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Review Article

Drugs in pregnancy and lactation

Ashfaque K. Shaikh*, Madhuri D. Kulkarni

[a]Department of Pharmacology, Government Medical College, Aurangabad (MS) 431001, India

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***Correspondence to:**
Dr. Ashfaque K. Shaikh,
Email: ashfaq05@gmail.com

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ABSTRACT

Drug use during pregnancy and lactation is an almost inevitable event. Some of the drugs may have adverse effects on the baby on exposure. It is therefore necessary for the physician to be aware of the changes in pharmacokinetics and pharmacodynamics during pregnancy. Knowledge about the known teratogens and drugs safe to be used during pregnancy is essential on the part of the prescribing physician. There are many factors affecting drug passage into the milk and thus affecting the child in some cases. There are also some drugs affecting lactation. All this data needs to be carefully studied by the physician.

Keywords: Pharmacokinetics, Pharmacodynamics, Pregnancy, Teratogen, Lactation

INTRODUCTION

Drugs are likely to be self-administered or prescribed by the physician during pregnancy. Intelligent use of drugs during pregnancy requires that the physician understands the interaction between drugs and pregnancy so as to avoid indiscriminate use of drugs with disastrous consequences such as the thalidomide tragedy. At the same time, over-cautious timidity on the part of the physician casts the pregnant mother as a therapeutic orphan. So it must be remembered that drugs given during pregnancy must be for the benefit of the mother without producing unwanted complications.[1]

PHARMACOKINETICS IN PREGNANCY

Maternal

Absorption: High circulating levels of progesterone slow the gastric emptying increasing the intestinal transit time. However slow drug absorption does not occur except at term when parenteral drug administration is preferred to obtain quick response. Increased emesis is seen due to morning sickness.

Distribution: Pregnancy is accompanied by an increase in total body water by up to 8 litres and a 30% increase in plasma volume, with consequent decrease in plasma albumin due to haemodilution. This may alter the Vd and plasma concentration of drugs given.

Metabolism: Hepatic drug metabolising enzymes are induced during pregnancy, probably by the high levels of circulating progesterone. This leads to rapid metabolic degradation, especially of lipid soluble drugs.

Excretion: During pregnancy, renal plasma flow increases by 100% and GFR by 70%. Drugs which are dependent for their elimination mainly on renal function are eliminated more rapidly than in the non-pregnant state.[1]

Foetal

Critical factors affecting placental drug transfer and drug effects on the foetus include:

1. *Physicochemical properties of the drug*

a) Lipid solubility: lipophilic drugs tend to diffuse readily across the placenta easily, whereas highly ionized drugs cross the placenta slowly and achieve very low conc. in the foetus. If high enough maternal-foetal conc. gradients are achieved, polar compounds cross the placenta in measureable amounts.

b) Molecular size: drugs with low mol. wt. cross the placenta easily.

2. *Rate at which the drug crosses the placenta and the amount of drug reaching the foetus*

a) Placental transporters: these transporters pump back the drug from the foetal blood back in to the maternal blood, e.g.: P-gp, BCRP, MRP3.

b) Protein binding: may also affect the rate and amount of transfer.

c) Placental metabolism: may convert toxic drugs to non-toxic metabolites or vice-versa.

3. *Duration of exposure to the drug*

Foetal drug metabolism: by the foetal liver may reduce the amount of drug in the foetal blood.

4. *Distribution characteristics in different foetal tissues*
5. *Stage of placental and foetal development at the time of exposure to the drug*
6. *Effects of drugs used in combination*[2]

PHARMACODYNAMICS IN PREGNANCY

Maternal drug actions: effects of drugs on the reproductive tissues (breast, uterus, etc.) may sometimes be altered; however, effects on other maternal tissues (heart, lungs, kidneys, CNS, etc.) are not changed significantly by pregnancy, although the physiological context may be altered.

Therapeutic drug actions in the foetus: foetus may be the drug target. E.g. Steroids used to stimulate foetal lung maturation when preterm birth is expected or phenobarbital given to mother near term to induce foetal hepatic enzymes so as to cause glucuronidation of bilirubin and thus reduce incidence of jaundice in the newborn.

Predictable toxic drug actions in the foetus: use of ACEI's during pregnancy can cause irreversible renal damage in the foetus due to foetal hypotension.

Teratogenic drug actions: drugs may interfere with the passage of O_2 or nutrients through the placenta and therefore have effects on the most rapidly metabolising tissues of the foetus. E.g. thalidomide, Vitamin A analogues or folate deficiency.[2]

TERATOGEN

In 1959, James Wilson proposed 6 basic principle of teratology. Fifty years later, these principles remain important basic tenets in the field of teratology. These principles include the following:

1. Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which it interacts with environmental factors.
2. Susceptibility to teratogens varies with the developmental stage at the time of exposure.
3. Teratogenic agents act in specific ways on developing cells and tissues to initiate abnormal developmental processes.
4. The access of adverse environmental influences to developing tissues depends on the nature of the influences.
5. The final manifestations of altered development are death, malformation, growth retardation and functional disorder.
6. Manifestations of altered development increase in frequency and in degree as dosage increases from no effect to 100 % lethality.[3]

To be considered teratogenic, a candidate substance or process should i) result in a characteristic set of malformations; ii) exert its effects at a particular stage of foetal development and iii) show a dose dependent incidence. Fewer than 30 drugs have been identified as teratogens, with hundreds of agents proved safe for the unborn. Baseline teratogenic risk in pregnancy (i.e., the risk of a neonatal abnormality in the absence of any known teratogenic exposure) is about 3 %.[2]

Modalities by which drugs can affect the foetus are:

1. Acting directly on the embryo to produce a lethal, toxic or teratogenic effect
2. Altering placental function
3. Changing the myometrial activity
4. Altering the biochemical dynamics of the mother[4]

EFFECT OF DRUGS ON PREGNANCY

Gestation may be divided into 4 major stages:

1. *Pre-implantation stage (blastocyst formation):* lasts 16 days; i.e. from conception to implantation. Shows "all-or-none" effect; i.e. either killing the embryo or not affecting it at all. No teratogenesis.
2. *Period of organogenesis (from 17th to 56th day):* During this period, drugs may produce a) no measurable effect; b) abortion; c) a sublethal gross anatomic defect; or d) a permanent subtle metabolic or functional defect
3. *2nd and 3rd trimesters:* drugs can cause teratogenicity or other effects such as retardation of physical or brain growth, behaviour defect, premature labour, neonatal toxicity or even post-natal effects such as cancer in later life.
4. *Labour-delivery stage:* danger of toxicity in the neonatal period.[1,4]

The FDA in 1979 had classified drugs in 5 categories on the basis of effects they produce in the foetus. It is as follows:

Category A: Human studies show no foetal risk, e.g. multivitamins, Mag. Sulphate.
Category B: No foetal risk in animal studies but there are no human studies, e.g. amoxicillin, paracetamol.
Category C: No adequate studies in animal/humans or there are adverse foetal effects in animal studies but no available human data, e.g. Morphine, atropine.
Category D: Evidence of foetal risk but benefits are thought to outweigh these risks, e.g. Aspirin, Phenytoin.
Category X: Proven teratogens, e.g. Estrogens, Thalidomide.[4]

Mechanism of action

There are 6 teratogenic mechanisms associated with medication use:

1. Folate antagonism
2. Neural crest cell disruption
3. Endocrine disruption
4. Oxidative stress

5. Vascular disruption
6. Specific receptor- or enzyme-mediated teratogenesis[5]

Many medications classified as class X are associated with at least one of these mechanisms.[6]

Drug	Teratogenic effect
Thalidomide	Phocomelia
Androgens & Progestins	Virilization
Tetracyclines	Discoloured & deformed teeth, retarded bone growth
Alcohol	Low IQ, Foetal alcohol syndrome
Antithyroid drugs	Foetal goitre and hypothyroidism
Isotretinoin	Craniofacial heart and CNS defects
Warfarin	Depressed nose; eye & hand defects, growth retardation
Phenytoin	Hypoplastic phalanges, cleft lip/palate, microcephaly
Carbamazepine	Neural tube defects; other abnormalities

Few drugs are studied for use during pregnancy & lactation and little guidance is available to physicians and patients. Thus most medications are used off-label during pregnancy. Most product monographs advise that drugs should not be used during pregnancy or lactation. For reasons such as cost & litigation, pharmaceutical companies do not address pregnancy. Information on the disposition of drugs during pregnancy is usually obtained post-approval and through voluntary ADR reporting.[7]

DRUG PRESCRIBING DURING PREGNANCY

Drugs may be prescribed for:

i. Treatment of common minor ailments; or
ii. Treatment of pre-existing or pregnancy aggravated medical illnesses[8]

i. Minor ailments

Analgesics & antipyretics: Paracetamol is safe in normally recommended doses.[1,8] Aspirin in neonates decreases platelet adhesiveness; in mothers causes greater intrapartum blood loss.[8]
Nausea & vomiting: Treatment required only for severe and prolonged symptoms. Meclizine and cyclizine are safe. There is a weak association between meclizine and congenital eye defects. Promethazine may be associated with increased incidence of congenital dislocation of hip. Metoclopramide maybe used in labour and during anaesthesia.[8]
Heartburn & dyspepsia: Non-absorbable antacids like aluminium hydroxide or magnesium trisilicate can be used. If taken in early pregnancy, there is an increased risk of congenital malformations.[8] Sucralfate, H_2 blockers and bismuth subsalicylate are safe.[1]
Constipation: Bulk laxatives containing bran, isapghula or methylcellulose are best for simple constipation. Stimulant laxatives may be uterotonic and hence are contraindicated.[8]
Common cold: Antihistaminics (non-sedating - loratadine, fexofenadine & cetirizine; sedating - chlorpheniramine, diphenhydramine) can be used. Oral decongestants - phenylephrine & pseudoephedrine can be used.[8]
Cough: Expectorants - guafenesin, ipecac, terpin hydrate can be used. Antitussives - codeine & dextromethorphan are effective.[8]

ii. Pre-existing or pregnancy aggravated medical illnesses

Bronchial asthma: Short acting beta sympathomimetics – salbutamol, terbutaline. Adv effects – maternal & foetal tachycardia, maternal hyperglycaemia and foetal hypoglycaemia. Long acting beta sympathomimetics – salmeterol – 2 puffs every 12 hrs.[8]

Inhaled steroids – beclomethasone dipropionate, budesonide are used. There is an increase in pre-eclampsia in asthamatic women treated with oral steroids. Nedocromil – inhaled anti-inflammatory agent with no systemic side effects.[8]

CVS diseases: Hypertension – methyldopa is the 1st line drug. It is safe throughout pregnancy. Side effects include drowsiness, depression and postural hypotension. Beta blockers like atenolol, acebutolol and labetolol should not be preferred during first 28 weeks. For hypertensive emergencies hydralazine 5-10 mg IV or labetolol 20 mg IV are useful. **(8)**

Heart failure – digoxin is drug of choice for maternal atrial flutter or fibrillation. Quinidine is relatively safe during late pregnancy to treat supraventricular tachycardia & some ventricular arrhythmia. **(8)**

Anticoagulants – Heparin is the drug of choice. **(8)**

Thrombolytic agents – Streptokinase, urokinase & t-PA are safe.[8]

CNS diseases: Epilepsy – Women with epilepsy are at an increased risk of having fetal malformations even without an exposure to an anticonvulsant medication. **(8)** Phenobarbitone, phenytoin and carbamazepine may be used during pregnancy. All the three drugs have some side effects as well as birth defects. Valproate is contraindicated during pregnancy. **(1)** All the epileptic pregnant women must receive folic acid 5 mg/day throughout pregnancy to reduce the risk of birth defects.[8]

Other psychotropic drugs – diazepam is not found to increase foetal anomalies. Lorazepam and midazolam are

not linked to adverse fetal outcomes other than transient sedation at birth. Alprazolam is used for panic disorders.[8] Chronic intake of BZD's is associated with withdrawal symptoms in the neonate.[1]

Anti-depressants – SSRI's (Fluoxetine & Sertraline) have not been found to cause birth defects. Tricyclic antidepressants cause limb deformities in 1st trimester.[8]

Anti-psychotic agents – Chlorpromazine and other phenothiazines cause no increased risk of malformations. Infants born to schizophrenic mothers are independently at an increased risk of malformations.[8] Lithium use is associated with neonatal goitre, CNS depression, hypotonia ("floppy baby" syndrome) and Ebstein's malformation. However the Ebstein's anomaly is detectable by USG and can be surgically corrected after birth.[9]

Diabetes mellitus: Diet restriction and insulin therapy should be initiated if needed. Oral hypoglycaemics cause fetal hyperinsulinaemia and are hence not used. They also increase malformations if taken in early pregnancy.[8]

Thyroid disorders: For thyrotoxicosis, Propylthiouracil is preferred to carbimazole, due to its greater protein binding capacity which allows less transfer to the foetus. Although Propylthiouracil associated liver failure in pregnancy may favour the use of Methimazole. Stable iodine and radioactive iodine are strictly contraindicated.[1,4]

Antibiotics & other antimicrobial agents: Beta lactam antibiotics are safe.[1] Cephalosporins have a short half-life and are safe. Aztreonam is also safe.[8]

Erythromycin base is safe but estolate should be avoided for fear of hepatotoxicity. Chloramphenicol is absolutely contraindicated as it can cause fetal bone marrow toxicity and grey baby syndrome in the neonate.[1]

Tetracyclines are avoided due to toxicity of teeth and bones. Co-trimoxazole is avoided in 1st trimester due to trimethoprim content and in 3rd trimester due to sulphonamide content (sulphonamide can cause kernicterus in the neonate by displacing bilirubin from albumin).[1]

Aminoglycosides are ototoxic to the foetus and should be avoided. If needed to treat systemic infection in mother, gentamicin or tobramycin is preferred.[1]

Nitrofurantoin for UTI; it is however associated with G6PD related hemolysis. Quinolones are best avoided.[8]

Tuberculosis – Rifampicin, Isoniazid & Ethambutol are safe. Ethambutol should be avoided during first 6-8 weeks. Pyridoxine supplements should be given with Isoniazid. Streptomycin is ototoxic and should be avoided.[1,4,8]

Antifungal agents – nystatin, miconazole and clotrimazole are used for monilial infections.[8]

Antiviral agents – acyclovir for primary herpes & possibly varicella infections. Zidovudine is safe.[8]

Antimalarials – chloroquine is safe. Quinine may be used to treat chloroquine resistant malaria. Primaquine is avoided as it may cause hemolysis in G6PD deficient individuals.[4]

Antiparasitic agents – lindane for treating scabies & lice.[8] Amoebiasis is treated with metronidazole, diodoquin and diloxanide. Large dose, short term therapy should be avoided.[1]

Anaesthetic agents: None of the currently used agent is a known teratogen.[8] Local anaesthetics if accidentally injected in frontal scalp during paracervical block can result in convulsions in the neonate.[4]

Vitamins: Large dose of vitamin K for prophylaxis against haemorrhagic disease of the newborn may result in hemolysis, jaundice and hepatoxicity. Vitamin A in large doses may produce kidney malformations, neural tube defects and hydrocephalus.[4]

DRUG USE IN LACTATION

Maternal medication use during pregnancy and medication use during breastfeeding are 2 different & unique situations. Almost all medications taken by a breastfeeding mother will enter the milk to a certain degree. The majority of them are found in such low doses in the breast milk that they have no clinical relevance for the infant. **(10)** Formula feeding is associated with higher morbidity and mortality in all socioeconomic groups.**(2)** Breast feeding is important not only from nutritional point of view but it also supplies IgA & IgM immunoglobulins which afford protection against gastroenteritis.[1]

Factors determining drug passage into milk

- Lipid solubility, pKa and protein binding capacity of the drug are important factors.[4]
- Drugs pass from maternal plasma into milk most often by passive diffusion, although active diffusion may occur in a few cases; e.g. Iodide.[1,10]
- The pH of milk is slightly lower than plasma (6.8 - 7.3). So drugs that are weak bases become more ionized with decrease in pH and tend to have a higher concentration in breast milk.[1,10]
- Maternal drug level is a prominent determining factor which influences passage and concentration of the medication in the breast milk. Drugs which are

highly protein bound are less likely to be transferred from maternal circulation into milk.[10]

Milk to plasma ratio (M/P ratio)

It is the ratio of drug concentration in breast milk to drug concentration in maternal plasma. A high M/P ratio indicates more drug in the breast milk.[10]

Some drugs may be having a high M/P ratio but are not orally bioavailable to the infant. On the other hand, clearance of medications is impaired in very young & premature infants. Conversely a drug with a high clearance rate could result in a low level of exposure for an infant, even with a high M/P ratio.[10]

Even for a lipid soluble, poorly protein bound, basic drug the M/P ratio does not exceed 4. Hence drug toxicity based on the principal pharmacological action of the drug is considered unlikely in breast fed infant. However toxicity based on idiosyncrasy or a particular sensitivity of the infant to very low doses may occur.[1]

Individual drugs

Analgesics: Ibuprofen – safe; Indomethacin – low transfer rate in milk; seizures have been reported in some cases. Aspirin is safe for short term dosing; theoretical risk of Reye's syndrome. Paracetamol – very little excretion in breast milk and is well tolerated by neonates and infants.[10]

Opioids: Morphine & fentanyl – low oral availability; safe. Meperidine – may cause seizures; codeine – sedation rarely.[10]

Anticoagulants: Heparin – safe; warfarin – highly protein bound, safe but observation needed.[4,10]

Corticosteroids: If given in large doses for extended periods can pose the danger of suppressing growth of the infant. They also interfere with endogenous steroid production of the infant.[4]

Antimicrobials: Penicillins – safe; may cause loose stools. Cephalosporins & Erythromycin – safe.[10]

Aminoglycosides are not considered dangerous as they are not absorbed from the gut.(1)

Sulphonamides – should be avoided in mothers whose infants have G6PD deficiency or hyperbilirubinaemia. If necessary, sulfisoxazole may be used as it is excreted in lowest amounts.[10]

Tetracyclines – amount absorbed by the infant is insignificant as it is precipitated by calcium in the milk. So it is safer upto 10 days. Long term use may however cause staining & mottling of teeth.[4,10]

Chloramphenicol is contraindicated.[10]

Chloroquine – retinal damage in infant.[1]

Metronidazole – if critically needed, a single dose regimen of 2 g may be given and breast feeding suspended for 24 hrs. Pumping & discarding the breast milk should be done during this period.[4]

Ketoconazole – being highly protein bound is safe. Acyclovir – safe.[10]

DRUGS TO BE AVOIDED DURING LACTATION

Drugs absolutely contraindicated are – anticancer drugs, radiopharmaceuticals, ergot & its derivatives (methysergide etc.), chloramphenicol, phenylbutazone, thiouracil, iodide and mercurials.[4]

Drugs with documented untoward effects on the breastfed infants –

Acebutolol – hypotension, tachypnoea; Atenolol – hypotension & cyanosis; Propranolol is the preferred alternative.[10]

Clemastine – drowsiness, feeding problems & neck stiffness; Cetirizine & Loratadine are safer alternatives.[10]

Amiodarone – long term use necessitates close monitoring & measurement of thyroid and CVS functions in infants.[10]

Chlorpromazine – sedation & decline in developmental score; Haloperidol – decline in developmental score.[10]

Diazepam – Midazolam is preferred as it has low oral bioavailability. Lamotrigine – infant plasma level should be monitored.[10]

Clofazimine – red tint & pigmentation of skin.[10]

Ephedrine – irritability.[1]

Aminophylline (200 mg or more) every six hours – irritability.[1]

Oral contraceptives – containing estrogen & progesterone may cause decrease in milk supply. Physicians should consider a progestin only agent or barrier methods as alternatives.[8] Also breast enlargement can occur in a male infant.[4]

Drugs which suppress or inhibit lactation are – Bromocriptine, Estradiol, large doses of oral contraceptives, Levodopa, Trazodone and Bendroflumethiazide.[4]

If the nursing mother must take medication and the drug is a relatively safe one, she should optimally take it 30 - 60 minutes after nursing and 3 - 4 hrs before the next feeding.[2,10]

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REFERENCES

1. Satoskar RS, Bhandarkar SD, Rege NN. Drugs, pregnancy and the infant. In: Satoskar RS, Bhandarkar SD, Rege NN, editors. Pharmacology and pharmacotherapeutics. 21st ed. Mumbai, India: Popular Prakashan Pvt. Ltd; 2009. p. 1094-104.
2. Koren G. Special aspects of perinatal & pediatric pharmacology. In: Katzung BG, Masters SB, Trevor AJ, editors. Basic and clinical pharmacology. 11th ed. New Delhi. Tata McGraw Hill; 2009. p. 1025-36.
3. Hodgson E. A Textbook of Modern Toxicology. 4th edition. John Wiley and Sons: New Jersey; 2010. p:268.
4. Mittal S, Seth V. Drugs in pregnancy and lactation. In: Seth SD, Seth V, editors. Textbook of pharmacology. 3rd ed. New Delhi: Elsevier; 2009. p. XV.3-12.
5. van Gelder MM, van Rooij IA, Miller RK, Zielhuis GA, de Jong-van den Berg LT, Roeleveld N. Teratogenic mechanisms of medical drugs. Hum Reprod Update 2010;16:378-94.
6. Tripathi KD. Adverse drug effects. In: Tripathi KD, editor. Essentials of medical pharmacology. 6th ed. New Delhi: Jaypee Brothers; 2008. p. 85.
7. Davis DB. Drugs in pregnancy--the issues for 2010. J Popul Ther Clin Pharmacol 2010;17(3):e332-5.
8. Mittal S, Gupta MM. Drugs used in pregnancy. In: Kohli K, Gupta M, Tejwani S, editors. Contemporary perspectives on clinical pharmacotherapeutics. 1st ed. New Delhi: Elsevier; 2006. p. 744-54.
9. Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Brunton LL, Chabner BA, Knollmann BC, editors. Goodman & Gilman's The pharmacological basis of therapeutics. 12th ed. New York: Mc Graw Hill; 2011. p. 417-55.
10. Della-Guistina K. Special considerations for drugs used during breastfeeding. In: Kohli K, Gupta M, Tejwani S, editors. Contemporary perspectives on clinical pharmacotherapeutics. 1st ed. New Delhi: Elsevier; 2006. p. 755-66.

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