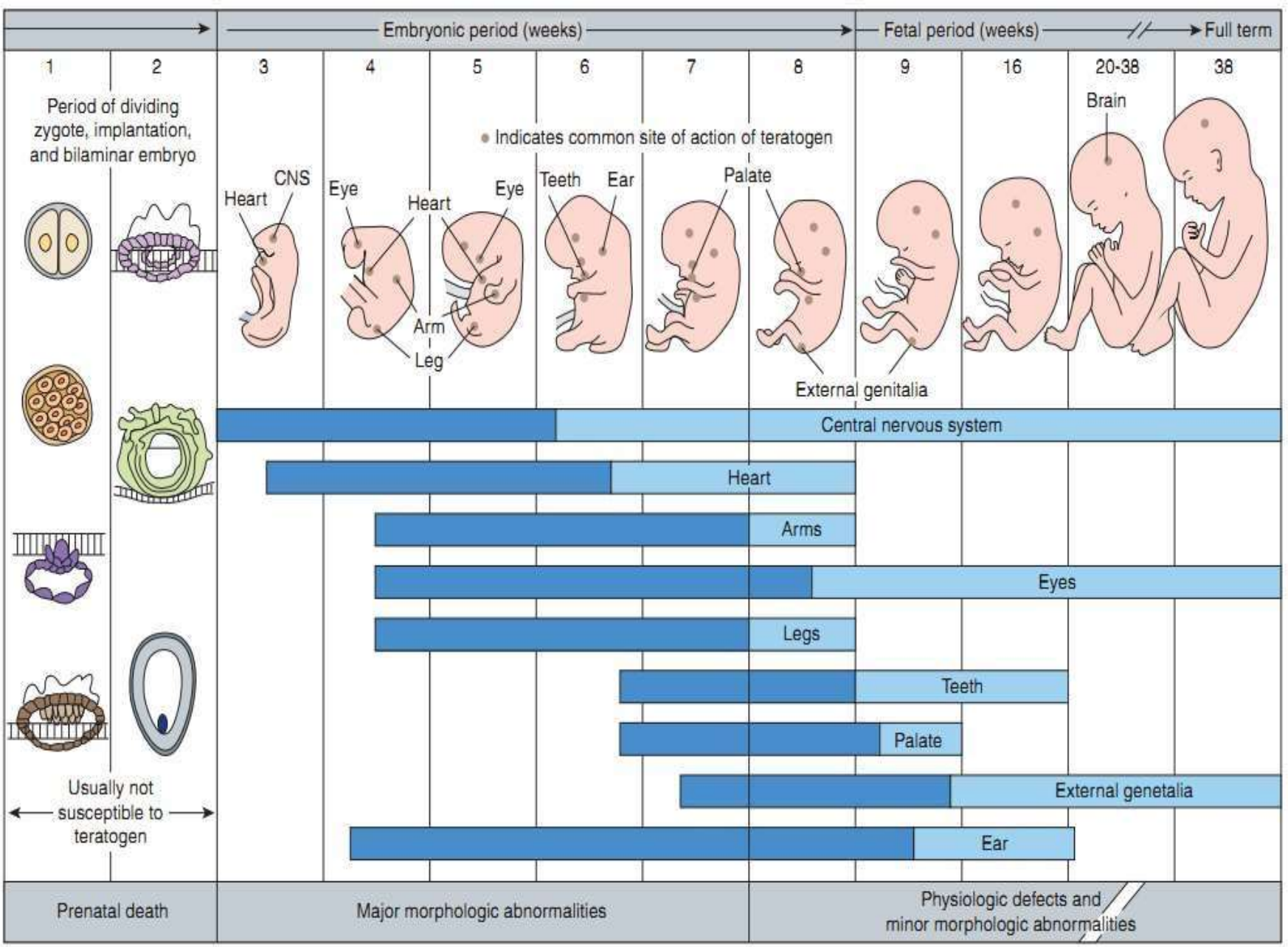
- Prenatal death may occur
- Abortion may occur due to oxytosics e.g. ergot alkaloids, anti metabolites

② Embryonic period-3-8 weeks - First trimester

- Gross malformations
- E.G. One time exposure to thalidomide through 4^{th} to 7^{th} week-causes missing limbs(phocomalia).

③Fetal period-9-40 weeks(term)

- Function problems rather than gross anatomy
- Learning deficits &/or behavioral abnormalities


Embryonic period (weeks)
Fetal period (weeks)
Full term
1
2
3
4
5
6
7
8
9
16
20-38
38
Period of dividing zygote, implantation, and bilaminar embryo
Indicates common site of action of teratogen
Heart
CNS
Eye
Heart
Eye
Teeth
Ear
Palate
Brain
Arm
Leg
External genitalia
Central nervous system
Heart
Arms
Eyes
Legs
Teeth
Palate
External genetalia
Ear
Usually not susceptible to teratogen
Prenatal death
Major morphologic abnormalities
Physiologic defects and minor morphologic abnormalities

Drug	Trimester	Effect
ACE inhibitors	All, especially second and third	Renal damage
Aminopterin	First	Multiple gross anomalies
Amphetamines	All	Suspected abnormal developmental patterns, decreased school performance
Androgens	Second, third	Masculinization of female fetus
Antidepressants, tricyclic	Third	Neonatal withdrawal symptoms have been reported in a few cases with clomipramine, desipramine, and imipramine
Barbiturates	All	Chronic use can lead to neonatal dependence
Busulfan	All	Various congenital malformations; low birth weight
Carbamazepine	First	Neural tube defects
Chlorpropamide	All	Prolonged symptomatic neonatal hypoglycemia
Clomipramine	Third	Neonatal lethargy, hypotonia, cyanosis, hypothermia
Cocaine	All	Increased risk of spontaneous abortion, abruptio placentae, and premature labor; neonatal cerebral infarction, abnormal development, and decreased school performance
Cyclophosphamide	First	Various congenital malformations
Cytarabine	First, second	Various congenital malformations
Diazepam	All	Chronic use may lead to neonatal dependence
Diethylstilbestrol	All	Vaginal adenosis, clear cell vaginal adenocarcinoma
Ethanol	All	Risk of fetal alcohol syndrome and alcohol-related neurodevelopmental defects
Etretinate	All	High risk of multiple congenital malformations
Heroin	All	Chronic use leads to neonatal dependence
Iodide	All	Congenital goiter, hypothyroidism
Isotretinoin	All	Extremely high risk of CNS, face, ear, and other malformations
Lithium	First, third	Ebstein's anomaly, neonatal toxicity after third trimester
Methadone	All	Chronic use may lead to neonatal abstinence

Drug	Trimester	Effect
Methotrexate	First	Multiple congenital malformations
Methylthiouracil	All	Hypothyroidism
Metronidazole	First	May be mutagenic (from animal studies; there is no evidence for mutagenic or teratogenic effects in humans)
Misoprostol	First	Möbius sequence
Mycophenolate mofetil	First	Major malformations of the face, limbs, and other organs
Organic solvents	First	Multiple malformations
Penicillamine	First	Cutis laxa, other congenital malformations
Phencyclidine	All	Abnormal neurologic examination, poor suck reflex and feeding
Phenytoin	All	Fetal hydantoin syndrome
Propylthiouracil	All	Congenital goiter
Smoking (constituents of tobacco smoke)	All	Intrauterine growth retardation; prematurity; sudden infant death syndrome; perinatal complications
Selective serotonin reuptake inhibitors (SSRIs)	Third	Neonatal abstinence syndrome, persistent pulmonary hypertension of the newborn
Tamoxifen	All	Increased risk of spontaneous abortion or fetal damage
Tetracycline	All	Discoloration and defects of teeth and altered bone growth
Thalidomide	First	Phocomelia (shortened or absent long bones of the limbs) and many internal malformations
Trimethadione	All	Multiple congenital anomalies
Valproic acid	All	Neural tube defects, cardiac and limb malformations
Warfarin	First	Hypoplastic nasal bridge, chondrodysplasia
	Second	CNS malformations
	Third	Risk of bleeding. Discontinue use 1 month before delivery.

- ④Late pregnancy

Effect	Likely drug
Masculinization	Sex hormones
Foetal goiter	Antithyroid drugs
Tooth and bone development	Tetracyclines
Growth retardation	Corticosteroids
Early closure of ductus arteriosus	NSAIDs e.g. aspirin, indomethacin
Onset of labour is delayed Impaired CNS development	NSAIDs e.g. aspirin, indomethacin

- ⑤ During labor

Effect	Drug
Respiratory depression	Opioid analgesics
Foetal distress (due to reduced uterine blood Flow)	Sedatives and GA
Prolongation of labour (uterine muscle relaxation)	Sedatives and GA
Foetal circulation	Tocolytic agents (β_2 agonists)
Hypotonia	Benzodiazepines
Floppy baby syndrome	Lithium
Impaired CNS development	Psychotropic drugs used during pregnancy

Others such as

- Thrombocytopenia due to sensitization by thiazide diuretics when given to mother
- Mercury may cause impaired brain development , cerebral palsy, mental retardation etc.
- Other fetal defects due to effect of drug on spermatogenesis are suspected

Why is identification of teratogenic agents sometimes difficult to identify?

- Incidence of congenital anomalies is generally low.
- Animal tests may not be reliable
- Prolonged or increased exposure maybe required.
- Effects maybe delayed or not reconized.
- Behavioral effects are difficult to document.
- Controlled experiments cannot be done on humans.

- Documentation is incomplete
- Only in a limited number of drugs is the teratogenic effects known or proven.
- Lack of proof of teratogenicity does not mean a drug is safe in pregnancy
- May mean there is a lack of research or information.

How Is Data Collected On Drugs Which Cause Problems In Pregnancies?

- No human experimentation
- Systematic collection and analyzing of data on drugs taken by pregnant clients.
- Reporting of information by health professionals.

FDA category of drugs used in pregnancy

Category	Description
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in late trimesters), and the possibility of fetal harm appears remote.
B	Either animal-reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Precautions While Prescribing During Reproductive Age & Pregnancy

1. In c/o contraception failure – Explain risk of drug already received & to continue pregnancy or abort
2. Similarly, in c/o post coital contraception
3. If a woman is being treated , explain risks to fetus & advise to avoid pregnancy till therapy completes
4. If a woman of reproductive age comes with any ailment pregnancy should be ruled out & then follow guideline as shown next

A. If not pregnant

i) Conception not desired : normal treatment

ii) Conception desired:

- Advise not to take any medication after last menstrual period
- Advise folic acid & iron supplements
- If diabetic start her on insulin
- Avoid self treatment if ill, consult doctor

B. If pregnant

- Advise same as 4.A.ii in last slide
- Avoid use of drug & treat minor problems without drugs
- Strictly avoid proven teratogens i.e. Cat. X & D
- If required prescribe proven safe drug
- Use minimal dose for shortest period of time
- If an unsafe or unproven drug has to be used than do α-fetoproteins at 16 weeks of gestation & high quality ultrasound at 18 weeks to asses anomalies

Education Of Pregnant/Pre-pregnant

- Provide accurate information with rationales
- Information should be current and based on evidence.
- Establish environment conducive to exchange of information - trust.
- Potential harm/risks. Common substances & OTC drugs to avoid in pregnancy- ASA, alcohol, increased doses of multivitamins, caffeine, cigarette smoking, etc.
- Avoid self treatment – OTCs
- Support
- Assist with coping if woman has taken a teratogenic agent..With guilt or fear…associated with drugs taken in pregnancy.

Common Medications Safe In Pregnancy

1.GIT conditions:

a) Nausea & vomiting:

pyridoxine with or without doxylamine,

meclizine, cyclizine, diphenhydramine

Avoid- neuroleptics , metochlorpromide (safe in 3rd trimester)

b) Constipation:

mild purgative , lubricant purgative (less safe)

Avoid- strong purgative as may cause abortion or premature labor pain

c) Heart burn:

milk of magnesia

Avoid- anticholinergics

d) Peptic ulcer:

sucralfate, bismuthsubcitrate & H_2 blockers

2.Hemopoetic

Iron, folic acid

no role of vit.B_{12}

3.Infections

a) Bacterial:

i. UTI

ampicillin, amoxycillin, cephalexin, cefadroxil, cefuroxime etc.

Avoid-fluoroquinolones

ii. Other

β-lactum antibiotics (penicillin G, penicillin V), ampicillin, amoxycillin, cloxacillin) , cephalosporins (cephalexim, cefadroxil, cefuroxime, ceftriaxone) , macrolides(erythromycin avoid estolate salt, azithromycin).

gentamycin & tobramycin only if serious infection

b) Malaria:

chloroquine, quinine (higher dose may induce labor), proguanil, pyrimethamine (with folic acid)

c) Amoebiasis:

metronidazole, diloxanide (avoid single large dose)

d) Worm infestations:

piperazine citrate, pyrantel pamoate, bephenium hydroxynaphthoate, praziquintal (teratogenic in animals not in humans)

e) Fungal infections:

miconazole, clotrimazole & nystatin

f) HIV infection:

none are safe but zidovudine and nevirapine are given to prevent vertical transmission

g) Tuberculosis:

INH and ethambutol, if 3rd needed rifampicin, pyrazinamide only in severe cases like meningitis

4. Endocrine disorders

a) Diabetes mellitus:

always use insulin

b) Hypothyroidism:

thyroxine

c) Thyrotoxicosis:

propylthiouracil

d) Corticosteroid are highly teratanogenic and must be avoided

5. Cardiovascular disorders

a) Hypertension:

α-methyl dopa oral & hydralazine in emergency

β blocker like labetolol (also can be given i.v.), atenolol

b) Thromboembolic disease:

LMWH (note just before labor)

Avoid- warfarin

6. CNS disorders

a) General anesthetics:

thiopentone sodium & nitrous oxide

b) Headache & Inflammation:

paracetamol, codeine preparation

Avoid- other NSAIDS

aspirin can be used in lowest doses upto 2 weeks before EDD

c) Epilepsy:

Avoid-Na valproate, phenytoin

d) Migraine:

paracetamol, propranolol, amitryptyline

e) Sedative :

benzodiazepine; e.g. diazepam

f) Antidepressant:

amitryptyline, imipramine

Avoid- Lithium (fetal cardiac anomalies)

7. Respiratory problems

a) cough:

codeine, dexomethorphan

b) Bronchial asthma:

β_2 agonists (e.g. salbutamol), aminophyline, disodium cromoglycate

8. Others

a) Corticosteroids must be avoided except at term for lung maturation with tocolytics
b) Fat soluble vitamins may cause subaortic stenosis & craniofacial anomalies , so avoid
c) Vaccines: only T.T. ; avoid live vaccines
d) avoid indigenous drugs

Drug Use During Lactation

- Most drugs are excreted into breast milk
- But they are less quantity
- Because of large volume of distribution in mother's body compared to small amount of milk
- Lipophilic drugs are readily excreted also non plasma protein bound
- pH of milk = 7.0 , slightly acidic
- Mainly transported by passive diffusion
- Adverse reaction in fetus due to

  i. slower elimination (more accumulation)

  ii. Sensitive & idiosyncratic reaction

- TRH & metochlorpramide ↑es lactation
- Ergotamine & bromocriptine ↓es lactation

  used in loss of fetus or newborn & in hyperprolactinaemia
- Most of the drugs & vaccines are safe
- Drugs which are to be avoided or monitored are discribed next

Chloramphenicol	Significant	Concentrations too low to cause gray baby syndrome; possibility of bone marrow suppression does exist; recommend not taking chloramphenicol while breast-feeding.
Chlorothiazide	Minimal	No adverse effects reported.
Chlorpromazine	Minimal	Appears insignificant.
Codeine	Variable, based on genetic polymorphism	Safe in most cases. Neonatal toxicity described when the mother is an ultra rapid 2D6 metabolizer, producing substantially more morphine from codeine.
Diazepam	Significant	Will cause sedation in breast-fed infants; accumulation can occur in newborns.
Dicumarol	Minimal	No adverse side effects reported; may wish to follow infant's prothrombin time.
Digoxin	Minimal	Insignificant quantities enter breast milk.
Ethanol	Moderate	Moderate ingestion by mother unlikely to produce effects in infant; large amounts consumed by mother can produce alcohol effects in infant.
Heroin	Significant	Enters breast milk and can prolong neonatal narcotic dependence.
Iodine (radioactive)	Significant	Enters milk in quantities sufficient to cause thyroid suppression in infant.
Isoniazid (INH)	Minimal	Milk concentrations equal maternal plasma concentrations. Possibility of pyridoxine deficiency developing in the infant.
Kanamycin	Minimal	No adverse effects reported.
Lithium	Variable	In some cases, large amounts in milk, but not in others.
Methadone	Significant	(See heroin.) Under close physician supervision, breast-feeding can be continued. Signs of opioid withdrawal in the infant may occur if mother stops taking methadone or stops breast-feeding abruptly.
Oral contraceptives	Minimal	May suppress lactation in high doses.
Penicillin	Minimal	Very low concentrations in breast milk.
Phenobarbital	Moderate	Hypnotic doses can cause sedation in the infant.
Phenytoin	Moderate	Amounts entering breast milk are not sufficient to cause adverse effects in infant.
Prednisone	Moderate	Low maternal doses (5 mg/d) probably safe. Doses 2 or more times physiologic amounts (> 15 mg/d) should probably be avoided.
Propranolol	Minimal	Very small amounts enter breast milk.
Propylthiouracil	Variable	Rarely may suppress thyroid function in infant.
Spironolactone	Minimal	Very small amounts enter breast milk.
Tetracycline	Moderate	Possibility of permanent staining of developing teeth in the infant. Should be avoided during

Drugs used during lactation & possible side effects