No.4

Doctor 2022 - أثر - Medicine - MU

Pharmacology Sheet

Doctor:

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Drug Prescribing in Pregnancy and Lactation

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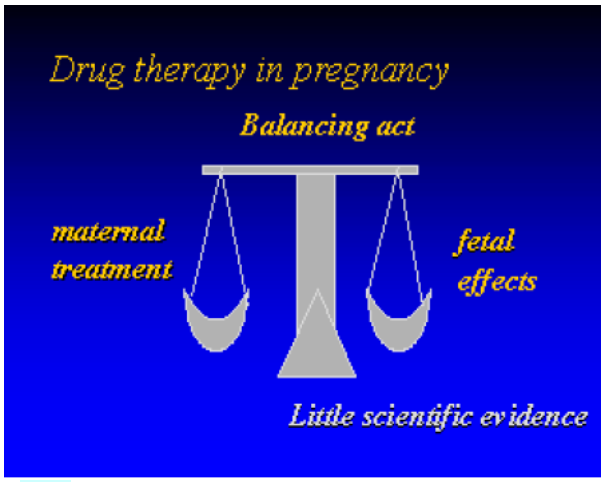
Drug Prescribing in Pregnancy and Lactation

Intro:



- **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, we deal with 2 different persons at the same time with different systems instead of only one.**
- **More than 50% of pregnant women take prescribed or non- prescribed (OTC) drug or use social drug (tobacco or an alcohol) or illicit drugs at some time during pregnancy.**
- **About 2-3% of birth defects result from drugs that are taken during pregnancy to treat a disorder or a symptom.**
- **Since the fetus has no immune system, the effect(s) of a drug on them in pregnancy will be high. That is why we limit the use of many antibiotics for example. Since all the drugs have side effects – despite its severity- there should be a balance between the risks and benefits.**
- **Generally, decreasing the dose of an X drug -> gives rapid effect -> faster elimination.**

Maternal Pharmacokinetic Change in pregnancy:

- **Most of the changes during/ after pregnancy are either due to: 1) increased hormones and/ or 2) increased fluids daily intake**
- ***Absorption*:**
  - **It depends generally on: 1) type of tissue and 2) amount of fluid present.**
  - **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 -> increase blood flow, so increase absorption of drugs administrated parenterally.**
  - **As a role of thumb, it is recommended that a pregnant woman to drink 2-3 liters of water daily to enhance both absorption and distribution (think of it as increasing the dissolution rate, the blood flow and the solubility GENERALLY).**
- ***Distribution:***
  - **Increased plasma volume and body fluids**
  - **Decreased plasma albumin, resulting in reduction in the available binding sites of drugs**

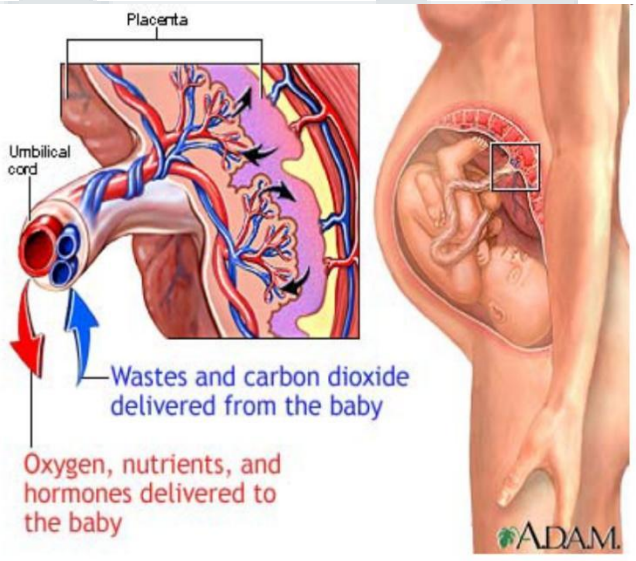
- Increased plasma albumin -> increases available binding sites -> increases binding of drug -> decreases the portion of a drug needed to exert a physiological action (free fraction of a drug) and vice versa.
- Albumin typically binds lipid soluble drugs (itself is hydrophilic but it has multiple hydrophobic pockets). So, if a drug is highly lipid soluble, it is recommended to decrease its dose in pregnancy to avoid reaching toxic threshold (albumin will bind a small portion while a larger one will be in the free fraction form to give an effect, which will be higher than usual if the dose was not adjusted). Moreover, lipid soluble drugs cross placenta more readily -> as placenta itself is considered a hydrophobic bilayer. Accordingly, water soluble drugs will not cross placenta easily.

** 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:***
  - CYP450 (Cytochrome P 4 50) has a crucial role in metabolism.
  - Estradiol and progesterone levels are increased, these affect drugs biotransformation on hepatic enzymes (by either increasing or decreasing their metabolism, you should memorize those special drugs and their effects). 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 normally are excreted easily
  - # Dose should be adjusted (increase or decrease): low molecular weight heparin, gentamicin (aminoglycoside)
  - As a role of thumb, the anti-coagulant of choice for pregnant women is low molecular weight heparin (LMWH) and for patients with mechanical heart valves it is warfarin.

Passage of Drugs Across Placenta:

- The placenta is fundamentally the organ of exchange for a number of substances, including drugs, between the mother and foetus (another correct spelling of fetus).
- The placenta functions fully for such transport by the fifth week of conception
- Excretion, metabolism and nutrients exchange occur through placenta.
- All in all, the placenta protects and controls everything that reaches the fetus.



Factors Affecting Placental Drug Transfer:

- To imagine this, we should first determine the structure of placenta (mainly lipid-based) and what substances can cross it (lipid soluble drugs).
  1. Lipid solubility
  2. Size of the molecule
  3. Blood flow
  4. Protein binding
  5. Effect of ph
  6. Placental metabolism
  - That being said, some drugs are known to be safe during pregnancy as insulin. So, a diabetic mother will be advised to take insulin as prescribed; because it will not cross the placenta (will not affect the fetus) yet it will prevent the baby from developing hypoglycemia shortly after birth (a common complication of Infants of Diabetic Mothers (IDM)).

1. Lipid Solubility:

- Lipid soluble drugs diffuse readily and enter the fetal circulation, e.g. thiopental -a highly lipid soluble drug used to induce general anesthesia mostly during (cesarean section). So, since lipid soluble drugs are more readily absorbed during pregnancy, Thiopental at low doses will give its anesthetic and sedative effects for a short duration, the patient will benefit from it and recover rapidly. However, if given in high doses, it may cause respiratory center depression where the patient might not be able to recover -> death.
- Propranolol – a beta receptor blocker- is used during cesarean section for augmenting the labor (when the labor is prolonged, it is given to increase the rate of uterine contractions to reduce the needed time). It is considered US FDA pregnancy category C (will be explained later).
- So, one more time, water soluble compounds will not easily cross placenta while lipid soluble (lipophilic) ones will.

2. Molecular Size:

- Molecular weight (M.W) influences rate of transfer and amount of drug transferred across placenta (the size of a drug molecule will determine its ability to cross the mother- fetus- placental barrier -> based upon this we will choose the drug that benefits the mother and does not put any risk on the fetus with any possible adverse effects):
  - Drugs with M.W of 250-500 D (Dalton) 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: water soluble, generally considered safer than oral anti-diabetics during pregnancy.) -> in the notes given it said "we should find an alternative for insulin?".
  - Warfarin has a M.W < 500 D, it crosses the placenta: unsafe anticoagulant

That is why LMWH is the DOC (drug of choice) for anti-coagulation during pregnancy.

3. 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 as a result of pathophysiologic condition (on either enzymes or hormones) (e.g. maternal hypertension)
- Generally, I want a water-soluble drug so it does not cross the placenta.
- That being said, a good drug to be used for maternal hypertension – which is common due to fluctuations in blood pressure during pregnancy- is Propranolol, although it is lipid soluble -> the benefits outweigh the risks especially with careful monitoring (remember, it is the second time we mention this drug in this lecture!).

4. Protein Binding:

- Albumin concentration in maternal blood is low, so unbound drug concentration is higher during gestation, making more drug available to cross the placenta
- E.g. drugs highly protein bound are: propranolol (there is a beta 2 mediated pathway for insulin secretion on pancreas, so when a beta blocker is used, there will be a reduction in insulin secretion. Third time's the charm!), salycilate, diazepam (has many uses: muscle relaxant, anti- depression, alcohol withdrawal symptoms and for some types of seizures by calming the brain and nerves, consuming alcohol will augment diazepam effects-> do not take the together).

5. 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

6. 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:

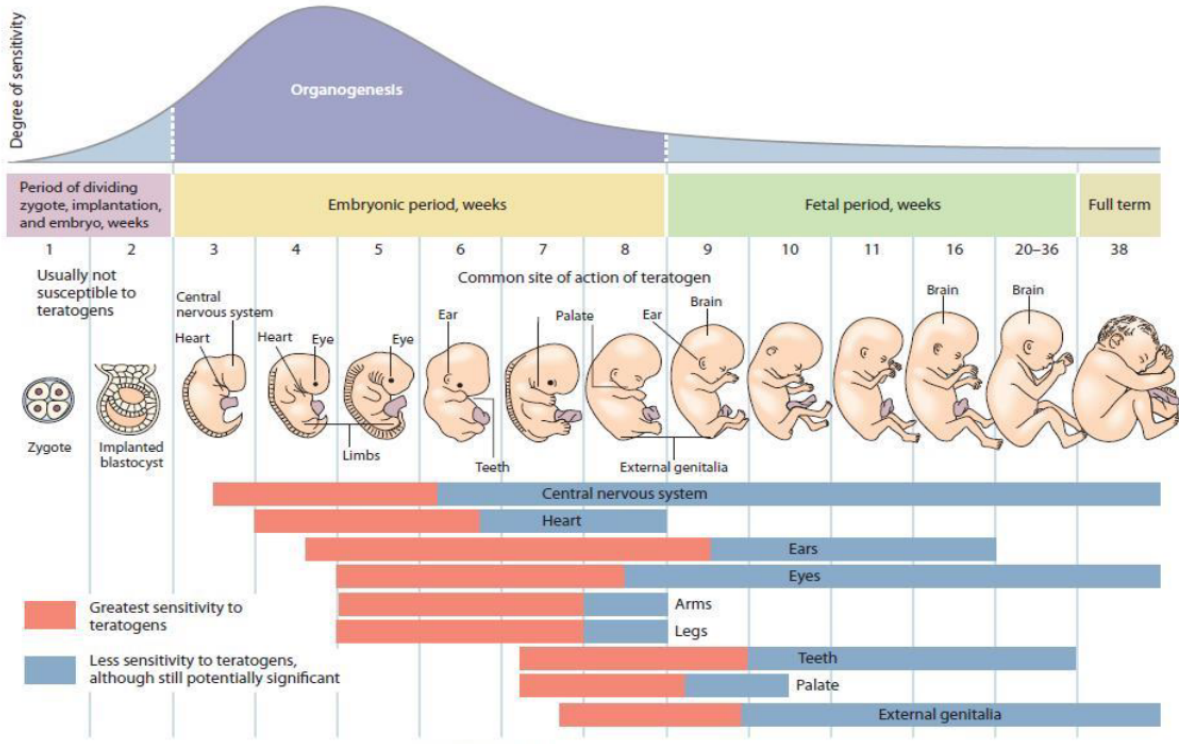
- The risk of a drug will differ from one time to another during pregnancy, that is why we need to locate the trimester not only the drugs used.
- Generally, the first 3 months are the most dangerous -> all drugs should be avoided including vitamins.
- Drugs can have harmful effects on the fetus at any 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, structural abnormalities (changes the structure of the body of the fetus), growth impairment, functional loss and behavioral changes.

** Refer to the next figure before proceeding with the following:

- 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.

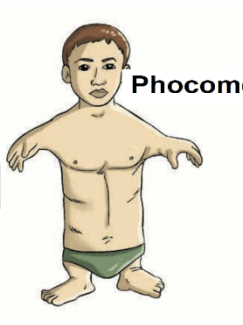
- Embryonic stage (weeks 3-8 post-conception)
  - The critical time for organogenesis is during the first 8 weeks of pregnancy .
  - Organogensis occurs during the embryonic stage "exception of CNS ,eye ,teeth, external genitalia and ears is complete by 10W" , so exposure in this time represents the 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 .

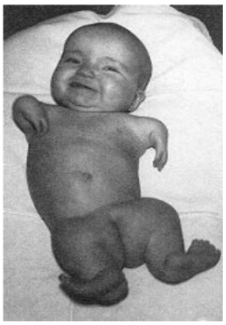
- After 8 weeks , most teratogenicity effect are related to fetal growth restrictions or functions deficits such as mental retardation .



Some Drugs Associated with Teratogenicity:

- (T1):
  - Thalidomide: phocomelia (shortness of limbs).
  - Cytotoxic drugs: multiple congenital malformations (like congenital heart disease)
  - Vitamin A derivates (isotretinoin): craniofacial defects
  - Lithium: ebstein anomaly of tricuspid valve
  - Steroids: cleft lip and or cleft palate
  - Warfarin: skeletal abnormalities. Note that any person who have had a heart surgery will use warfarin indefinitely.





- T2 and T3:
  - Tetracycline: tooth and bone defects
  - Chloramphenicol: Grey baby syndrome (grey discoloration of the baby's skin), intra-uterine foetal death
  - Aminoglycoside: ototoxicity (problems in hearing), 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, because tetracyclines prevent the absorption of calcium -> lead to teeth and bone defects.

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, ββ-lactams, erythromycins, αα-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)

** it is important to memorize drugs' names, especially in the FDA classification.

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 highe 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 (BMS)
Cancer Chemotherapy (cytotoxic drugs)	Anti- cancer activity, damage normal tissue
Radioactive iodine	Thyroid Suppression
Tetracycline	Permanent discoloration of teeth (yellow)

** to be memorized too

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.

يا فتى
إن لم تصنعك الأحداث اليوم، ولم تغيّر فيك شيئًا حتى اللحظة، فهذا مؤشر موات، فما الذي سيحركك إذًا ومتى؟
تفقّد هذا النابض فيك، وقل له: أين أنت من الحق، وعن أي باطل ستحيد، وتوكّل على الحيّ الذي لا يموت وسبّح بحمده
وكفى به بذنوب عباده خبيرًا