Volume : 2 | Issue : 6 | June 2013 • ISSN No 2277 - 8179

Research Paper

Special Aspects of Pregnancy Medication

Medical Science

KEYWORDS : pregnancy, medication, placental transfer, teratogenic effects

Dr. Sowmya Sham Kanneppady	Post Graduate Student, Department of Pharmacology, KVG Medical College and Hospital, Sullia, Karnataka, India.
Dr. S. Vijaya Raghavan	Professor & Head, Department of Pharmacology, KVG Medical College and Hospital, Sullia, Karnataka, India.
Dr. Manohar Harle	Professor, Department of Pharmacology, KVG Medical College and Hospital, Sullia, Karnataka, India.
Dr. Sham Kishor Kanneppady	Reader, Department of Oral Medicine and Radiology, Century International Institute of Dental Sciences and Research Centre, Poinachi, Kasaragod, Kerala, India.

ABSTRACT

Treating pregnant women presents a unique problem in which drugs are given to treat mother but fetus too becomes recipient. In addition certain physiological changes which occur during pregnancy result in pharmacokinetic variations of prescribed drug. Thus special caution has to be taken while prescribing medication to pregnant women. This review considers teratogenic aspects of drugs given during pregnancy.

Introduction

Drug therapy during pregnancy is one of the most neglected areas in drug development and clinical pharmacology. Treating pregnant women presents a unique problem in which drugs are given to treat mother but fetus too becomes recipient. [1] Avoiding medication is desirable but it is not possible because some women enter pregnancy with previous medical conditions (like bronchial asthma, epilepsy, migraine) and some may develop new medical conditions (like gestational diabetes, hyper/hypothyroidism, hypertension) which require prompt pharmacological interventions. Failure to manage such conditions can adversely affect the health of mother and fetus. [2] While treating pregnant women, placental transfer of drugs leading to teratogenic effects on the fetus is the major concern and we must keep in mind two separate individuals, mother and fetus, decision must be based on risk benefit ratio of both.

The pharmacologic and toxic effects of drugs on the mother and the fetus are governed by a complex but integrated set of variables consisting of mother, uterus, placenta, amniotic fluid and fetus. During pregnancy, as the above mentioned components are constantly and dynamically change, treating pregnant women presents pharmacological challenge to clinicians. For ethical reasons, human fetus is beyond the reach of pharmacological investigations, thus experimental animals have been widely used to seek pharmacologic and toxicological data. [1]

The concern about medication use during pregnancy and lactation had been influenced by historical events, including thalidomide crisis in 1960's and the teratogenic effects discovered related to the use of diethylstilboestrol in 1971. [3] Thus, in 1979 Food and Drug Administration (FDA) developed a system that classifies drugs given during pregnancy into 5 categories A, B, C, D and X (Table 1).

Frequency of drug use in pregnancy

Vitamins especially folic acid, minerals, iron and dietary supplements are essential for the health of mother and fetus which must be prescribed to all pregnant women. 8% of pregnant women need drug treatment due to various chronic diseases and pregnancy related complications. [4] About 13% of pregnant women take dietary herbal supplement [5] and 59% of pregnant women are prescribed medication other than vitamin or mineral supplement. More than 90% of pregnant women take prescription or nonprescription (over-the-counter) drugs or use social drugs such as tobacco or alcohol or illicit drugs at some time during pregnancy. [6]

Pharmacokinetic changes during pregnancy

Pregnancy is a state in which unique physiological changes do occur which can affect the pharmacokinetic aspects of prescribed medication. These changes include gastric emptying and small intestine motility, which is reduced in pregnancy due to elevated progesterone. An increase in gastric pH increases ionizations of weakly acidic drugs decreasing their absorption. An increase in the cardiac output and tidal volume increases the alveolar uptake of the drugs administered through inhalational route, requiring lesser dose of volatile anesthetic if required during pregnancy. Drug absorption from intramuscular delivery is usually enhanced by increased tissue perfusion secondary to vasodilatation. [7] An increase in the plasma volume by 30-50% increases the cardiac output, renal blood flow and glomerular filtration rate which lead to sub therapeutic levels of drug in plasma as a result of dilution of plasma and also due to increased clearance of drugs excreted by the kidney. Increase in the total body fat increases the volume of distribution of fat soluble drugs especially in last trimester. Decrease in the plasma albumin level and lower affinity of proteins to bind with the drug result in increase of free unbound drug which is easily metabolized and excreted. This unbound free drug is also available for transfer of drug across the placenta. Mean maternal plasma levels of antibiotics such as ampicillin, cefazolin, kanamycin, and gentamycin are lower during pregnancy than when not pregnant. [8] A decrease in plasma albumin concentration during pregnancy increases the volume of distribution for highly protein bound drugs e.g. anticonvulsants. [2] Examples of drugs with decreased protein binding and increased free fractions during pregnancy are diazepam, salicylic acid, sulfisoxazole, and phenytoin. [8] This increase in free fraction did not correlate entirely with decrease in albumin but also was related to increase in nonesterified fatty acids which further displace drugs from its binding sites. [9] Concurrent use of other common medications during pregnancy such as antacids, iron and vitamins could also bind and inactivate some drugs.

Placental transfer of drugs

For a drug to cause its effects on the fetus it must cross placenta which acts as a semi permeable barrier. [2] Passage of drug across the placenta is governed by following factors:

1. Plasma protein binding: As the maternal plasma albumin level decreases and it has lower affinity to bind with the drug, it increases the free unbound concentration of drug which crosses the placenta. On the fetal side though fetal albumin level is 15% higher than maternal albumin but it has lower affinity to bind with drugs, again increasing the

Volume : 2 | Issue : 6 | June 2013 • ISSN No 2277 - 8179

levels of free unbound drug.
2. pH difference: Fetal plasma is slightly acidic than maternal plasma. Weakly basic drugs and unionized free forms of drugs cross the placenta. [10] Once it crosses placenta, the drug gets ionized in fetal acidic environment leading to ion trapping.
3. Lipid solubility and ionization: Highly lipid soluble, less ionized drugs easily cross the placenta.
4. Molecular weight: Drugs with high molecular weight (>1000MW) cross placenta poorly. For example, heparin having a large molecular weight of >5000MW crosses placenta poorly.
5. Placental transporters: Most drugs cross the placenta by simple diffusion, but some are transported by placental transporters. Many transporters are present on the brush border (maternal facing) membrane and basal membrane (fetal facing) of syncitiotrophoblast which function to transport either physiological substrates or xenobiotics. ATP Binding Casettee Transporters are the group of efflux transporters which extrude the xenobiotics entering the fetal compartment, thus protecting the fetus from toxic or teratogenic effects. They are p-glycoprotein (P-gP), BCRP, multidrug resistance proteins 1, 2 and 3 (MRP1, MRP2 and MRP3 respectively). It may be preferable to treat pregnant women with drugs that are P-gP such as paclitaxel.

Placenta acts as a site of metabolism. Prednisolone and hydrocortisone are metabolized by the placenta to inactive compounds. In fetus, oxidative dealkylation is more efficient than hydrolysis. CYP3A7 is mostly expressed in the fetal liver but CYP2C proteins are absent in the fetal liver. Hydroxylation of tolbutamide and demethylation of diazepam depend on CYP2C activity. CYP1A2 and CYP2D6 are not expressed in the fetus and *N*-demethylation of caffeine and theophylline is particularly deficient (CYP1A2 is involved). Glycine and sulfate conjugation are more efficient than glucoronide conjugation. Phenytoin, phenobarbitone, tolbutamide and nalidixic acid have a longer half-life in neonates than in adults. Trapping effect of drugs in the amniotic fluid after excretion by the fetal kidney occurs because of slow equilibrium between fetal and maternal compartments. Fetal swallowing may allow certain drugs to be recirculated.

Fetal effect of use of drugs in pregnancy

Drugs are given to treat the mother for certain conditions that arise during pregnancy. Some drugs are given by keeping fetus as targets of drug action. For example corticosteroids are given to cause lung maturation in expected preterm labor. Drugs which have the potential to cause teratogenic effects are the major concern while treating pregnant women. There are three periods in fetal development for drug-related teratogenic and toxic effects: (1) fertilization and implantation (days 0 to 17): at this stage a fetotoxic agent have all or none effect. Either they cause death of the embryo and spontaneous abortion which leads to delayed menstruation or embryo is not effected resulting in normal pregnancy (2) organogenesis (days 18 to 55): this is the most sensitive period for development of malformations; and (3) fetal period (56 days to birth): in this stage, drugs can decrease cell size and number or affect the organization of the cerebral cortical layers. [11]

Treating pregnant women with safer drugs

Drugs should be avoided for minor manageable ailments. If a drug has to be used, prescribe one whose safety in pregnancy is already known (Table 2), which exists in a market for a long period than using a new drug of which safety profile is unknown. Use single drug instead of unnecessary combinations. It is necessary to use non-teratogenic drugs instead of teratogenic drugs whenever possible. For example, use heparin as an anti-coagulant instead of warfarin which has a definite risk of teratogenecity.

Conclusion

Drugs are required to treat certain medical conditions present in pregnant women. Not all the medications are harmful to the fetus. Our knowledge regarding the possible fetal risk allows us to avoid those medications and select the alternative drugs. Using medications which are substrates for efflux transporters will minimize the fetal exposure. Understanding the physiological changes and pharmacokinetic variation of drugs in pregnancy allows us to modify the dose of drug to attain maximum therapeutic effect in this special population.

Tables

Table1. FDA risk categories of pregnancy

FDA Categories	Explanation and examples
A	Human studies show no fetal risk- safest drugs which includes prenatal vitamins
B	Animal studies have failed to show fetal risk, adequate human studies are lacking or human studies have failed to show teratogenic risk, but animal studies have shown risk to the fetus. E.g. penicillin, cefaclor, paracetamol
C	Lack of adequate studies both in human and animal fetuses or have shown adverse effects but potential benefits outweigh the risk. E.g. morphine, codeine, corticosteroids, adrenaline
D	Evidence of fetal risk in humans, but potential benefits may be acceptable despite the risk. E.g. phenytoin, valproate
X	Contra indicated drugs during pregnancy, risk clearly outweighs the benefits E.g. isotretinoin, warfarin

Table 2. Safer drug alternative while treating pregnant women

Drug class/ conditions in pregnancy	Safe drugs
Nausea and vomiting	High carbohydrate diet, doxylamine and pyridoxine combination , anti histaminics like promethazine, cyclizine
Gastritis and GERD	Antacids and metoclopramide are safer
Constipation	High fibre diet with plenty of fluids, Ispaghul, lactulose can be given
Tuberculosis	Isoniazide
Malaria	Chloroquine, proguanil
Hypertension	Alpha methyl dopa, labetalol, atenolol, pindolol, nefidipine
Deep vein thrombosis/ thromboembolism	Heparin/LMW heparins
Diabetes	Dietary restrictions and human insulin
Thyrotoxicosis	Propylthiouracil preferred over carbimazole
Epilepsy	Phenobarbitone, phenytoin and carbamazepine may be used. vitamine K1 and folic acid supplementation along with the above anti-epileptic agents
Systemic bacterial infection	Penicillin G, ampicillin, amoxicilline-clavulanate, cloxacillin, cephalosporins,
Hypothyroidism	Thyroxine
Antidepressants	Fluoxetine
Bronchial asthma	Inhalational salbutamol, salmeterol, budesonide, beclomethasone, sodium chromoglycate

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