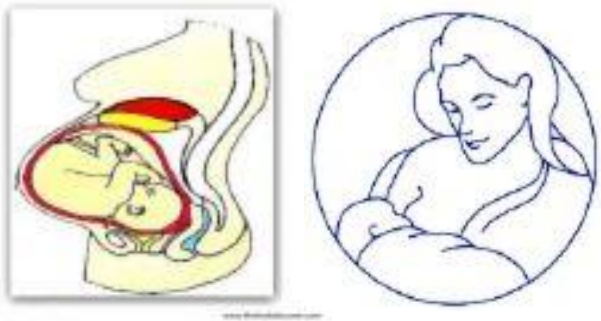
Drug Prescribing in Pregnancy and Lactation



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Drug use in pregnancy and lactation is a critical decision where the physician should weigh between the drug benefit for the mother and on the other side, the potential risk to the embryo/fetus.

More than 50% of pregnant women take prescribed or non prescribed (OTC) drug or use social drug (tobacco an alcohol) or elicit drugs at some time during pregnancy .

About 2-3% of birth defects result from drugs that are taken during pregnancy to treat a disorder o symptom

Maternal pharmacokinetic change in pregnancy:

- ***Absorption:***
  - **Decreased** gastrointestinal **motility and tone** (probably from increased progesterone production), and **HCL** formation in the stomach. So, **delay absorption** of drugs in the **small intestine**.
  - Peripheral **vasodilatation**, so **increase absorption** of **drugs** administrated **parenterally**

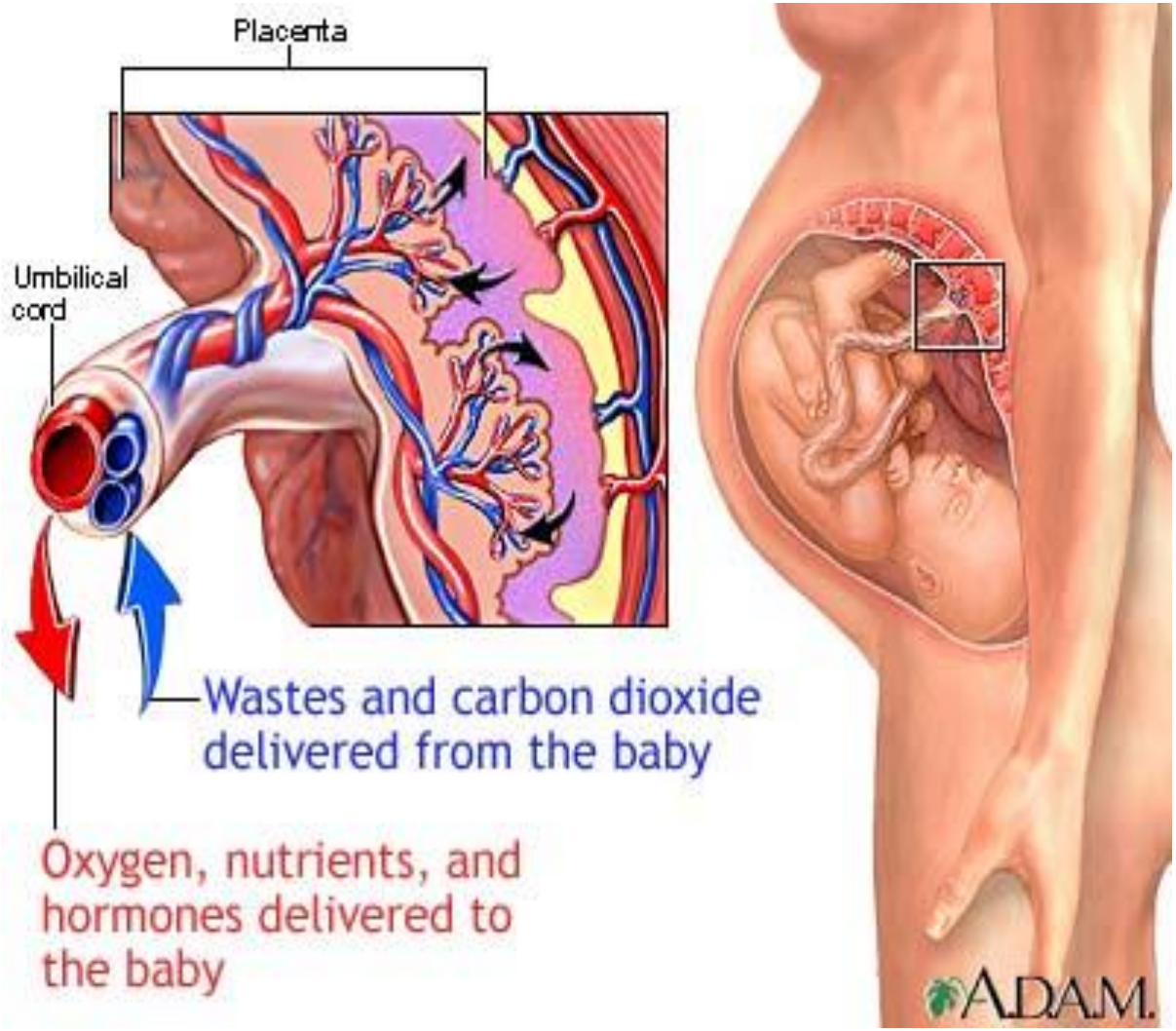
- ***Distribution:***
  - **Increased** plasma **volume** and body **fluids**
  - **Decreased** plasma albumin, resulting in reduction in the available binding sites of drugs

In conclusion, the net result of increased plasma volume and decreased plasma protein binding sites is **unaltered free drug concentration for many (but not all) drugs**

- ***Metabolism:***
  - **Estradiol and progesterone** levels are **increased**, these **affect drugs biotransformation** on hepatic enzymes. They induce metabolism of some drugs and inhibition of others. The **biliary excretion** of certain drugs is **slowed** due to estradiol induced cholestasis

- ***Elimination:***
  - **Renal blood flow and glomerular filtration rate** are **increased,** so **increase the elimination** of drugs that are normally excreted by the kidney.
  - **# Dose should be adjusted (increase or decrease): low molecular weight heparin, gentamicin (aminoglycoside)**

Passage of drugs across placenta



The placenta is the organ of exchange for several substances, including drugs, between the mother and foetus. The placenta functions fully for such transport by the fifth week of conception

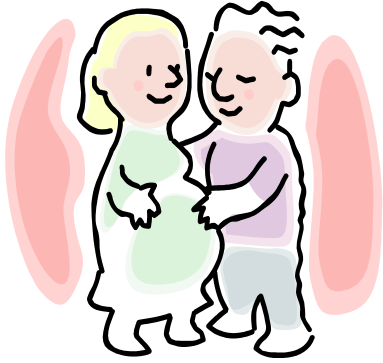
Factors affecting placental drug transfer

- Lipid solubility
- Size of the molecule
- Blood flow
- Protein binding
- Effect of ph
- Placental metabolism

- **Lipid solubility:**
  - **Lipid soluble drugs** diffuse readily and **enter the fetal** circulation, e.g. thiopental (cesarean section)

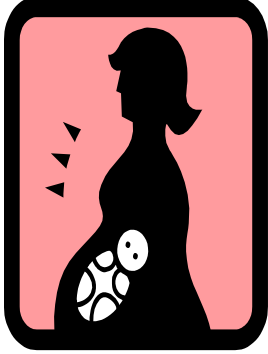
- **Molecular size:**
  - Molecular weight (M.W) **influences** rate of transfer and amount of drug transferred across placenta
    - Drugs with M.W of 250-500 D cross easily
    - Drugs with M.W of 500-1000 D cross with more difficulty
    - Those with M.W >1000 D not cross (e.g.: heparin, insulin)

    - Warfarin has a M.W < 500 D, it crosses the placenta: unsafe anticoagulant.



- **Blood flow:**
  - **Increased** during gestation
  - Placental rate of drugs transfer is determined by blood flow for most lipophylic compounds
  - Changes in blood flow may occur because of **pathophysiologic condition** (e.g. maternal hypertension)

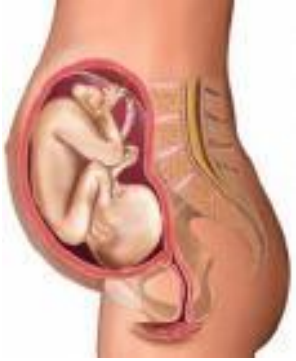
- **Protein binding:**
  - **Albumin** concentration in maternal blood is **low**, so unbound drug concentration are higher during gestation, making **more drug** available to **cross the placenta**
  - E.g. drugs highly protein bound are propranolol, salicylate, diazepam



- **Effect of pH:**
  - Fetal blood is more acid (pH=7.3) than maternal blood (pH=7.4)
  - **Weakly acidic** and **weakly basic** drugs tend to **rapidly** diffuse **across the placental** membrane
  - **Highly ionized** drugs e.g. succinylcholine and tubocurarine, **cross placenta slowly**, not significant concentrations in the fetus

- **Placental metabolism:**
  - Human **placenta** has the capacity to **biotransformation** many xenobiotics and endogenous substances, hence the nature of the compound reaching the foetal circulation

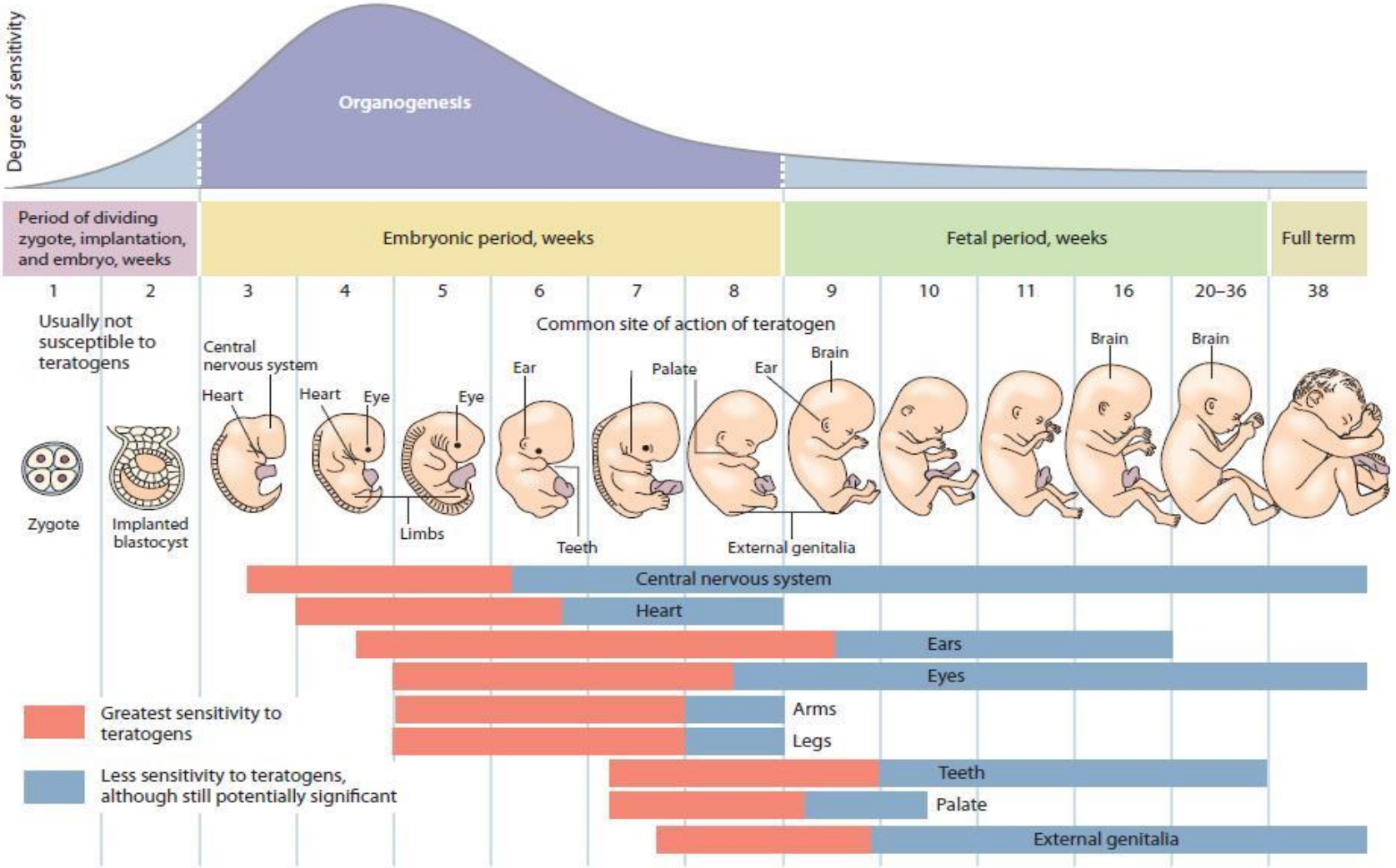
The timing of embryo/foetus exposure to drug determines its:



●Drugs can have harmful effects on the fetus at any time during pregnancy

- During **first trimester** (T1)drugs may produce **congenital abnormalities** (teratogenesis)
- The period of **greatest risk** is from **3-12th week**
- During **second and third trimesters** (T2,T3) drugs may affect **growth and functional development** of the fetus (e.g. brain development)

Teratogenic effects include: loss of pregnancy (Abortion), structural abnormalities, growth impairment (Growth retardation), functional loss and behavioural changes.


Degree of sensitivity
Organogenesis
Period of dividing zygote, implantation, and embryo, weeks
Embryonic period, weeks
Fetal period, weeks
Full term
1
2
3
4
5
6
7
8
9
10
11
16
20–36
38
Usually not susceptible to teratogens
Common site of action of teratogen
Central nervous system
Heart
Heart
Eye
Eye
Ear
Palate
Ear
Brain
Brain
Brain
Zygote
Implanted blastocyst
Limbs
Teeth
External genitalia
Central nervous system
Heart
Ears
Eyes
Arms
Legs
Teeth
Palate
External genitalia
Greatest sensitivity to teratogens
Less sensitivity to teratogens, although still potentially significant

- During the **first two weeks** of gestation, teratogenic agents usually kill the embryo rather than cause congenital malformations.
- Establishment of full implantation of the fertilized egg takes 1 to 2 weeks .

Teratogenic exposure during this stage elicit an " **all-or-nothing " response** , leading either to death of the embryo or completely normal development of fetus .

- Major malformations are more common in early embryos than in newborns; however, most severely affected embryos are spontaneously aborted during the first six to eight weeks of gestation.

Embryonic stage **(weeks 3-8 post-conception)**

The critical time for organogenesis is during the first 8 weeks of pregnancy .

Organogensis occurs during the embryonic stage “exception of CNS ,eye ,teeth, external genitalia and ears is complete by 10W” , so exposure in this time represents the greatest risk of **major birth defect** .

- During organogenesis between 3rd and 8th weeks, teratogenic agents are more likely to cause major congenital malformations.

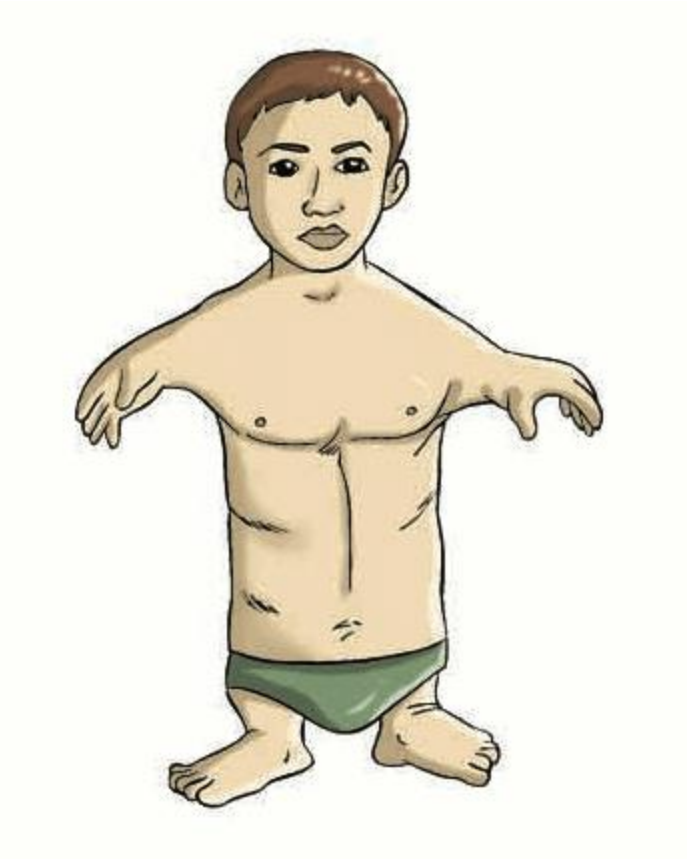
- For this reason , women are often advised to avoid or minimize all drug use in the first trimester .

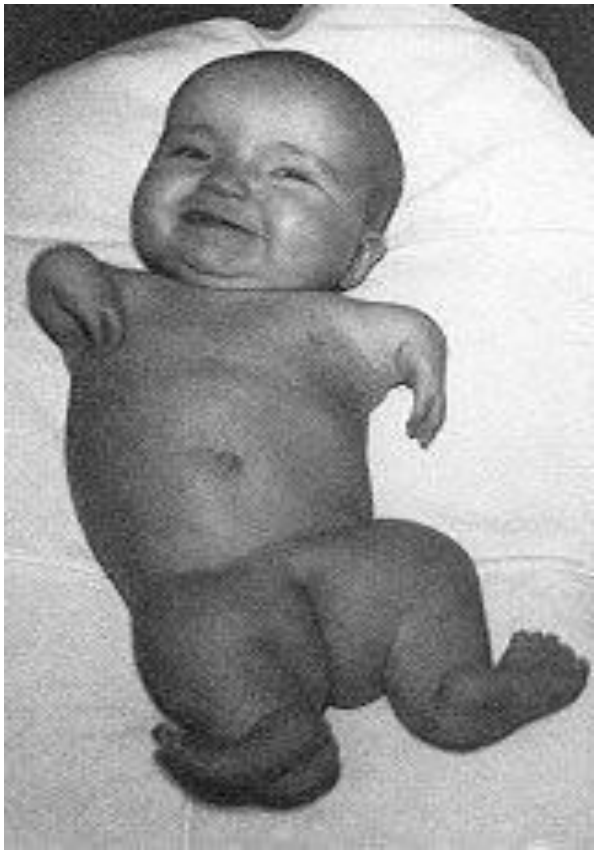
- After 8 weeks , most teratogenicity effect are related to fetal growth restrictions or functions deficits such as mental retardation .

Some drugs associated with teratogenicity

- (T1):
  - Thalidomide: phocomelia
  - Cytotoxic drugs: multiple congenital malformations
  - Vitamin A derivates (isotretinoin): craniofacial defects
  - Lithium: ebstein anomaly of tricuspid valve
  - Steroids (Prednisone): cleft lip and or cleft palate
  - Warfarin: skeletal abnormalities

Phocomelia

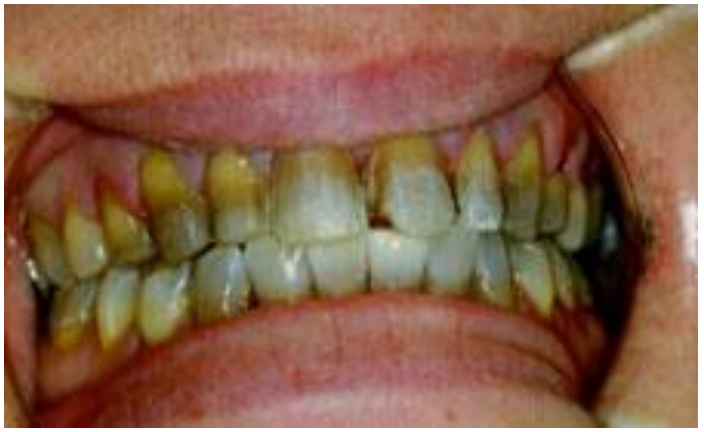




- T2 and T3:
  - Tetracycline: tooth and bone defects
  - Chloramphenicol: Grey baby syndrome, intra-uterine foetal death
  - Aminoglycoside: ototoxicity, nephrotoxicity
  - Fluoroquinolone (Ciprofloxacin/UTI): interference with cartilage growth
  - Phenytoin: craniofacial defect, mental deficiency
  - warfarin: CNS malformations
  - ACE inhibitors: irreversible renal damage
  - Tobacco smoking: retarded fetal growth

Tetracycline-Induced Discoloration of Teeth

because of
1. the risk of Mother hepatotoxicity
2. the potential for permanent discoloration of teeth in the fetus (yellow or brown in appearance), as well as impairment of fetal long bone growth



Selection of drugs during pregnancy

- **Selecting** drugs that have been used for the **longest** period with **safety**
- Whenever possible the selected drugs should be given in the **lower end of the dosing range** to minimize foetal drug exposure
- Pregnant women are **discouraged** from **self- medication** and **encouraged** to consult their **health care** provider
- A commonly used **source of information** about **drug safety** in **pregnancy** is the classification of drugs according to the degree of their potential risk during pregnancy by the **FDA:**

FDA Classification

- **Category A**: controlled studies in animals and pregnancy women have not shown risk of foetal abnormalities (Thyroxine)
- **Category B**: animal studies have not shown risk but there no controlled studies in pregnancy women (e.g. paracetamol, β-lactams, erythromycins, α-methyldopa, NSAIDs)
- **Category C**: animal studies may have shown risk but studies in pregnancy women have not done (anti-psychotics, tricyclic anti-depressants, H1-antihistamines, most cardiac medicines, laxatives, steroids, metronidazole)
- **Category D:** positive evidence of some human risk, but benefit may outweigh risk in some circumstances (e.g. anti-epileptics, alcohol, BDZs, lithium, warfarin, ACE inhibitors, tetracyclines, chloramphenicol, aminoglycosides)
- **Category X:** highly teratogenic. Too dangerous for prescribing (e.g. cytotoxic drugs, vitamin A analogues, thalidomide)

Drugs Used During Lactation

- The route of maternal drug administration, dose, Pk, the type of medication, etc…, have influence on breast milk drug concentration

- A drug taken 30-60 minutes after breast feeding, and 3-4 hours before next feeding, reduced the amount of drug in baby blood

- The baby's age and maturity level, the frequency and volume of feeding (the baby who is nursing once or twice a day, will receive less of a drug than the baby who is totally breastfed and may nurse 10-12 times a day)

- The benefits of breastfeeding are well known and undisputed, so doctors should recommend a mother wean only when there is scientific documentation that a drug will be harmful to her infant.

- If the drug is contraindicated in breast feeding, bit it should be given for the maternal benefit, and there is no other alternative:

The nursing mother should use an electric pump to maintain her milk supply during the period of weaning.

Factors affecting drug breastfeeding transfer

- Medication enters the breast mainly via passive diffusion or sometimes via active transport. The passage of drugs to milk is directly proportional to the maternal plasma concentration
- The breast milk PH is slightly more acid (pH=7.2) than plasma (pH=7.4), therefore, basic drugs are more un-ionizable (more lipid soluble) in blood than in milk
- Lipophilic drugs that pass to breast milk get more ionized fraction (due to higher acidity of milk) and trapped in milk

- Drugs which are more lipophilic tends to concentrate in the hind-milk than in the fore-milk which has less lipid content.
  - Note: Hind-milk is released in the last few minutes of nursing, fore-milk is released from beginning until the last few minutes of the nursing
- Plasma ratio indicates the drug passage into brest milk from the maternal plasma. The ratio 1 indicates that the concentration in milk is the same as that in plasma

Some drugs Should be Avoided During Lactation

Drug	Effect
Aspirin	Reye's syndrome
Chloramphenicol	Bone marrow suppression
Cancer chemotherapy (cytotoxic drugs)	anti-cancer activity, damage normal tissue
Radioactive iodine	Thyroid suppression
Tetracycline	Permanent discoloration of teeth (yellow)

General guidelines for taking drugs while nursing

- **Only** take a medication if it is **really needed**
- Consider **alternative**, non-drug therapy if possible
- If there is a choice, **delay starting** the drug until the baby is older (a drug which might cause problems for a newborn may be fine for an older, large, more mature infant)
- Use the **lowest** possible **dose** for the **shortest** possible **time**
- **Schedule the doses** so that the lowest amount gets into the milk (take it soon after a feeding, preferably a night feeding, rather then right before nursing)
- **Watch** for **baby's reactions** such as sleepiness, rashes, diarrhoea, colic, etc.