

PRINCIPLES OF DRUG USE IN PREGNANCY AND LACTATION

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INTRODUCTION

About 35% pregnant women take medication (other than vitamins and iron) at least once during prenatal period, although only 6% in the first trimester. The percentage has dropped from 80% since 1960's to present. There has also been a significant reduction in the percentage of women taking self administered drugs– from 64% to around 9% over the same period.¹

Mass media has played an important role in reducing the drug use in pregnancy by driving continued attention towards drug induced fetal abnormality. At least half the pregnancies in North America are unplanned, thus every year hundreds of thousands of women expose their fetus to a wide range of drugs before they know they are pregnant.²

With the increasing age at which women elect to have children, more of them have been taking long term medication for chronic conditions when they embark on pregnancy.³

Women suffering from certain medical conditions which were previously considered incompatible with pregnancy (SLE, certain types of heart disease), now have the opportunity of motherhood due to dramatic improvements in pregnancy outcome, with such conditions.⁴

Congenital defects are present in 2 to 3% of babies at birth. The majority (2/3rds) are of unknown aetiology, with a quarter having a genetic cause, while 3 to 5% may be due to intrauterine infections, and a similar number due to underlying maternal disease such as diabetes. Only a small proportion, around 1 to 2% of the total, is to be associated with drug treatment.

Pharmacokinetics during Pregnancy:

Most of the available information on Pharmacokinetics of drugs during pregnancy has been obtained from animal experiments and may not be directly applicable to humans. Although pregnant women do not differ from non pregnant ones in their response to drugs, certain quantitative differences do occur because of maternal physiological adaptation to pregnancy, with consequent alterations in Pharmacokinetics of the drugs. Further, the fetus has its own Pharmacokinetic peculiarities.

Drug absorption:

Alterations in drug absorption during pregnancy is accountable to high circulating progesterone levels which retards gastric emptying as well as gut motility, thus increasing intestinal transit time. Administration of antacids and iron also interfere with the absorption of certain drugs. Drug compliance is poor in pregnancy because of nausea and fear of possible adverse effects.

Drug distribution:

Pregnancy is accompanied by an increase in total body water by upto 8 litres and a 30% increase in plasma volume, with consequent decrease (0.5-1.0 g%) in plasma albumin due to hemodilution. Drugs which have low lipid solubility and high plasma protein bound (eg. warfarin, benzodiazepines) have low apparent volume of distribution (V_d). The V_d of such drugs increases markedly during pregnancy. The protein bound fraction of the drug in plasma diminishes and so there is decrease in total concentration of drug in plasma. Although, the fraction of unbound drug increases, greater pharmacodynamic effect is prevented by more rapid elimination of drug by metabolism and/or excretion. The therapeutic range for drugs whose use is monitored by measurement of total plasma concentration (eg. phenytoin) is adjusted downwards to make allowance for the above mentioned changes.

Drug metabolism:

Drug metabolism is not much effected in pregnancy. The contribution of the placenta and the fetal liver to the clearance of drugs from the maternal body is very small.

Drug excretion:

During pregnancy, the renal plasma flow increases by 100% and the glomerular filtration rate by 70%. In addition to this there is increase in the unbound fraction of drug in plasma. Hence, drugs which mainly depend on kidneys are eliminated more rapidly than in non-pregnant state. Examples are ampicillin, aminoglycosides, cephalexin and digoxin. The conventional dose of ampicillin needs to be doubled during pregnancy if it is used for a systemic infection in mother, but for UTI dose remains the same. Likewise an increase in dose of cefuroxime and lithium is needed. For phenytoin (whose unbound plasma level diminishes due to more rapid metabolism, in addition to total plasma level), an increase in daily dose by 25-100mg is required to maintain good seizure control; similar increase is also required in the dose of phenobarbitone and carbamazepine. In spite of pharmacokinetic alterations, (benzodiazepines, aspirin, propranolol, sulfafurazole and metronidazole) doses remain same.

TIMING OF EXPOSURE AND PREGNANCY OUTCOME

Teratogenic effects include malformations that occur during the period of organogenesis or that subsequently cause alterations in the structure or function of organ systems formed during organogenesis. Other manifestations of teratogens include growth restriction or fetal death and carcinogenesis. In addition, some drugs such as retinoids, which are high-grade teratogens, may exert their effect for up to 2 years after the last dose.⁵

- The timing of exposure to a particular drug is a critical factor in assessing the nature and extent of any adverse effects.⁵
- Four important phases are recognised in human development:
 - Pre-implantation stage(blastocyst formation): It lasts about 16 days from conception to implantation. Exposure to harmful drugs (such as anticancer drugs) can kill the embryo or else the damaged cells are replaced by undifferentiated cells which have the potential to develop normally. During this period of implantation and blastocyst formation, any adverse effect is an 'all or none phenomenon.' The result of an insult will either be death and abortion/ resorption or intact survival through multiplication of the totipotential cells.
 - Period of organogenesis (post conception day 17th to 56th day): Pre implantation stage and the stage of organogenesis together constitute the first trimester. Exposure to harmful drugs (and other environmental influences) during the period of organogenesis can cause congenital malformations(teratogenicity)or abortion.
 - The second and third trimesters: period of considerable growth and development of teeth, bones and in central nervous system, endocrine, genital and immune systems. During this period, drugs can cause either teratogenesis or a variety of other effects such as retardation of physical or brain growth, behavioural teratogenicity, premature labour, neonatal toxicity and even post natal effects such as cancers.
 - A short labour-delivery stage: Drug administration during this period is mainly fraught with danger of toxicity in the neonatal period.

PRESCRIBING PRINCIPLES

Prescribing drugs to a pregnant women:

- Treat minor ailments without drugs
- If a drug must be prescribed it should be one which is known to be safe during pregnancy
- Prefer a drug which has been in use for long periods of time to a newly introduced drug as the safety of the latter for the fetus is not likely to be known completely.⁶
- Tailor the dose of drug to the pregnant state as most of them are to be given for the shortest period of time required at the lower end of their therapeutic range. However, because of pharmacokinetic factors (increased body weight and more rapid clearance),the dose of certain drugs such as lithium, digoxin and phenytoin is likely to be higher than in the non pregnant state.
- Discourage the patient from self administering OTC drugs.⁶
- Advise the patient that absolute safety of the fetus cannot be guaranteed even by not prescribing any drug to women between the ages of 15 and 45. Therefore, do not sacrifice the mother's interest for the sake of the fetus.
- Drugs should be prescribed only for clear indications and where the benefits (usually for the mother) outweigh the potential risks (usually to the fetus).
- Encourage pre-conceptual counselling in all patients with chronic medical disorders and in particular those taking long term drug therapy. If this has not been possible, review all drug regimens as early in pregnancy as possible, avoiding polypharmacy as far as possible.⁶

Drugs used in various disorders during pregnancy.**1) Diabetes mellitus⁷:**

a) *Pre-existing diabetes*: For risk of teratogenesis and prolonged neonatal hypoglycemia Oral hypoglycemic drugs are not used in pregnancy. Short acting and intermediate acting human insulins are preferred. Maternal insulin requirements reach 2-3 times than the usual during third trimester.

b) *Gestational diabetes*: is mild form of diabetes diagnosed in gestational age and managed by diet modification, if necessary once daily insulin is enough.

c) *Treatment during labour*: After delivery insulin requirements falls rapidly and dosage regimens can be complicated further by breast feeding. So dosage adjustments is essential.

2) **Tuberculosis**⁸: in prenatal period, INH and ethambutol are considered as safe first line drugs. Rifampicin may be added as a third drug with due consideration of its hepatotoxic potential. But streptomycin is contraindicated.

3) **Heart diseases**⁹: The treatment is similar to that of non-pregnant women.

Ionotropic drugs: Digoxin, dobutamine, amrinone; β - Blockers: Metoprolol, bisoprolol.

Antiarrhythmic drugs: Membrane stabilizing agents like Quinidine, procainamide, flecainamide; β blockers like propranolol, esmolol; agents widening AP like amiodarone, bretylium; calcium channel blockers like verapamil, diltiazem.

As GFR enhances during pregnancy digoxin clearance will increase, so require dosage alterations.

Changes in plasma protein concentration will enforce change in quinidine dose as it is 80% protein bound.

4) **Antihypertensive Drugs**⁷: Drug treatment may be required for pre-existing hypertension as well as for pregnancy-induced hypertension and pre-eclampsia.

- Methyldopa, although crosses the placenta, is considered a safe drug throughout pregnancy in the treatment of pre-existing and pregnancy-induced hypertension.
- Beta blockers are also considered safe in pregnancy and may be better tolerated than methyldopa. Beta blockers cross the placenta producing a harmless reduction in fetal heart rate, but not the reactivity on CTG monitoring.
- If treatment is commenced before 28 weeks there is a gestationally adjusted reduction in birth weight but subsequent infant growth is unaffected. In general, if treatment is commenced before 28 weeks, methyldopa may be a better first choice.
- Calcium channel blockers effectively control antenatal and postnatal hypertension. No long term studies are available for assessment of fetal risk. Nifedipine is also used to inhibit pre-term labour and delivery. Owing to the relatively quick onset of its action, nifedipine can be used in treatment of acute hypertension instead of parenteral drugs.
- Thiazide diuretics, though safe in terms of adverse effects, should be restricted for treatment of heart failure than hypertension.
- Hydralazine is a vasodilator and is used parenterally for rapid control of acute hypertension. Per orally, in conjunction with methyldopa or beta blockers is an effective second line agent.
- Angiotensin converting enzyme inhibitors often prescribed to the young patient with essential hypertension or diabetics with microalbuminuria (owing to its additional renoprotective effect) are contraindicated in pregnancy. Intrauterine death in animal studies, oligohydramnios, fetal anuria and stillbirth in humans later in pregnancy, have been reported.

5) **Antiretroviral Agent**⁷: Antiretroviral drugs used in the management of HIV infection and AIDS, zidovudine and lamivudine (nucleoside reverse transcriptase inhibitors) appear to be safe for use in pregnancy. Reports show insufficient evidence to establish a causal relationship between exposure to antiretroviral drugs and a small number of cases (8 cases of children) with mitochondrial dysfunction. Neviparine (non nucleoside reverse transcriptase inhibitor) also appears safe, but efavirenz is absolutely contraindicated in pregnancy.

6) **Psychotropic Drugs**⁷:

- Neuroleptics are unlikely to be prescribed in pregnancy, but women on long term treatment or prophylaxis for functional psychosis may present with pregnancy. The high lipid solubility of these drugs and their active metabolites, means that stopping these drugs in someone already pregnant will have little, if any, immediate effect on the environment of the fetus. Currently studies fail to show a teratogenic effect of neuroleptic drugs taken in early pregnancy, especially trifluoperazine, and no lasting behavioural or developmental effects have been shown in children following exposure to neuroleptics in late pregnancy.
- More commonly used antiemetic, prochlorperazine appears to be safe in large scale surveillance studies. Chlorpromazine, due to its hypotensive effects, is best avoided immediately before and during delivery.
- Structurally synonymous to neuroleptics, tricyclic antidepressants do have considerable overlap in their pharmacological effects. Withdrawal reaction have been reported in some neonates born to mothers who received TCAs in the last month of pregnancy, including abdominal cramps, restlessness, insomnia and fever. Often dose reduction towards term is aimed for, planning to restart medication immediately postpartum. Drugs of choice in depression are TCAs and fluoxetine is used as an alternative.

- Lithium carbonate by far most effective controller of manic depressive illness, by definition, includes women of childbearing age. Proved fact that lithium when prescribed in first trimester is known to cause ebstein's anomaly. Lithium clearance doubles during pregnancy and dose incline may be required to maintain serum concentration at therapeutic levels. Postpartum dose decline is essential as there is abrupt fall in clearance may precipitate toxic levels. There is no evidence of withdrawal reaction or behavioural abnormality in neonates exposed to lithium in utero, but breastfeeding is contraindicated as levels of lithium in breast milk approach adult serum therapeutic levels. Patients using lithium in the second and third trimesters should be routinely assessed by ultrasound for increased amniotic fluid volume. Alternatives to lithium in the treatment of mania or bipolar affective disorder in pregnancy are chlorpromazine and haloperidol.
- Monoamine oxidase inhibitors such as tranylcypromine, phenelzine and isocarboxazid are contraindicated in pregnancy due to their potentially fatal interaction with drugs normally used in anaesthesia.
- In terms of anxiolytics and hypnotics, benzodiazepines (BZDs) are the only agents that should be considered, barbiturates now being obsolete for these purposes.
- Although studies show BZDs in early pregnancy appear safe, there are numerous case reports showing pyloric stenosis, cardiac defects and inguinal herniae with their use in the first trimester. Abrupt withdrawal in pregnancy is not justified, due to the incapacitating nature of withdrawal reactions with distorted sensory perceptions. Withdrawal is likely to be worse if the initial benzodiazepine is shorter acting. A gradual dose reduction after switching to a long acting benzodiazepine such as chlordiazepoxide is the preferred method.
- Evidence to show that diazepam accumulates in the fetus is available and thus large single doses or sustained prenatal use in III trimester can lead to 'floppy infant syndrome' characterised by hypotonia, respiratory embarrassment, difficulty in sucking and hypothermia. A withdrawal syndrome in infants whose mothers have been on regular BZDs is also well documented.

Diazepam readily enters breast milk and the newborn continues to have an impairment to metabolise the drug. Lorazepam is associated with neonatal hypotonicity, but does not enter breast milk in significant amounts, while oxazepam appears to be metabolised satisfactorily by the neonate after the second or third day. Therefore, the latter may be a better choice for the breastfeeding mother if a benzodiazepine is required.

7) Anticoagulants¹²:

- Heparin (both unfractionated and low molecular weight) does not cross the placenta, therefore it has no teratogenic effect and is the anticoagulant of choice in the antenatal period, probably with the exception of patients with mechanical valves. However, it is associated with reversible loss of bone mineral density following prolonged use and in certain individuals may cause thrombocytopenia.
LMW heparins have the advantage of once daily dosage, more predictable bioavailability and less risk of loss of bone mineral density. An alternative to heparin for thromboprophylaxis in prenatal life for lower risk individuals is low dose aspirin, but patients with recurrent venous thromboembolism, inherited clotting abnormalities or antiphospholipid syndrome should receive heparin.
- Oral anticoagulants are associated with teratogenicity and spontaneous miscarriage reported around 25% of cases. Especially warfarin used in the first trimester, results in chondrodysplasia punctata and nasal hypoplasia. The incidence rates varies between 10 and 25%. Abnormalities associated with use of warfarin in later pregnancy are of the central nervous system under the collective term dorsal midline dysplasia, encompass absence of corpus callosum, Dandy Walker syndrome and encephaloceles.

As pregnancy is a risk factor for venous thromboembolism, Warfarin has a clear role in the management of certain types of cardiac patients during pregnancy such as those patients who have metallic valve replacements, pulmonary hypertension and atrial fibrillation. In these patients the aim is to maintain the INR around three, to minimise teratogenic effects of warfarin on the one hand, whilst maintaining satisfactory anticoagulation on the other.

8) Anticonvulsants⁸

- Studies have proved the teratogenic potential of phenytoin, primidone, phenobarbitone, carbamazepine and sodium valproate
- Monotherapy is preferred over polytherapy the risk of malformation increases synergistically. The incidence of congenital malformations in epileptic mothers prescribed a single anticonvulsant, is around 6% compared with a background rate of 2%. Well, over 90% of mothers on anticonvulsants will have a normal pregnancy and deliver a healthy infant.

Several major malformations caused by anticonvulsants have been reported. (Table 1)

Table 1. Major congenital malformations associated with various anticonvulsants.

| Defect | Associated anticonvulsant |
|--------------------------|---------------------------------------------------|
| Neural tube defects | Sodium valproate (1-2%) and carbamazepine(0.5-1%) |
| Orofacial clefts | Phenytoin |
| Congenital heart defects | Phenytoin and valproate |

- *Minor malformations* associated with anticonvulsant use in pregnancy known as the ‘fetal anticonvulsant syndrome’ encompass dysmorphic features (V-shaped eyebrows, low-set ears, broad nasal bridge and irregular teeth), hypertelorism and hypoplastic nails and distal digits.
- BZDs such as clonazepam are not teratogenic. Few data are available about the use of newer anticonvulsants such as vigabatrin, lamotrigine and gabapentin in human pregnancy, especially as they are often used in combination with other anticonvulsants. Animal studies have suggested only a potential risk with vigabatrin and advised to coadminister high dose folic acid (5 mg/day as opposed to 400 mcg) periconceptually and throughout the first trimester of pregnancy with anticonvulsant, as one mechanism of teratogenesis is thought to be folate deficiency through the interference with folate metabolism.
- Prenatal screening for neural tube defects and congenital malformations with maternal serum alphafetoprotein and detailed ultrasound at 18 to 20 weeks should be offered, along with a further ultrasound at 22 weeks if cardiac abnormalities are suspected on the earlier scan.
Vitamin K, at a dose of 10 mg/day, should be prescribed for all pregnant epileptic women on treatment during the last 4 weeks of pregnancy. This is to reduce the risk of haemorrhagic disease of newborn in the offspring, as hepatic enzyme inducing drugs may result in reduced levels of vitamin K dependant coagulation factors. Breast-feeding whilst on anticonvulsants is safe.

9) Immunosuppressants and Corticosteroids¹³:

- These are of utmost importance in patients with autoimmune conditions such as rheumatoid arthritis and SLE and following organ transplantation.
- Reports show that there is a good pregnancy outcome in women taking azathioprine, though some infants have lymphopenia, growth restriction and an increase in chromosomal breakages.
- Cyclosporin appears safe in pregnancy but breastfeeding is not recommended.
- Corticosteroids such as prednisolone are safe in pregnancy and lactation, though additional peripartum doses are required to cover delivery.

10) Vasopressor agents (noradrenaline, dopamine, and dobutamine) all decrease the uterine blood flow and may stimulate uterine contractions. their use in pregnancy is justified only if mother’s survival is at stake.

11) Deep vein thrombosis: is treated with heparin. The use of streptokinase is associated with risk of bleeding.

12) Thyrotoxicosis: Low dose propylthiouracil is preferred over carbimazole. Whereas Stable iodine and radioactive iodine are contraindicated.

13) Antibiotics^{7,9}: In Pregnant women, use of antimicrobial agents is different to that of non pregnant patients. Adverse effects have been proven with very few antibiotics and therefore treatment of pregnant women should be with standard adult doses for an adequate duration and as dictated by the underlying condition.

- **Bacteriuria and Cystitis:** Covert bacteriuria and cystitis represent the commonest causes for prescribing antibiotics to pregnant women. The antibiotics of choice include amoxycillin (or ampicillin), cephalixin and co-amoxiclav. The latter two may be a better choice as up to 50% of Gram negative bacteria responsible for UTIs may be resistant to amoxycillin. Considering the theoretical concern of trimethoprim as folate antagonist as it is placed under FDA Pregnancy Risk Category C when used in UTI after I trimester should be co-administered with folic acid. The fluoroquinolones (ciprofloxacin, ofloxacin, etc) are best avoided, although no human data on teratogenesis are available; there are reports of irreversible arthropathy from animal studies.
- **Sore Throats:** The majority of sore throats are viral and self limiting in nature. Occasionally, in severe cases where superimposed or secondary bacterial infection is suspected, the antibiotic of choice is penicillin or erythromycin if the woman is allergic to penicillin.
- **Bronchial Infections:** Effective drug for bacterial bronchial infections is ampicillin or amoxycillin. However since 10 to 20% of Haemophilus influenza may be resistant, the combination of amoxycillin with clavulanic acid may be a better option. Streptococcus pneumoniae accounts for the majority of lobar pneumonias and benzylpenicillin (or erythromycin if allergic to penicillin) is the antibiotic of choice.
- **Bronchial asthma:** results are excellent with inhaled beta adrenergic agonists, inhaled glucocorticoids or with aminophyllin. However, IV salbutamol used to delay labour is known to cause pulmonary edema especially in individuals with mitral stenosis. Corticosteroids are administered concurrently to promote fetal lung maturation. This therapy cannot used in hypertensives, and in diabetes subjects (as IV salbutamol can cause severe hyperglycemia and ketoacidosis).
- **Allergic rhinitis:** treated either locally (glucocorticoids, decongestants) or systemically with antihistaminics (diphenhydramine, dimenhydrinate, tripelemamine).
- **Malaria¹⁵:** Being a major cause of abortion, preterm labour and perinatal death prophylaxis and treatment is essential for malaria. Prophylaxis of chloroquine 300mg weekly commence one week before and continued for a month after visiting endemic areas. Prophylaxis for endemic areas of chloroquine resistant Plasmodium falciparum a combination of chloroquine 300 mg weekly and proguanil 200mg a day should be prescribed. Treatment of malaria caused by P.vivax, P. ovale or P. malariae should be with chloroquine; primaquine should be withheld until after the pregnancy to avoid the risks of haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficiency. If the pathogenic organism is P. falciparum from an area known to have chloroquine resistance, treatment is with quinine followed by a three day course of Sulfadoxine and Pyrimethamine. If the parasites persist in their asexual form, a week's course of erythromycin should be prescribed.
- **Venereal Disease:** Venereal disease such as gonorrhoea and syphilis should be treated as in the non pregnant individual. For syphilis, treatment should be with benzylpenicillin or penicillin G as a single IM dose of 2.4 million units for primary, secondary and early latent syphilis and the same dose for 3 consecutive weeks for late latent syphilis Aqueous procaine penicillin may also be used but requires a longer course of daily treatment (6 to 900,000 units for 10-21 days). Considering the cure rate in excess of 98% and efficacy in preventing vertical transmission penicillin is preferred over alternative i.e erythromycin which could be used when mother is allergic to former. Latter may require repeated courses with meticulous assessment of active infection in neonates. Patients need to be warned that after the first course of treatment, especially with secondary syphilis, there is a risk of Jarisch-Herxheimer reaction, that may precipitate premature labour, so treatment after 20 weeks is best carried out in hospital. Treatment of gonorrhoea depends on the severity of the infection and sensitivities need to be tested, as penicillin resistant strains, though uncommon, may be responsible.

Test of cure, contact tracing and screening for other STDs are important. For uncomplicated genital infection a single dose of ciprofloxacin may be adequate but this regimen is not justified during gestation. Recommended regimens include spectinomycin 2 g IM or a combination of probenecid 1 g orally with, either aqueous procaine penicillin G 4.8 million units IM or amoxicillin 3 g orally followed by a seven day course of erythromycin 500 mg qds. For disseminated infections, hospital admission and intravenous cephalosporins may be required. Breastfeeding is not contraindicated.

In chlamydial infections: For known reasons, doxycycline has been replaced with erythromycin 500mg 6 hourly for 7 days, though the cure rates are lower comparatively (98% and 93% respectively) with amoxicillin and clindamycin are considered when above therapy is not well tolerated. Contact tracing for the past 30 days is essential followed by counseling and treatment.

In herpes infections: A component of TORCH, effective drug would be acyclovir for infection such as primary genital herpes or varicella. In spite of evidence of no increased fetal malformations or adverse fetal outcome routine use in pregnancy is not recommended. Best results are observed in overwhelming varicella infection. Topical acyclovir seldom cause systemic effects so use in genital and orolabial herpes is justified. While ribavirin is CI based on animal studies which proved teratogenic, no such reports are available regarding amantidine use.

Toxoplasmosis: Records show that the incidence rates are lower in first trimester of transplacental infection but the infection is severe, while the fetal infection is not uncommon in III trimester though fail to produce overt disease at birth. Objective of treatment for maternal toxoplasmosis is to bring down vertical transmission rates which spiramycin 3g/day reduces by 60%.

Diagnosis of fetal toxoplasmosis is by amniocentesis / fetal blood sampling for specific IgM. If there are structural abnormalities, termination of pregnancy is the best option. In cases of fetal infection without ultrasound evidence of fetal damage or where TOP is unacceptable to the parents, treatment with 3 weekly cycles of pyrimethamine, sulphadiazine and folic acid alternating with spiramycin is recommended for the remainder of the pregnancy.

Helminthiasis caused by *Ascaris* and *Trichuris* are best left alone in pregnancy if asymptomatic. If symptomatic, treatment with 4 g of piperazine is appropriate. Hookworm infections causing anaemia can be treated by 5 g bephenium or pyrantel pamoate at a dose of 10 mg/kg. During lactation, chloramphenicol known to cause grey baby syndrome, while tetracyclines causes dental discolouration both are not advised. Metronidazole, although safe, does change the taste of breast milk.

14) ANALGESICS AND ANTI-INFLAMMATORY DRUGS ^{11,14}:

- Paracetamol is safe in pregnancy and lactation. For headaches (tension headaches, migraine) paracetamol and codeine are the drugs of choice. Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) may be used but not advised in III trimester
- NSAIDs used in pregnancy and lactation should be those with a short half life and inactive metabolites such as ibuprofen, to minimise effects on the fetus.
- Babies born pre-term after exposure to indomethacin given to delay pre-term delivery, have a higher neonatal morbidity, with necrotising enterocolitis, intracranial haemorrhage and patent ductus arteriosus.
- Sulphasalazine has been shown to be safe in pregnancy and lactation but folate supplementation is recommended as it impairs folate absorption

15) VACCINES IN PREGNANCY ⁴:

Table 2

| Considered safe | Contraindicated during pregnancy or safety not established | Optional Vaccines |
|--------------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Tetanus and diphtheria toxoids (Td) Hepatitis B Influenza Meningococcal Rabies | BCG Measles Mumps Rubella Varicella FluMist | Anthrax Hepatitis A Japanese encephalitis Pneumococcal Polio (IPV) Typhoid (parenteral and Ty21a) Vaccinia Yellow fever |

16) ANAESTHESIA AND ANALGESICS IN OBSTETRICS¹⁶:

- **Sedatives and analgesics:** Pethidine (analgesic in labour used mostly during first phase); 100 mg(1.5mg/kg body wt) IM. As it crosses placenta watch for respiratory depression. Other drugs are pentazocin:dose-30-40mg i.m,shorter action and major disadvantage being drug dependence.
- **Tranquilisers:** Diazepam(5-10mg) used in pre-eclampsia,shouldnot be given in preterm labour. When used in labour causes neonatal hypotonia and hypothermia.
- **Inhalational methods:**premixed nitrous oxide and oxygen(50% nitrous oxide and 50 % oxygen mixture) entonox apparatus. Side effects:hyperventilation,dizziness,hypocapnia; methoxyflurane, isoflurane,enflurane.
- **Spinal anaesthesia :**1 ml hyperbaric lignocaine(5%)into subarachnoid space of L3,L4.
- **In cesarean section:** Thiopentone sodium,200 to 250 mg(4mg/kg) as a 2.5% soln i.v, followed by suxamethonium 100mg. Complication of GA is popularly called as mendelsons syndrome ie.aspiration of gastric contents

DRUGS WITH PROVEN TERATOGENIC EFFECTS HUMANS⁸:

| Category | Drug | Teratogenic effect |
|------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibiotics | Aminoglycosides Tetracyclines Quinolones Sulphonamides | Deafness, vestibular damage Anomalies of teeth and bone Animal studies-only irreversible arthropathies Hyperbilirubinaemia, kernicterus |
| Anticholinergics | | Neonatal meconium ileus |
| Anticoagulants | Warfarin | Skeletal & CNS defects, Dandy walker syndrome |
| Anticonvulsants | Carbamzepine Phenytoin Valproic acid Paramethadione, trimethadione | Neural tube defects Growth retardation & CNS defects Neural tube defects CNS & facial abnormalities |
| Antidepressants | Lithium carbonate | Ebstien's anomaly, hypotonia, reduced suckling & hyporeflexia |

Table3 summarises teratogenic and fetal effects of common medications

| | | |
|-------------------|------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antihypertensives | ACE inhibitors Beta blockers | Prolonged renal failure in neonates, decreased skull ossification, renal tubular dysgenesis. Growth restriction, neonatal bradycardia,hypoglycemia |
| Antithyroid drugs | Propylthiouracil, Methimazole | Fetal & neonatal goiter& hypothyroidism Aplasia cutis, Fetal & neonatal goiter & hypothyroidism |
| Cytotoxic drugs | Aminopterin & methotrexate Cyclophosphamide | CNS & limb malformations CNS malformations & secondary cancer |
| Diuretics | Frusemide Thiazides | Decreased uterine blood flow, hyperbilirubunaemia Neonatal thrombocytopenia |
| Hypoglycemics | | Neonatal hypoglycemia |

| | | |
|-------------------------|---------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| NSAIDs | Indomethacin | Premature closure of ductus arteriosus necrotizing enterocolitis, neonatal pulmonary HTN |
| | Salicylates | Haemorrhage |
| Prostaglandin analogues | Misoprostol | Abortion, induction of labour |
| Recreational drugs | Ethanol | Fetal alcohol syndrome (pre & post natal growth restriction, CNS anomalies, characteristic facial features) |
| | Cocaine | Growth retardation, placental abruption, uterine rupture |
| Systemic retinoids | Isotretinoin, etretinate | CNS, craniofacial, CVS and other defects. |
| Sex hormones | Danazol & other androgenic drugs Diethylstilboestrol | Masculinization of female fetuses Vaginal ca, genitourinary defects in males & female offsprings. |
| Sedatives | Thalidomide | Limb shortening and internal organ defects |
| Psychoactive drugs | Barbiturates, opioids, & Benzodiazepines | Neonatal withdrawal syndromes when drugs taken in late pregnancy. |
| | Phenothiazines | Neonatal effects of impaired thermoregulation, extra pyramidal effects |

MANAGEMENT OF PREGNANCY AND POTENTIAL TERATOGENESIS⁹:

- The risk of teratogenesis is commonly seen in patients taking long term medication for a chronic condition, who ideally should be counselled prior to pregnancy and made aware of the risks of fetal malformation and how these risks can be reduced. The second group is those patients taking a single course of treatment and who are unaware of early pregnancy. The management of exposure to potential teratogens in pregnancy relies on accurate determination of the history of exposure including the gestational age at exposure, as well as up-to-date information on the teratogenic potential of the agent in question at the particular gestation of exposure.
 - Accurate dating of pregnancy is essential and this can be performed by a combination of early dating scan, menstrual and conception history.
 - Fetal malformations associated with teratogens affect the CNS, CVS, limb defects, orofacial clefting and multisystem defects. The majority of malformations are detectable on detailed ultrasound scanning at 18 to 20 weeks. Where cardiac abnormality is suspected from an earlier scan a repeat scan around 22 weeks may be helpful.
 - In cases where neural tube defects are one of the manifestations of exposure to a particular teratogen, maternal serum alpha-fetoprotein estimation may also be of great value.
 - Further management will depend on the established risks from exposure to the teratogen at a particular gestation time along with the wishes of the couple after comprehensive counselling.

DRUGS USED IN LACTATION:

Most drugs are secreted in the breast milk the dose at which it reaches the baby are clinically insignificant considering the dilution of the drug in the mother and the small volumes of milk the neonate feeds on.

- Drugs can be considered in three broad categories with respect to breast feeding:
 - Drugs that cannot be detected in the baby, examples warfarin and aminoglycosides, that are not absorbed from the gastrointestinal tract of normal infants.
 - Drugs that are detectable in the baby in clinically insignificant amounts, such as non narcotic analgesics, NSAIDs, penicillins, cephalosporins, antihypertensive drugs, bronchodilators and most anticonvulsants except barbiturates.
 - Drugs that reach the neonate in sufficient amounts to cause adverse drug reactions in fetus. Examples benzodiazepines reported to cause lethargy, barbiturates causing drowsiness, amiodarone with a theoretical risk of hypothyroidism, tetracyclines and potential risk of teeth discolouration, combined OCP and risk of diminishing milk supply and reduction in nitrogen and protein content, ephedrine associated with irritability, cytotoxic drugs and immune suppression/ neutropenia, and aspirin with the risk of Reye's syndrome.

Pharmacokinetics^{7,8}:

Most of the lipid soluble drugs enter the breast milk, not necessarily in significant amounts to cause adverse reactions in neonates. Although the amounts are so small, that loss of drug in milk is of no importance, as a mechanism of elimination for mother. Even small amounts sometimes do cause adverse reactions in suckling child.

There is a pH gradient between plasma (7.4) and breast milk(6.9). Generally, milk levels of basic drugs will be higher than those of acidic drugs. Weak acids such as penicillins, aspirin, sulphonamides, diuretics and barbiturates are present in milk at levels less than half of corresponding maternal plasma level(milk /plasma <0.5). In contrast, weak bases like erythromycin, histamine H₂ antagonists and isoniazid have milk /plasma >1. Therefore the basic drug, being predominantly nonionised at plasma alkaline pH can diffuse through the mammary epithelium and get accumulated in the milk. Once diffused into the milk, these drugs cannot be reabsorbed back to plasma as they get substantially ionized due to relatively acidic pH of milk. Hence, basic drug [tetracyclines, ergotamine, morphine, metronidazole, carbimazole, bromocriptin, estrogen/progesterone, diazepam, antihistamines] are secreted more in breast milk as compared to acidic drugs. Drugs which are highly protein bound in maternal plasma have lower potential to achieve high breast milk levels irrespective of their pka value. Eg. Warfarin is 95% protein bound in maternal plasma and appears in very small quantities in breast milk.

Certain nonelectrolytes like ethanol and urea readily enter the breast milk, independent of milk pH. Certain acidic drugs although being less secreted can serious side effects in neonates. eg. sulfonamides [kernicterus and allergy], penicillins [allergy], ampicillins [diarrhoea], dapsone [haemolytic anaemia], phenindione [bleeding], phenobarbitone [drowsiness], phenytoin [methemoglobinaemia] and theophylline [restlessness].

Guidelines to be prescribed for breast feeding mothers⁶:

- Unnecessary drug use should be avoided and use of over-the-counter (OTC) products limited. Breastfeeding mothers should seek advice for minor ailments from the physician.
- The benefit/risk ratio should be assessed for both mother and infant.
- Use of drugs known to cause serious toxicity in adults or children should not be recommended.
- Drugs licensed for use in infants do not generally pose a hazard.
- Neonates(particularly premature infants)are at greater risk from exposure to drugs via breast milk because of immature excretory functions and consequent risk of drug cumulation.
- A regimen and route of administration which presents the minimum amount of drug to the infant should be chosen and followed up for any adverse reactions by drug monitoring.
- Long acting formulations of drugs likely to cause serious side-effects (e.g.antipsychotic agents) are best avoided as it is difficult to time feeds to avoid significant amounts of drug in breast milk.
- Multiple drug regimes may pose an increased risk, especially when adverse effects such as drowsiness are addictive.
- New drugs,for which little data are available are best avoided.

Drugs which increase lactation are⁷:

- Metoclopramide: increases milk supply by blocking dopamine, which results in an increase in prolactin levels. Not effective in all women who have normal to increase prolactin levels.
- Amisulpride: antipsychotic and antidepressant, but also increases serum prolactin levels and increased breast milk.

Drugs which decrease lactation are⁷ :

- Bromocriptine
- Diuretics

Table-4 Safety of drugs during lactation¹⁴:

| Drug | Comments |
|-----------------------|------------------------------------------------------------------------|
| Amiodarone | Theoretical risk of thyroid disturbance because of high iodine content |
| Antineoplastic agents | Theoretical risk of blood dyscrasias |
| Chloramphenicol | Theoretical risk of blood dyscrasias |

| | |
|---------------------------------------------|-----------------------------------------------------------------------------|
| Dapsone | Haemolytic anemia reported |
| Doxepin | Case report of profound respiratory depression on 75 mg daily |
| Ergotamine | Risk of ergotism in infants |
| Gold salts | Risk of hypersensitivity reactions and of haematological and renal toxicity |
| Iodides(including some Cough preparations) | Theoretical risk of thyroid disturbance. |
| Indomethacin | Case of infant convulsions reported |
| Lithium | Tremor and involuntary movements reported |
| Oestrogens(high dose) | May cause feminization of male infants |
| Phenindone | Case of hematoma & abnormal blood coagulation reported. |
| Radioisotopes | Radiation exposure |
| Vitamin D (high dose) | Case reported of hypercalcemia in infant. |

CONCLUSION

- Fetal safety is a major concern, so effective drugs that have been in use for long periods are preferable to new alternatives that, although potentially more specific with fewer adverse effects in adults, are more likely to have an unknown safety profile in fetuses.
- In order to minimise fetal risk, minimum effective dose should be prescribed bearing in mind the pharmacokinetics alterations in pregnancy, although sometimes higher than normal adult doses may be required.
- Counselling is imperative before prescribing and women should be discouraged from taking OTC drugs. Essential factors such as risk versus benefit ratio are considered during counselling.
- For teratogenesis to be ascribed to a particular drug, certain patterns of defects should be seen when exposed to that drug at a particular gestation time, the evidence being stronger if the defect caused has a biologically plausible mechanism of teratogenesis and/or has been proven in animal models.
- Alongside the risk of teratogenesis, there is however also the risk of misinformation about teratogenesis and the potential for unnecessary terminations or avoidance of much needed therapy. Women and their unborn offspring need to be protected from both these risks.
- Most drug labels will have the warning 'not to be used in pregnancy unless benefits outweigh risk', putting heavy responsibility on the physician and making women reluctant to take the prescribed medication. One should always be prepared to consult colleagues or experts in the field if in doubt.

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