Guest Editorial

DRUGS IN PREGNANCY: AN UPDATE

In order to simplify the criteria whether a drug can be used during pregnancy or not United States Food and Drug Administration (USFDA) has classified all the drugs into five categories. Categories A and B medications usually are considered safe in humans. Category C drugs have not been definitively shown to be unsafe to human fetuses, but reasons exist to be cautious while prescribing them. Category D drugs are those with evidence of human fetal risk based on previous human studies, but the benefits of treatment prevail over the risks.

United States Food and Drug Administration Classification System (US-FDA)

FDA *category*	*Pregnancy category definition*
A	Controlled studies showed no risk to humans.
	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	No evidence of risk in humans.
	Animal studies have revealed no evidence of harm to the fetus. However, there are no adequate and well-controlled studies in pregnant women.
	or
	Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Risks cannot be ruled out in humans.
	Animal studies have shown an adverse effect, and there are no adequate and well-controlled studies in pregnant women.
	or
	No animal studies have been conducted, and there are no adequate and well-controlled studies in pregnant women.
D	Clear evidence of risk in humans.
	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Drugs contraindicated in human pregnancy.
	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

The decision whether to recommend a drug for a pregnant woman or not, must be made by the physician while considering many factors like route of administration, gestational age of the fetus or embryo, absorption rate of the drug, whether the drug crosses the placenta or not, the necessary effective dose of the drug, molecular weight of the drug, whether monotherapy will suffice or if multiple drugs are required to be effective, and also the mother's genotype. Potential harm to the mother on stopping or not prescribing the drug at all is of utmost importance among these factors along with the risk to the fetus. The decision therefore totally depends upon, 'Does the benefit of the drug outweigh over its risks?'

In the Indian setup, most of the pregnancies are complicated by infections and therefore deciding upon which antibiotic to use has always been a dilemma.

What makes antibiotic usage during pregnancy even trickier is the fact that there are marked and progressive physiological changes during pregnancy, and the drug disposition can be altered. Some of these are as follows:

- Gastrointestinal motility is impaired and therefore drug absorption is reduced.
- Volume of drug administration is increased as plasma volume is expanded.
- Due to decrease in serum albumin and increase in α-1 acid glycoprotein the unbound fraction of acidic drug increases while that of basic drugs decreases.
- Renal blood flow is markedly increased and hence increased clearance of the drugs.
- Due to induction of the hepatic microenzymes many of the drugs are cleared rapidly.

Drugs can affect the Fetus at Three Stages

Before day 31: During this phase, drug produces all or none effect. The conceptus either survives without anomalies or does not survive at all. As there are only few cells during this early stage, so any damage at this stage is either irreparable or lethal.

Day 31 to day 71: This is the most critical period for organ formation and most of the teratogenic effects are therefore precipitated during this phase.

Day 71 onwards: During this phase, growth of the organs formed during organogenesis occurs and teratogenic effects can occur but are less common than the second phase.

Although a large number of studies have been conducted by researchers and the pharmaceutical companies till date, the license to market the drug is usually obtained before its long-term effects have been studied. Therefore, the usage of antibiotics must be individualized depending upon the patient requirements.

Individual Drug Status and Considerations during Pregnancy

Drugs	*Consideration*	*Teratogenecity*	*Category*
Cephalosporins			
Cefazolin	Safe	No teratogenecity	B
Cefadroxil			B
Cephalexin			B
Cefuroxime			B
Cefaclor			B
Cefotaxime			B
Ceftazidime			B
Cefixime			B
Cefriaxone	Safe Can interfere with hemostasis due to its hypoprothombinimic action.	No Vitamin K should be given to infant if given near to term.	B
Cefoperazone	Safe Can derange liver enzymes and can interfere with hemostasis by having similar effect as that of ceftriaxone.	No	B
Cefpirome	Can derange liver enzymes and can lead to eosinophillia, thrombocytopenia.	No	B
Penicillins are considered safe Can be used with beta lactamase inhibitors like clavulanic acid and sulbactum			
Amoxicillin	Should be avoided in women at risk of preterm delivery due to increased risk of neonatal necrotizing enterocolitis.	No	B
Ampicillin	Safe	No	B
Methicillin			B
Piperacillin			B
Mezlocillin			B
Cloxacillin			B
Carbenicillin	Safe to use however can lead to pregnancy induced hypertension and interferes with platelet function.	No	B
Meropenem	Safe	No human data; however, there is no evidence of	B
Ertapenem		increased risk of major congenital malformations with other beta-lactam antibiotics.	B
Sulfonamides	Contraindicated	Association with neural tube defects (NTDs), cardiovascular malformations and facial cleft as a result of antifolate effect. In third trimester, as they increase the risk of kernicterus in the fetus.	C
Tetracyclines	Contraindicated Can lead to acute fatty liver of pregnancy.	Can lead to yellowish discoloration of teeth and growth retardation due to its deposition in small bones.	D
Chloramphenicol	Contraindicated	No	C

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Macrolides	Can be used	Not expected to increase risk of major congenital Malformations.	B
Azithromycin			
Clindamycin			B
Clarithromycin			C
Vancomycin	Should be avoided, associated with maternal nephrotoxicity and ototoxicity?		C
Nitrofurantoin	Should be avoided.	Papillary adenomas and growth retardation in neonates.	C
Tigecycline	No reports on use during human pregnancy. Tigecycline is structurally related to tetracycline and thus should be avoided after 15 weeks of gestation.	Use of an alternate agent with a known safety profile would be preferred.	D
Aminoglycosides			
Amikacin	Contraindicated	Theoretical risk of ototoxicity and nephrotoxicity.	D
Gentamicin			D
Tobramycin			D
Kanamycin			D
Streptomycin			D
Flouroquinolones			
Levofloxacin	Contraindicated	Teratogenic effects have been seen in experimental animals like decreased placental light, cartilage lesions and embryonic losses.	C
Norfloxacin			C
Ofloxacin			C
Ciprofloxacin			C
Moxifloxacin			C
Linezolid	Can be used if benefits outweighs the risk?	Not expected to increase risk of major congenital Malformations.	C
Antifungal agents			
Miconazole	Safe if used topically.	Syndactylia, oligodactylia and dystocia have been seen in animals.	C
5-Flucytosine	Use only if the potential benefit outweighs the risk.	Can lead to encephaloceles, macroglossia and major skeleton defects.	C
Ketoconazole	Should be avoided Local application is safe.	Leads to increased placental weight. Has been associated with abortions, supranumery ribs, renal pelvis dilatation and delayed ossification.	C
Itraconazole	Should be avoided.	Associated with increased CNS and skeletal abnormalities.	C
Fluconazole	Inhibits estrogen synthesis in fetus.		C
Griesofulvin	As it interferes with mitosis can lead to formation of conjoined twins if used in 1st trimester.		C
Antivirals			
Acyclovir	Contraindicated for systemic administration.	Head and tail development in lower animal fetuses.	B
Famcyclovir			C
Gancyclovir			C
Amantadine	Use only if clearly indicated.	At high doses may lead to cardiac malformations.	C
Foscarnet	No human data in 1st trimester. Case reports describe treatment in 2nd and 3rd trimester with no adverse effects in the neonates. Should be used only when the benefit outweighs the unknown risk to the fetus. Due to potential for renal toxicity, close follow-up of the fetus and monitoring of amniotic fluid volume is recommended.		C
Antitubercular drugs			
Isoniazid	Safe		C
Rifampicin		When used in last weeks of pregnancy, can lead to postnatal hemorrhage in mothers and infants.	C
Rifabutin			B
Ethambutol		Optic neuritis has not been shown in infant.	C

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Pyrazinamide	Should be avoided.		C
PAS	Has increased incidence of hepatotoxicity in mothers.		C
Ethionamide	Contraindicated	Teratogenic effects have been shown in the animals.	D
Cycloserine	Contraindicated Increased risk of psychosis in mothers		C
Streptomycin	Contraindicated		D
Antimalarials			
Chloroquine	Safe	Not expected to increase risk of major congenital malformations.	C
Quinine			C
Mefloquine			C
Primaquine	Contraindicated Prophylactic administration of this drug should be with-held until after delivery.	Associated with hemolysis in newborn.	C
Artesunate	Limited human data, mostly on use in 2nd and 3rd trimester. Should be used only when the benefit outweighs the unknown risk to the fetus.	Not expected to increase risk of major congenital malformations.	
Drugs used for hyperuricimea			
Allopurinol	Animal studies using high doses have revealed evidence of fetotoxicity and teratogenicity; it is not clear if these effects are a result of direct toxicity or maternal toxicity. There are no controlled data in human pregnancy.	Allopurinol should only be given during pregnancy when benefit outweighs risk.	C
Febuxostat	Febuxostat was not teratogenic in animal studies at high human doses; however, increased neonatal mortality and a reduction in febuxostat is only recommended for use during pregnancy when benefit outweighs risk. The neonatal body weight gain was observed when pregnant rats were treated with oral doses up to 40 times the human equivalent. There are no adequate and well-controlled studies in pregnant women.		C

Commonly used Drugs and Safer Alternatives

Condition/drug	*Safety uncertain* *(strictly contraindicated drugs are marked with asterisk)*	*Safer alternative*
Antiemetics	Domperidone*, ondansatron	Promethazine, doxylamine, dicyclomine, metoclopramide
Antacid	Cimetidine, casapride*, mosapride, lansoprazole	Ranitidine, pantoprazole
Laxatives	Senna, bisacodyl, docusates	Lactulose, isapghul, dietary fibers
Antidiarrhoels	Diphenoxylate atropine, loperamide	Ors
Analgesics	Aspirin, Cox-2 inhibitors, morphine*, tramadol	Paracetamol, ibuprofen (low dose)
Cold cough remedies	Codeine, dextramethorphan	Xylometazoline nasal drops, Chorpheniramine can be given safely
Antiallergics	Cetrizine, fexofenadine, astimazole*	Chlorpheniramine, promethazine
Antiamoebic	Metronidazole, tinadizole	Diloxanide furoate, paramomycin
Antihelmenthic	Albendazole*, mebendazole*, ivermectin, diethylcarbamazine*	Piperazine niclosamide, praziquintel
Anti retroviral	Didanosine, abacavir, indinavir, ritonavir, efavirenz	Zidovudine, lamivudine, nevirapine, nelfinavir, saquinavir
Antihypertensives	ACE inhibitors*, ARBs*, thiazides, furosemide, propanolol	Methyl-dopa, hydralazine, atenolol, metoprolol, nifedipine, prazosin, clonidine
Antidiabetics	Metformin, acarbose*, sulphonylurea*, pioglitazone, gliptins	Preferably insulin to be used, however, metformin and giblencamide have been given successfully in some trials
Antithyroid drugs	Carbimazole, methimazole, radioactive iodine*	Propyl thiouracil
Antiasthamatics	Theophylline, montelukast, systemic corticosteroids	Inhaled agents must be preferred
Antipsychotics	Chlorpromazine, clozapine, olanzapine, resperidone	Haloperidol, trifluperazine
Antidepressants	Dothiepin*, scitalopram, sertraline, trazodone, venlafaxine	Amitriptylline, imipramine, fluoxetine

Antiepileptics in Pregnancy

No drug has been proven to be completely safe in pregnancy however as the seizure itself is harmful to the mother and fetus, it is advised that any patient on antiepileptic drugs should be continued on the same drugs as prescribed before conception. However, if possible valproate should be avoided or switched to some other drugs if pregnancy is to be planned. Carbamazepine, lamotrigine and levitiracetam are relatively safe.

If initiation of antiepileptics is required phenobarbitone is the drug of choice.

Drugs used for Urinary Tract Infections

- Ampicilin, cotrimoxazole can be given.
- Meropenem and piperacillin-tazobactum can be given in resistant cases.
- Nitrofurantoin and flouroquinolones are better to be avoided.

Drugs used for Upper and Lower Respiratory Tract Infections

- Macrolides like azithromycin, clarithromycin can be given safely.
- Cepholsporins, meropenem can be used if associated with septicemia.

Drugs used for Tuberculosis

- Isoniazid, rifampicin, ethambutol can be given safely.
- Safety regarding pyrazinamide (PZA) cannot be assured, but when used for 6 months regimen, the benefits may outweigh the possible risks.
- Streptomycin may cause congenital deafness, as this drug interferes with the development of ear and must be avoided.
- Other injectables like amikacin, kanamycin and capreomycin may also cause fetal nephrotoxicity and ototoxicity and should be avoided.
- Ethionamide and prothionamide are contraindicated in pregnancy, as they are found teratogenic in animal studies.
- Cycloserine crosses placenta, and since its safety in pregnancy is not established, it should be avoided and used only if no other suitable alternatives are available.

Important Note

Readers may find it surprising that though certain drugs are placed in category C yet the comment reads that they are safe since many infections during pregnancy have to be treated carefully and therefore even they are placed in category C they can be used safely.

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