~ Drugs in pregnancy ~

1. **Category A:** No evidence of fetal risk and is safe to use during in pregnancy.
2. **Category B:** Relatively safe.
3. **Category C:** Information about fetal risk is not available but risk can NOT be ruled out.
4. **Category D:** Positive evidence of fetal risk.
5. **Category X:** Definite fetal risk and the drug is contraindicated during pregnancy.

* Thalidomide : Teratogenic (limb deformity)
* . Corticosteroids → ⊕ lung maturation if preterm birth is expected
  . Phenobarbital → ⊕ bilirubin conjugation (↑ glucuronidation) → ↓ incidence of jaundice in newborns.
  . Zidovudine → ↓ HIV transmission to fetus [3 antiroviral agents → eliminate transmission almost entirely]

Mechanism

* Folic acid → ↓ neural tube defects (Spina bifida)
* Folic acid antagonist, Retinoic acid, Endothelin receptor blockers (bosentan) → Neural crest ¢ disruption
* Vit A analogs (Isotretinoin, Etretinate) → disrupt ¢ differentiation.
* (DES) Diethyl stilbesterol (sex hormones) → ↑ risk of vaginal adenocarcinoma in daughters, & hypospadias in sons, later in life. (endocrine disruption)
* Oxidative stress → irreversible damage of DNA, pr, lipids
* Vascular disruption → hypo\hyperperfusion, hypoxia, obstruction
* Smoking → CVS, MSS, GIT, & facial defects, preterm, Abortion...

Malformations ~

* Thalidomide → Phocomelia, heart defects, gut atresia (Known)
* Penicillamine → loose skin (K)
* Warfarin → Saddle nose, Retarted growth, limbs . eyes . CNS defects (K)
* Corticosteroids → Cleft palate, congenital cataract
* Androgen → Musculinisation in ♀
* Estrogen → Testicular atrophy in ♂
* Stilbestrol → Vaginal adenosis & Ca, Cervical Ca (later in life) } Sex hormones
* Phenytoin → Cleft\lip palate, Microcephaly, Mental retardation (K)
* Valporate → Neural tube defect || (K)
* Carbamazepine → Neural tube defect || (Suspected)
* Folate antagonists → Neural tube defect ||, Hydrocephalus, Cleft palate (K)
* Aminoglycosides → Deafness
* Tetracycline → Staining of bones & teeth, Thin tooth enamel, Impaired bone growth (S) especially in 2nd+3rd trimesters
* Ethanol → especially in 2nd+3rd trimesters → Fetal Alcohol Syndrome (CNS + facial development affected) (K)
* Retinoids → Hydrocephalus (K)
* Methotrexate
* Cyclophosphamide
* Lithium
* Coumarins

Adverse effects ~

* Thiopental → Sedation\apnea in newborn
* Opioids → apnea in newborn \ dependance in fetus
* Salicylates → ↑ bleeding + delay labor causing weak placenta → less nutrients → ↓ birth weight
* ACE ⊖ → Oligohydramnios, renal failure (K)
* NSAIDs

Factors affecting placental transfer:

→ Physiochemical properties
→ Duration of exposure
→ Pharmacokinetics:

↳ lipid solubility (α) & polarity (1/α).
* Lipophilic → diffuse readily
* Highly ionized (Tubocurarine ↳ for m. relaxation) → cross slowly
  ↳ if high enough, measurable amount might cross.
* Salicylate → Small unionized amount can cross.

↳ Molecular size: (1/α)
* 250 - 500 ↑ cross easily
* 500 - 1000
* > 1000
* Heparin & Insulin
  ↳ large size → can't cross

↳ pH [mother: 7.4 - fetus: 7.3]
* Weak base, pKa > 7.4 → more ionized in fetus → ion trapping → higher fetal levels.

↳ Placental transporters
P. glycoprotein transporter pumps back some drugs into maternal circulation (.anti Cancer .anti HIV)

↳ Protein binding:
. Fetal proteins binding affinity < maternal proteins
↳ Sulfonamides, barbiturates, phenytoin, local anesthetic agents, glyburide (hypoglycemic agent. (although we only give insulin))

↳ Placental & fetal drug metabolism.
* Phenobarbital
  ↳ Oxidized by placenta
* Ethanol, Smoking, benzapyrenes
  ↳ formation of toxic metabolites by placenta

* Teratogenic drug
  ↳ result in a characteristic set of malformations.
  ↳ Exert its effects at a particular stage of fetal development (organogenesis).
  ↳ Dose dependent incidence
    ↳ So we give the lowest effective dose, for the shortest duration possible

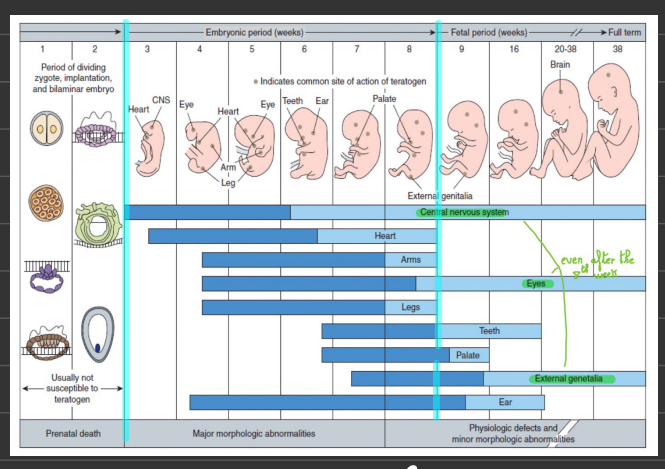
* Factors affecting the production of congenital malformations:

① → Dose

② → Developmental stage; within first 2 weeks → no malformation - peak: 2nd - 8th week
- Blastogenesis (day 1 → 8): . exposure might kill the blastocyte
  . ¢ are totipotent → if damaged can be replaced
- Embryogenesis (2nd → 8th week)
  ↳ organogenesis → greatest risk
- Fetogenesis (> 8 weeks)
  ↳ CNS, eyes, external genitalia

③ → Genetic susceptibility of embryo

④ → Status of the mother; < 18 . > 35 - malnutrition - diseases...



- Some drugs have the potential to be teratogenic. (not to all)
- The baseline risk of congenital malformations is 3-6%.
- 3% of congenital malformations are severe.
- < 1% of congenital malformations are due to drugs.
- Genetic causes are responsible for 15-25% of cases.
- Maternal conditions and infections, and environmental factors account for 10% of cases.
- 65-75% of cases are mostly idiopathic.

Note!! . The risk of neonatal abnormality in the abscence of any known teratogen is 3-6 %.
. effective old drugs are preferable to new alternatives
↳ we have more info about.