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Clinical Focus on High-Risk Pregnancy

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Medications

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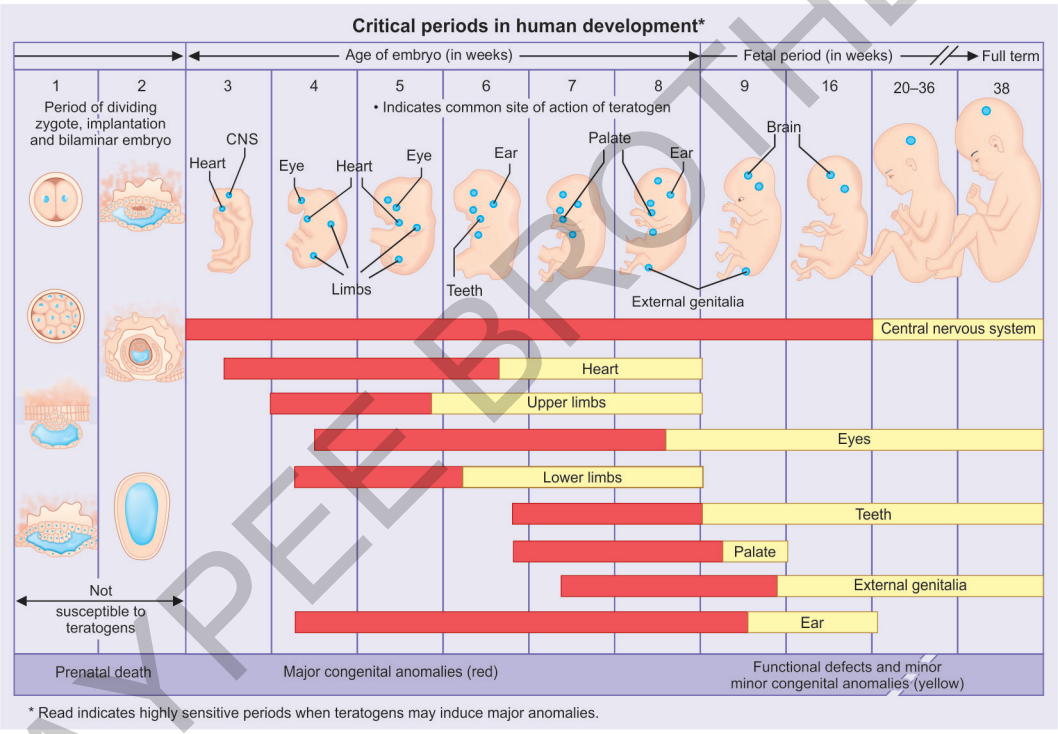
CHAPTER 2

Teratogens

Ruchika Garg, Prabhat Agrawal

INTRODUCTION



* Read indicates highly sensitive periods when teratogens may induce major anomalies.

In order to simplify the criteria whether a drug can be used during pregnancy or not the United States Food and Drug Administration Drug (US-FDA) has classified all the drugs in to 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 **(Table 1)**.

The decision whether to recommend a drug for a pregnant woman or not, must be made by the physician while considering many factors such as route of administration, gestational age of the fetus or embryo,

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TABLE 1: The United States Food and Drug Administration (US-FDA) drug classification system.

*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 • 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 • 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

*FDA categorization of drugs for use in pregnancy.

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:

- 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 α1-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.

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DRUGS CAN AFFECT THE FETUS AT THREE STAGES

1. *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.
2. *Day 31–ay 31:* This is the most critical period for organ formation and most of the teratogenic effects are therefore precipitated during this phase.
3. *Day 71 onward:* 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* **(Tables 1 and 2)**.

TABLE 2: Individual drug status and considerations during pregnancy.

Drug	*Consideration*	*Teratogenicity*	*Category*
Cephalosporins			
Cefazolin	Safe	No teratogenicity	B
Cefadroxil			B
Cephalexin			B
Cefuroxime			B
Cefaclor			B
Cefotaxime			B
Ceftazidime			B
Cefixime			B
Ceftriaxone	• Safe • Can interfere with hemostasis due to its hypoprothrombinemic 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 eosinophilia, thrombocytopenia	No	B
Penicillins are considered safe Can be used with β-lactamase inhibitors such as clavulanic acid and sulbactam			

Contd…

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Drug	***Consideration***	***Teratogenicity***	***Category***
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 increased risk of major congenital malformations with other β-lactam antibiotics	B
Ertapenem			B
Sulfonamides	Contraindicated in third trimester as they increase the risk of kernicterus in the fetus	Association with neural tube defects (NTDs), cardiovascular malformations and facial cleft as a result of antifolate effect	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
Macrolides			
Azithromycin	Can be used	Not expected to increase risk of major congenital malformations	B
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

Contd…

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Drug	***Consideration***	***Teratogenicity***	***Category***
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
Fluoroquinolones			
Levofloxacin		• Teratogenic effects have C • Seen in experimental animals such as decreased placental light, cartilage lesions, and embryonic losses	
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	Syndactyly, oligodactyly, 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, supranumerary ribs, renal pelvis dilatation, and delayed ossification	C
Itraconazole	Should be avoided	Associated with increased central nervous system (CNS) and skeletal abnormalities	C
Fluconazole	Inhibits estrogen synthesis in fetus		C

Contd…

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Contd…

Drug	***Consideration***	***Teratogenicity***	***Category***
Griseofulvin	As it interferes with mitosis can lead to formation of conjoined twins if used in first 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 first trimester • Case reports describe treatment in second and third 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
Pyrazinamide	*Should be avoided* Has increased incidence of hepatotoxicity in mothers		C
PAS			C
Ethionamide	*Contraindicated*	Teratogenic effects have been shown in the animals	D
Cycloserine	*Contraindicated* Increased risk of psychosis in mothers		C
Streptomycin	*Contraindicated*		D

Contd…

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Contd…

Drug	*Consideration*	*Teratogenicity*	*Category*
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 withheld until after delivery	Associated with hemolysis in newborn	C
Artesunate	• Limited human data, mostly on use in second and third 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 hyperuricemia			
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		C
	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		

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

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TABLE 3: Commonly used drugs and safer alternatives.

Condition/drug	*Safety uncertain*	*Safer alternative*
Antiemetics	Domperidone*, ondansetron	Promethazine, doxylamine, dicyclomine, metoclopramide
Antacid	Cimetidine, cisapride*, mosapride, lansoprazole	Ranitidine, pantoprazole
Laxatives	Senna, bisacodyl, docusate	Lactulose, isabgol, dietary fibers
Antidiarrheals	Diphenoxylate atropine, loperamide	ORS
Analgesics	Aspirin, Cox-2 inhibitors, morphine*, tramadol	Paracetamol, ibuprofen (low dose)
Cold cough remedies	Codeine, dextromethorphan	Xylometazoline nasal drops, chlorpheniramine can be given safely.
Antiallergics	Cetirizine, fexofenadine, astemizole*	Chlorpheniramine, promethazine
Antiamebic	Metronidazole, tinidazole	Diloxanide furoate, paromomycin
Antihelminthic	Albendazole*, mebendazole*, ivermectin, diethylcarbamazine*	Piperazine, niclosamide, praziquantel
Antiretroviral	Didanosine, abacavir, indinavir, ritonavir, efavirenz	Zidovudine, lamivudine, nevirapine, nelfinavir, saquinavir
Antihypertensives	ACE inhibitors*, ARBs*, thiazides, furosemide, propranolol	Methyldopa, hydralazine, atenolol, metoprolol, nifedipine, prazosin, clonidine
Antidiabetics	Metformin, acarbose*, sulphonylurea*, pioglitazone, gliptins	Preferably insulin to be used, however metformin and glibenclamide has been given successfully in some trials
Antithyroid drugs	Carbimazole, methimazole, radioactive iodine*	Propylthiouracil
Antiasthmatics	Theophylline, montelukast, systemic corticosteroids	Inhaled agents must be preferred.
Antipsychotics	Chlorpromazine, clozapine, olanzapine, resperidone	Haloperidol, trifluoperazine
Antidepressants	Dothiepin*, escitalopram, sertraline, trazodone, venlafaxine	Amitriptyline, imipramine, fluoxetine

(ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers)
*Strictly contraindicated drugs.

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before conception. However if possible valproate should be avoided or switched to some other drugs if pregnancy is to be planned. Carbamazepine, lamotrigine, and levetiracetam are relatively safe.

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

DRUGS USED FOR URINARY TRACT INFECTIONS

- Ampicillin and cotrimoxazole can be given.
- Meropenem and piperacillin-tazobactam can be given in resistant cases.

- Nitrofurantoin and fluoroquinolones are better to be avoided.

DRUGS USED FOR UPPER AND LOWER RESPIRATORY TRACT INFECTIONS

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

DRUGS USED FOR TUBERCULOSIS

- Isoniazid, rifampicin, and 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 such as 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.

TERATOGENIC DRUGS

To date, very few drugs are proven teratogens. However, malformations induced by drugs are important because they are potentially preventable. Proper prescribing of drugs in pregnancy is a challenge and should provide maximal safety to the fetus as well as therapeutic benefit to the mother.

PLACENTAL TRANSFER

The rate of placental transfer is affected by metabolism and gestational age, and the protein binding, ionization, lipid solubility, and molecular weight of the drug. Almost all drugs are able to pass freely through the placenta, with only those with a molecular weight of >1,000 Da being unable to do so, e.g., insulin and heparin.

TERATOGENICITY

If exposure in utero causes structural or functional abnormalities in the fetus or in the child after birth. Neuropsychological and behavioral abnormalities may also occur after drug exposure. Some antiepileptic drugs and drugs of abuse have been associated with learning and behavioral problems following in utero exposure.

TIMING OF EXPOSURE

During the preimplantation stage, in pregnancy, exposure to a drug is unlikely to produce a teratogenic effect due to an inbuilt "recovery process" in the conceptus. If a teratogenic insult occurs and there is damage to only a small number of cells then "compensation" occurs whereby the remaining viable cells continue to divide to replace any that were damaged.

However, if a large number of cells are damaged then implantation will not occur. This is known as the "all or nothing" or

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totipotent period. The 10 weeks following implantation are the most sensitive as this is the time during which major structural changes and organogenesis are taking place. It is during this period that the neural tube closes and major organs and limbs develop. While the first trimester is the most sensitive period to structural malformations, some drugs may affect the fetus in the later stages of pregnancy, so care should be taken when prescribing throughout pregnancy.

Angiotensin-converting enzyme (ACE) inhibitors in the second and third trimesters can cause serious adverse effects such as oligohydramnios, growth retardation, lung and kidney hypoplasia, and hypocalvaria.

GENERAL PRINCIPLES OF PRESCRIBING IN PREGNANCY

- Involve the woman, and her family where appropriate, in all decisions about treatment.
- Not treating mental illness in pregnancy or the postpartum period may be associated with adverse outcomes.
- Establish a clear indication for drug treatment.
- Choose treatments with the lowest known risk.
- In choosing consider the implications for breastfeeding and the benefits of avoiding the need to switch drugs.
- Use lowest effective dose for the shortest period necessary.
- Be aware of drug interactions, particularly with nonpsychotropics, and aim for monotherapy.
- Where there is no clear evidence-base that one drug is safer than another, the safest option is not to switch. The only drug with a clear indication for switching on safety grounds is valproate.

Be aware of the potential effects of pregnancy and childbirth on drug pharmacokinetics and pharmacodynamics.

Long-term neurodevelopmental effects of psychotropic medications in pregnancy and breastfeeding are extremely limited.

- Close monitoring for change in mental state where a woman decides to cease her usual medication.
- Where there is known risk, ensure that women are offered appropriate fetal screening and monitoring of the neonate for adverse effects.
- Premature or ill babies are more at risk of harmful drug effects.
- Monitor the infant for drug side effects, feeding patterns, growth, and development.
- Caution women against sleeping in bed with the infant, particularly if taking sedative drugs.

The risk posed by drug use in pregnancy can be minimized through prepregnancy counseling. When prescribing for a patient planning pregnancy or a patient who has become pregnant, consideration should be given whether drug is absolutely essential. When prescribing it is important to balance the risk of treatment to the fetus against the risk to both mother and fetus from failing to treat the maternal condition. Each case should be individualized.

All drugs in pregnancy should be prescribed in the lowest possible dose for the shortest possible time.

INTERPRETING PREGNANCY OUTCOME DATA

Robust pregnancy outcome data especially for new drugs are lacking. This is partly due to ethical constraints of enrolling pregnant women into clinical trials.

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TABLE 4: Selected drugs or substances suspected or proven to be human teratogens.

Alcohol	Methimazole
ACE inhibitors	Methylmercury
Aminopterin	Methotrexate
Androgens	Misoprostol
Bexarotene	Mycophenolate
Carbamazepine	Paroxetine
Chloramphenicol	Penicillamine
Chlorobiphenyls	Phenobarbital
Cocaine	Phenytoin
Corticosteroids	Radioactive iodine
Cyclophosphamide	Ribavirin
Danazol	Streptomycin
DES	Tamoxifen
Efavirenz	Tetracycline
Etretinate	Thalidomide
Leflunomide	Tobacco
Lithium	Tretinoin
Valproate	Warfarin

(DES: diethylstilbestrol)

PROVEN TERATOGENIC DRUGS IN HUMANS

Alcohol

The fetal alcohol syndrome is characterized by intrauterine growth retardation (IUGR), microcephaly, developmental delay, and dysmorphic faces. Cleft palate and cardiac anomalies may also occur. Thus, alcohol is one of the most frequent nongenetic causes of mental retardation as well as the leading cause of preventable birth defects in the United States.

Angiotensin-converting enzyme inhibitors (captopril, enalapril, and lisinopril) and angiotensin receptor blockers:

There use in late pregnancy has been associated with renal insufficiency. IUGR, prematurity and complications of oligohydramnios (fetal limb contractures, lung hypoplasia) have been reported with their use in late pregnancy. Teratogenic risk with first trimester use of them appears to below.

Carbamazepine: Exposure causes 1% risk of neural tube defects (10 times their baseline risk).

Phenytoin: It causes fetal hydantoin syndrome with craniofacial dysmorphology, growth retardation and cardiac defects.

Valproate: First trimester exposure is associated with neural tube defects.

Cocaine: It is associated with abruption placentae, prematurity, fetal loss, decreased birth weight, microcephaly, and limb defects.

Coumarin anticoagulants (warfarin): The critical period of exposure for the *fetal warfarin syndrome* appears to be between 6 and 9 weeks of gestation. Second and third trimester exposure is associated with hemorrhage leading to disharmonic growth and deformation.

DES: Clear cell adenocarcinoma of vagina is associated with first trimester exposure. Hypoplastic, T-shaped uterine cavity, and septa are also reported.

Antineoplastic Agents

Folic acid antagonists: Aminopterin and methotrexate.

Central nervous system (CNS) defects facial anomalies and mental retardation occur following first trimester exposure. After a review of 20 first-trimester exposure, Feldkamp and Carey (1993) calculated that a doses of 10 mg/week is necessary to produce abnormalities.

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Cyclophosphamide: First trimester use is associated with missing and hypoplastic digits, cleft palate, and imperforate anus. Nurses who administer cyclophosphamide may be at increased risk for fetal loss, but there are no adequate epidemiological studies.

Isotretinoin: It is prescribed for acne and causes a pattern of anomalies called retinoic acid embryopathy.

Psychiatric Medications

- *Lithium:* Ebstein's anomaly (a rare malformation of tricuspid value) is caused by it.
- *Selective serotonin reuptake inhibitors (SSRIs): Paroxetine* exposure is associated with congenital cardiac malformations and persistent pulmonary hypertension in the newborn. *American College of Obstetricians and Gynecologists* (2007) concluded that SSRIs are not major teratogens and treatment must be individualized.

Misoprostol

First-trimester exposure is associated with limb defects with or without *Moebius sequence*.

Prescribing Misoprostol in Obstetrics and Gynecology

Routes of administration: Oral, vaginal, sublingual, buccal, or rectal.

Vaginal misoprostol is associated with slower absorption, lower peak plasma levels, and slower clearance, similar to an extended-release preparation.

Vaginal misoprostol is also associated with a greater overall exposure to the drug [area under the curve (AUC)] and greater effects on the cervix and uterus.5 There is, however, a wide variation in the absorption of misoprostol through the vaginal epithelium among different women. *There is no clinically significant difference between vaginal misoprostol that is administered dry and vaginal misoprostol moistened with water, saline, or acetic acid.*

Misoprostol is considered a teratogen. The absolute risk of congenital malformations is 1%.

Breastfeeding: Misoprostol is excreted into breast milk levels become undetectable within 5 hours of maternal ingestion. Women should be advised that misoprostol may cause infant diarrhea.

Tetracycline: Yellowish brown discoloration of teeth may occur with exposure of drug after 17 weeks of gestation.

Hormones

Androgenic progestins: Norethindrone (a progesterone only contraceptive) causes virilization of 1% of exposed female fetus.

Androgens: Exposure of a female fetus to anabolic steroids results in varying degrees of virilization.

Danazol: Virilization of female fetus.

Corticosteroids

First trimester exposure is associated with increased incidence of facial clefts. However, they are not considered to represent a major teratogenic risk.

Methylmercury

Prenatal exposure is associated with developmental delay and neurological

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abnormalities. Ingestion of contaminated fish (enters the echosystem through industrial pollution) may expose the fetus to it.

Antivirals

- *Ribavirin:* It is highly teratogenic in all animal species studied.
- *Amantadine:* There is possible association with cardiac defects.

POSSIBLE TERATOGENIC DRUGS IN HUMANS

- *D-penicillamine*—connective tissue disorders (cutis laxa).
- *Methimazole*—scalp defects (aplasia cutis congenita).
- *Diazepam*—first trimester exposure has been associated in small studies with a small increase in the incidence of cleft lip and palate. Larger studies did not confirm the association.

Fluconazole and Itraconazole

There have been several reports of skull abnormalities and limb defects with their exposure. Despite this large cohort studies suggest that neither drug is teratogenic.

Leflunomide: It is used to treat rheumatoid arthritis. In animals, its use is associated with hydrocephalus, skeletal anomalies.

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Clinical Focus on
High-Risk Pregnancy


Neharika Malhotra


Jaideep Malhotra


Narendra Malhotra


Ashwini Kale


Shreya Prabhoo


Sheeba Marwah


Jaydeep Tank

Every pregnancy is high risk and we need to have protocols to assess anatally and flag the risk factors. This book simplifies the management of high risk pregnancy.

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