Safety of Medicines in pregnancy: General Principles
Drug Use in Pregnancy

- Multinational WHO study: 86% of pregnant women took drugs; Average of 2.9 prescriptions.

- Most commonly prescribed: *Antimicrobials, analgesics, anti-emetics, tranquilisers.*

- over-the-counter use of drugs is common- pregnancy is a symptomatic and medicalised condition
Thalidomide

- Marketed in the 1950s as a sedative
- Standard animal studies failed to identify this risk
- 1/3 of women taking thalidomide in the 1st trimester gave birth to infants with birth defects.
- More than 6000 cases before thalidomide was withdrawn.
Drug Use in Pregnancy

Most drugs NOT tested on pregnant women.

“Use in pregnancy is not recommended unless the potential benefits outweigh the potential risk to the fetus.”

We need to make decisions of risk vs benefit with limited information.
Teratogenicity

Fetal exposure may result in:

- Spontaneous abortion, foetal resorption
- IUGR, congenital malformations/ mutation
- Psychomotor abnormalities
- Intellectual abnormalities
- Behavioral abnormalities
- Carcinogenesis
Teratogenicity

Modifying influences:

1. Gestational period in which drug is taken: 
   Period of organogenesis (4th - 14th week) has highest frequency of morphological defects

2. Dose and duration of therapy.
Teratogenicity

Modifying influences:

3. Degree of drug transfer across placenta
   - Low molecular weight = more transfer
   - Un-ionised
   - Lipid soluble

4. Genetic predisposition and environmental factors.
Teratogenicity

Behavioral teratogens:

- Growth and development of the CNS continues throughout pregnancy and beyond ...

- Period during which fetus is susceptible to behavioral toxicity is longer than that for structural malformations.

- Regard **ALL** CNS-active drugs as potential determinants of behavioral disturbances.
Non-teratogenic effects

- In 2\textsuperscript{nd} and 3\textsuperscript{rd} trimesters.

- Influences: dose and duration of therapy and nature of the drug.

- Examples
  - Dependence and withdrawal (alcohol, benzodiazepines, opiates).
  - Ototoxicity: aminoglycosides.
  - Premature closure of the ductus arteriosus: NSAIDs.
Effect of Pregnancy on Drugs

- Increased plasma volume ... increased volume of distribution.
- Decrease in serum proteins ... changes in drug binding.
- Alterations in GIT function ... changes in drug absorption.
- Increased renal elimination and variable changes in hepatic metabolism.
Challenges in Determining Causality

- Factors in determining causality
  - Strength of the association
    - Needs very specific and possibly unique pathognomonic lesion
    - Plausible temporal exposure
  - Consistency of the observed evidence
  - Temporality of the relationship
    - Time of exposure during pregnancy
  - Dose-response relationship
    - Also duration of exposure
  - Confounding factors
    - Other exposures – drugs/ environmental/chemical
    - Background rate of problem
Methods available for safety monitoring

- Animal toxicity studies
- Spontaneous reports
- Pregnancy registries
- Case Control Study
- Cohort Study