Drugs in pregnancy

BY

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HARMFUL EFFECTS ON THE FETUS

Because experience with many drugs in pregnancy is severely limited, it should be assumed that all drugs are potentially harmful until sufficient data exist to indicate otherwise

- In the placenta, maternal blood is separated from fetal blood by a cellular membrane Most drugs with a molecular weight of less than 1000 dalton can cross the placenta.

- This is usually by passive diffusion down the concentration gradient, but can involve active transport.

- The rate of diffusion depends first on the concentration of free drug (i.e. non-protein bound) on each side of the membrane, and second on the lipid solubility of the drug,diffusion occur if the drug is unionized.

- Placental function is also modified by changes in blood flow, and drugs which reduce placental blood flow can reduce birth weigh

e.g **atenolol cause** small reduction in birth weight.

- The stage of gestation influences the effects of drugs on the fetus.

❖It is convenient to divide pregnancy into four Stages:

- fertilization and implantation (17 days),
- The organogenesis/embryonic stage (17–57 days),
- the fetogenic stage
- delivery.

❖FERTILIZATION AND IMPLANTATION

- Animal studies suggest that interference with the fetus before 17 days gestation causes abortion.

- if pregnancy continues the fetus is unharmed.

ORGANOGENESIS/EMBRYONIC STAGE

- At this stage, the fetus is differentiating to form major organs, and this is the critical period for teratogenesis.
- Some drugs that are teratogenic in humans

- Androgens
- Cytotoxic agents
- Alcohol
- Warfarin
- Retinoids
- Most anticonvulsants
- Ribavarin

Progestogens
Danozol
Diethylstilbestrol
Radioisotopes
Some live vaccines
Lithium

FETOGENIC STAGE

- In this stage, the fetus undergoes further development and maturation

- **ACE inhibitors** and angiotensin receptor blockers cause fetal and neonatal renal dysfunction.

- Drugs used to treat maternal hyperthyroidism can cause fetal and neonatal hypothyroidism.

- **Tetracycline** antibiotics inhibit growth of fetal bones and stain teeth.
- **Anticonvulsants** may possibly be associated with mental retardation.
- **Cytotoxic drugs** can cause intrauterine growth retardation and stillbirth

- Aminoglycosides cause fetal VIIIth nerve damage.

- Opioids and **cocaine** taken regularly during pregnancy can lead to fetal drug dependency.

- **Warfarin** can cause fetal intracerebral bleeding.

- **Indometacin**, a potent inhibitor of prostaglandin synthesis, is used under specialist supervision to assist closure of patent ductus arteriosus in premature infants.

- DELIVERY

➢ Some drugs given late in pregnancy or during delivery may cause particular problems.

➢ **Pethidine**, administered as an analgesic can cause fetal apnoea treated with naloxone.

➢ **Warfarin** given in late pregnancy causes a haemostasis defect in the baby, and predisposes to cerebral haemorrhage during delivery.

PHARMACOKINETICS IN PREGNANCY

ABSORPTION

- Gastric emptying and small intestinal motility are reduced. This is of little consequence unless rapid drug action is required.

- Vomiting associated with pregnancy may make oral drug administration impractical.

DISTRIBUTION

- During pregnancy, the blood volume increases

➢ For water-soluble drugs (which usually have a relatively small volume of distribution), this increases the apparent volume of distribution and, although clearance is unaltered, their half-life is prolonged.

➢ During pregnancy, the plasma protein concentration falls and there is increased competition for binding sites due to competition by endogenous ligands, such as increased hormone levels.

METABOLISM

Metabolism of drugs by the pregnant liver is increased, largely due to

- enzyme induction,
- raised hormone levels.
- Liver blood flow does not change.

This may lead to an increased rate of elimination of those drugs (e.g. **theophylline**), for which enzyme activity rather than liver blood flow is the main determinant of elimination rate.

RENAL EXCRETION

- Excretion of drugs via the kidney increases because renal plasma flow almost doubles and the glomerular filtration rate increases by two-thirds during pregnancy. This has been documented for

digoxin, **lithium**, **ampicillin**, **cefalexin** and **gentamicin**.

PRESCRIBING IN PREGNANCY

- Prescribing in pregnancy is a balance between the risk of adverse drug effects on the fetus and the risk of leaving maternal disease untreated.

Therefore:

- minimize prescribing;
- use 'tried and tested' drugs whenever possible in preference to new agents;
- use the smallest effective dose;
- remember that the fetus is most sensitive in the first trimester;
- consider pregnancy in all women of childbearing potential;

ANTIMICROBIAL DRUGS

- The safest antibiotics in pregnancy are the penicillins and cephalosporins.
- **Trimethoprim** is a theoretical teratogen as it is a folic acid antagonist.
- the aminoglycosides can cause ototoxicity.
- There is minimal experience in pregnancy with the fluoroquinolones (e.g. **ciprofloxacin**) and they should be avoided.
- **Erythromycin** is probably safe.
- **Metronidazole** is a teratogen in animals, but there is no evidence of teratogenicity in humans,
- antiviral agents should be avoided in pregnancy.
- malaria . Fortunately, the standard regimens of intravenous and oral quinine are safe in pregnancy.

ANALGESICS

- Opioids cross the placenta. when the use of opioids, such as **pethidine**, depresses the fetal respiratory centre and can inhibit the start of normal respiration.

- If the mother is dependent on opioids, the fetus can experience opioid withdrawal syndrome during and after delivery, which can be fatal. In neonates, the chief withdrawal symptoms are tremor, irritability, diarrhoea and vomiting.

- **Chlorpromazine** is commonly used to treat this withdrawal state.

- **Paracetamol** is preferred to aspirin when mild analgesia is required.

In cases where a systemic anti-inflammatory action is required (e.g. in rheumatoid arthritis), **ibuprofen** is the drug of choice.

Non-steroidal anti-inflammatory drugs can cause constriction of the ductus arteriosus. Occasionally, this may be used to therapeutic benefit.

ANAESTHESIA

- Local anaesthetics used for regional anaesthesia readily cross the placenta.
- when used in epidural anaesthesia, the drug remains largely confined to the epidural space.
- **pethidine** frequently causes vomiting and may

also lead to neonatal respiratory depression..

- **naloxone** (an opioid antagonist) must always be available. Respiratory depression in the newborn

ANTI-EMETICS

- avoiding large volumes of fluid and raising the head of the bed.
- If symptoms are prolonged or severe, drug treatment may be effective.
- An antihistamine, e.g. **promethazine** or **cyclizine** may be required. If ineffective, **prochlorperazine** is an alternative.
- **Metoclopramide** is considered to be safe and efficacious in labour and before anaesthesia in late pregnancy,

but its routine use in early pregnancy cannot be recommended.

DYSPEPSIA AND CONSTIPATION

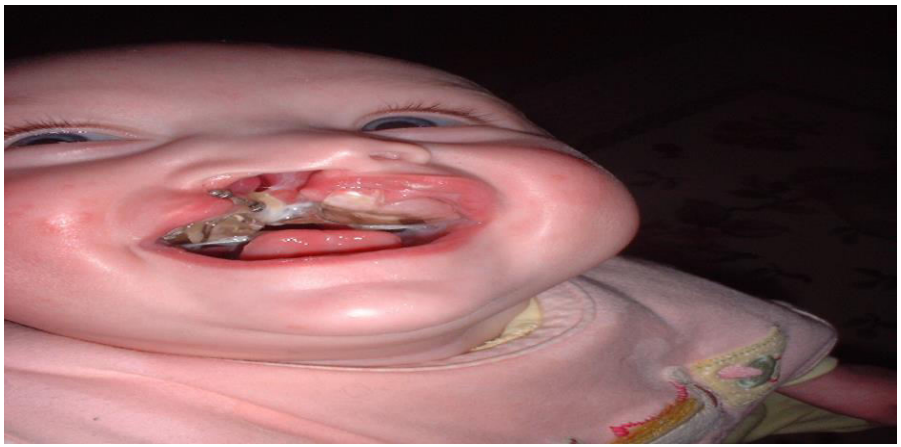
- The high incidence of dyspepsia due to gastro-oesophageal reflux is probably related to the reduction in lower oesophageal sphincter pressure.
- Nondrug treatment (reassurance, small frequent meals and advice on posture) should be pursued in the first instance, particularly in the first trimester.
- most cases occur later in pregnancy when non-absorbable antacids, such as alginates, should be used.
- In late pregnancy, **metoclopromide** is particularly effective as it increases lower oesophageal sphincter pressure.
- H2-receptor blockers should not be used for nonulcer dyspepsia in this setting.
- Constipation should be managed with dietary advice.
- Stimulant laxatives (bisacodel,castor oil,cascara) may be uterotonic and should be avoided if possible

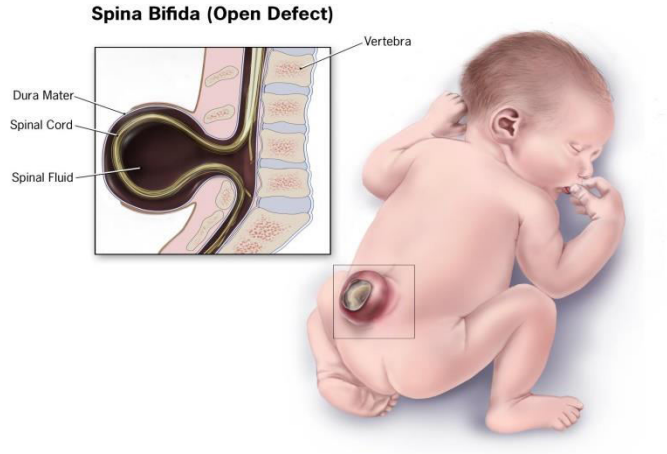
PEPTIC ULCERATION

- Antacids may relieve symptoms.
- **Cimetidine** and **ranitidine** have been widely prescribed in pregnancy without obvious damage to the fetus.
- There are inadequate safety data on the use of **omeprazole** or other proton pump inhibitors in pregnancy.
- **Sucralfate** has been recommended for use in pregnancy in the USA, and this is rational as it is not systemically absorbed.
- **Misoprostol**, a prostaglandin which stimulates the uterus, is contraindicated because it causes abortion

ANTI-EPILEPTICS

- All anticonvulsants are teratogens
- **phenytoin** is associated with cleft palate and congenital heart disease)
- the association of spina bifida with many anti-epileptics, e.g. **sodium valproate** and **carbamazepine** therapy.





ANTI-EPILEPTICS

- Epilepsy in pregnancy can lead to increased fetal and maternal morbidity/mortality.
- The benefits of good seizure control outweigh drug-induced teratogenic risk.
- Give a full explanation to the mother (preferably before pregnancy): most epileptic mothers (90%) have normal babies.
- • Advise an increase in the standard dose of folic acid up to 12 weeks.
- The routine injection of vitamin K recommended at birth counteracts the possible effect of some anti-epileptics on vitamin K-dependent clotting factors.

- Magnesium sulphate is the treatment of choice for the prevention and control of eclamptic seizures.
- If epilepsy is well controlled, do not change

therapy.

- Monitor plasma concentrations (levels tend to fall, and note that the bound : unbound ratio changes); the guide to the correct dose is freedom from fits and absence of toxicity.
- Owing to the changes in plasma protein binding, it is generally recommended that the therapeutic

range is 5–15 mg/L, whereas in the non-pregnant state it is 10–20 mg/L. This is only a rough guide, as protein binding varies.

ANTICOAGULATION

Warfarin

- has been associated with nasal hypoplasia when given in the first trimester.
- with CNS abnormalities after administration in later pregnancy.
- as well as a high incidence of haemorrhagic complications towards the end of pregnancy.

- **Low molecularweight heparin (LMWH)**

which does not cross the placenta, is the anticoagulant of choice in pregnancy in preference to unfractionated heparin which induced thrombocytopenia.

- **LMWH** is given twice daily in pregnancy due to the increased renal clearance of pregnancy
- Self-administered subcutaneous **LMWH** must be substituted for **warfarin** before six weeks' gestation

- Patients with prosthetic heart valves present a special problem, and in these patients, despite the risks to the fetus, **warfarin** is often given up to 36 weeks.

- The prothrombin time/international normalized ratio (INR) should be monitored closely if **warfarin** is used.

HORMONES

- **progestogen** (or oestrogen) present in the oral contraceptive the risk applies to large doses.
- Corticosteroids do not appear to give rise to any serious problems when given via inhalation or in short courses. Transient suppression of the fetal hypothalamic–pituitary–adrenal axis has been reported.
- Rarely, cleft palate and congenital cataract have been linked with steroids in pregnancy, but the benefit of treatment usually outweighs any such risk.
- **Iodine** and antithyroid drugs cross the placenta and can cause hypothyroidism and goitre

TRANQUILLIZERS AND ANTIDEPRESSANTS

- Benzodiazepines accumulate in the tissues and are slowly eliminated by the neonate, resulting in:

- prolonged hypotonia ('floppy baby'),
- subnormal temperatures (hypothermia),
- Periodic cessation of respiration and poor sucking. There is no evidence that the phenothiazines, tricyclic antidepressants or **fluoxetine** are teratogenic.

- **Lithium** can cause fetal goitre and possible cardiovascular abnormalities

Thank you