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Review Article

Drug safety in pregnancy

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Abstract

The safety of drug use in pregnancy is often an enigma. Pregnant women are a particularly vulnerable population and health-care professionals should be familiar with the medications that can be used. Patient's apprehension about drug use in pregnancy is also an important concern. This article is framed with a motive to discuss the commonly used drugs and their safety profiles in pregnancy.

Keywords: FDA categories of drugs, drug use in pregnancy, drug safety in pregnancy

Introduction

Nearly all drugs in pregnancy are used off-label because of the paucity of research and clinical trials. The study of medication use in pregnancy is hampered at least in part by the difficulty of studying this special population given the vulnerability of the developing fetus. In addition, there are numerous physiological changes in pregnancy such as alterations in blood volume, plasma proteins, gastric emptying and transit time that affect the dosing and distribution of drugs. The decision about whether or not to prescribe a medicine depends on the risks and benefits. Ideally the patient and the health-care provider should make the choice together.

To provide therapeutic guidance, a system for rating drug safety in pregnancy was developed in 1979 by the Food and Drug Administration (FDA). The Food and Drug Administration is the oldest comprehensive consumer protection agency in the U.S. federal government whose origins can be traced back to 1848[1]. The system was designed to assist physicians by simplifying risk-benefit information with categories represented by letters that are listed in the classification shown here[2,3,4]. It does not include any risk conferred by the agents or their metabolites that are present in breast milk[3]. The same guidelines are followed in India as well[3].

UNITED STATES FDA PHARMACEUTICAL PREGNANCY CATEGORIES[2,3,4]

- **Pregnancy Category A**: Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)
- **Pregnancy Category B**: Animal reproduction studies have failed to demonstrate a risk to the fetus and 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 in any trimester.

- ❖ **Pregnancy Category C**: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- ❖ **Pregnancy Category D**: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- ❖ **Pregnancy Category X**: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience and the risks involved in the use of the drug in pregnant women clearly outweigh potential benefits.

There is an additional category, **Pregnancy Category N**, which is transitional identification indicating that the FDA has not yet classified the drug into a specified pregnancy category.

Having an overview of the classification, now we enumerate the commonly used medications, their FDA categories and their safety profiles.

I. ANALGESICS

- **NSAIDs** should generally be avoided in pregnancy (despite Category B before third trimester.). First trimester use has been associated with miscarriage risk and premature ductus arteriosus closure has been reported in third trimester. Second trimester use is likely safe[5].
- **Tramadol** should be avoided in pregnancy owing to fetal toxicity reported in animals (highest in first trimester). Respiratory symptoms and with drawl symptoms in newborn have been associated with third trimester use. Second trimester use may be safe[5].
- **Opioids** should be avoided in pregnancy unless there is no viable alternative. First trimester use is especially risky and is associated with heart defects and spina bifida[5].
- **Aspirin** should be used only for specific indications in pregnancy. It is associated with risk of neonatal hemorrhage, IUGR, and perinatal death. Low dose aspirin may be safer[5].

To summarize into FDA categories[3,5] :

- ➢ **Category B**
  : Acetaminophen or Paracetamol (analgesic of choice in pregnancy).
  : NSAIDs (Ibuprofen, Indomethacin, Ketoprofen, Naproxen) in first and second trimester only.
- ➢ **Category C**
  : Barbiturates (Class D if prolonged use or high dose).
  : NSAIDs (low dose Aspirin, Diclofenac, Ketorolac) in first and second trimester only.
- ➢ **Category D**
  : Aspirin
  : All NSAIDs in third trimester.
  : Prolonged use or high dose of any narcotic.
- ➢ **Category X**
  : Ergotamine.

II. ANTI-MICROBIAL AGENTS

ANTIBIOTICS:

Antibiotic use in pregnant women has become an increasing concern due to threat of bioterrorism.

- As a group, **Penicillins** are probably the safest anti-microbial to use during pregnancy[6].
- All **Cephalosporins** cross the placenta although their half-life is likely shorter during pregnancy because of increased renal clearance. As a group, they are listed in Category B[6].
- **Azithromycin** has proven efficacy for treatment of community-acquired pneumonias and chlamydial cervicitis. It is listed as a Category B drug[6].
- **Clindamycin** is also safe and placed in FDA Category B[6].
- **Aztreonam** is a monobactam used primarily as an aminoglycoside alternative[6].
- **Nitofurantoin** is commonly used for urinary infections during pregnancy (Category B)[6].
- Association of "gray baby syndrome" with **Chloramphenicol** and "irreversible arthropathy" with **Fluoroquinolones** keeps these drugs in Category C and are not recommended during pregnancy except for resistant infections[6].
- **Tetracyclines** (Doxycycline) stand in group D and are to be avoided[3].
- Commonly used **tuberculostatic drugs** include rifampicin, isoniazid and ethambutol. Streptomycin should be avoided[3,6].

Classification into FDA Categories is as follows[3,6]:

- **Category B**: Penicillins, Cephalosporins, Azithromycin.
- **Category C**: Chloramphenicol, Ciprofloxacin, Levofloxacin, Gentamicin, Rifampin.
- **Category D**: Doxycycline.

ANTIFUNGALS:

Vaginal candidiasis is common during pregnancy. **Clotrimazole** use is safe[3,6]. **Fluconazole** and **Itraconazole** are Category C anti-fungal agents to be used only in immuno-compromised patients[3,6].

ANTI-MALARIALS:

Most anti-malarials are listed in category C**.**

- **Chloroquine** is a valuable first-line anti-malarial (category C)[3,6].
- **Mefloquine** has been reported safe for chloroquine-resistant malaria[3,6].
- **Quinine** (Category C) and **quinidine** are reserved for severely ill women with chloroquine-resistant malaria[3,6].
- **Artemether-Lumefantrine** has been assigned to Category C by the FDA on the basis of animal data which shows an association with fetal loss and deformity. It is being used for multi-drug resistant strains of falciparum malaria[7].

III. ANTI-EMETICS[3,6,8]

- **Category A**: Pyridoxine(Vitamin B_6), Doxylamine
- **Category B**: Meclizine, Ranitidine, Ondansetron, Metoclopramide
- **Category C:** Promethazine (Phenargan)

- **Pyridoxine or Vitamin B_6,** a water-soluble vitamin and essential co-enzyme in the folate metabolism pathway was first referenced for use in treating nausea and vomiting of pregnancy in 1942. No teratogenic risks have been associated with the use of pyridoxine and it is considered FDA Pregnancy Category A.
- **Antihistamines** are most widely used first-line medication for women who have nausea and vomiting of pregnancy. **Doxylamine** is assigned Category A and **Meclizine** Category B by the FDA.
- Among **H_2-receptor antagonists**, **Ranitidine** is considered safe and listed in Category B.
- Among **dopamine agonists**, **Metoclopramide** has recently been shifted from Category C to Category B.

Promethazine is not used as first-line and is kept in Category C.

- **Serotonin antagonists** like **Ondansetron** have not been extensively evaluated in pregnant women but there are no associations reported with malformations after first trimester use. Ondansetron has been assigned Pregnancy Category B.

IV. ANTI-EPILEPTIC DRUGS[3,6,9]

The most commonly used anti-epileptic drugs are teratogenic. Major malformations associated with anti-epileptics include congenital heart defects, oro-facial clefts, neural tube defects and microcephaly. Minor anomalies include digital hypoplasia, hypertelorism and mental subnormality. Well-defined fetal syndromes have been associated with **phenytoin**, **valproate** and **carbamazepine**.

FDA Categorization of anti-epileptic drugs is as follows:-

- **Category C** :Felbamate, Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine, Tiagabine, Topiramate, Zonisamide.
- **Category D**: Carbamazepine, Phenobarbital, Phenytoin, Primidone, Valproic acid.

Nonetheless, epileptic seizures are potentially dangerous both to the pregnant woman and her fetus. In general, treatment is advisable, although the recommendation should be to use mono-therapy at the lowest dose and avoid valproate.

V. ANTI-HYPERTENSIVE DRUGS[3,6,10]

- Most of the anti-hypertensive drugs belong to FDA Category C.
- Currently, the first-line agents that are widely used are **Methyl dopa** and **Labetalol** with **Nifedipine** as the second-line treatment followed by other drugs.
- **Beta-blockers** have also been extensively used and appear to be relatively safe with the exception of **Atenolol** which has been associated with numerous reports of both malformation and physiological disturbances.
- **Angiotensin-converting enzyme inhibitors**, **angiotensin-II receptor blockers** and the new **direct renin inhibitors** that probably have similar effects warrant close attention and have been associated with fetal and neonatal renal failure, limb contractures, hypotension, skull ossification etc.

FDA Categories are as follow:

- **Category B**: Methyl dopa.
- **Category C**: Labetalol, Nifedipine, Hydralazine, Beta-receptor blockers.
- **Category D**: ACE-inhibitors, Angiotensin receptor antagonists

VI.ANTI-RETROVIRAL THERAPY[3,6,11]

Anti-retroviral therapy in HIV patients is obligatory even during pregnancy. It is often difficult to distinguish between the effect of disease and the effect of its treatment. The choice of regimen should take into account current adult treatment guidelines, what is known about the use of specific drugs in pregnancy and the risk of teratogenicity. **Efavirenz** is teratogenic in non-human primates and regimen that does not include efavirenz should be preferred.

FDA Pregnancy Categories for anti-retrovirals:

Nucleoside and nucleotide analogue reverse transcriptase inhibitors:

- **Category B**: Didanosine, Tenofovir.
- **Category C:** Abacavir, Lamivudine, Stavudine, Zidovudine.

Non-nucleoside reverse transcriptase inhibitors:

- **Category B**: Nevirapine.
- **Category C**: Delavirdine.
- **Category D**: Efavirenz.

Protease inhibitors:

- **Category B**: Nelfinavir, Ritonavir.
- **Category C**: Indinavir, Lopinavir/Ritonavir.

Fusion inhibitors:

- **Category B**: Enfuvirtide(T-20).

Cellular chemokine receptor (CCR5) antagonist:

- **Category B**: Maraviroc.

Integrase inhibitor:

- **Category C**: Raltegravir.

Conclusion

The safe use of drugs during pregnancy is an area that warrants more attention. Pregnant women and the potential impact on the developing fetus are often excluded from clinical trials that explore the safety and effectiveness of a potential drug therapy in humans. Our present knowledge of real and potential dangers of drugs in pregnancy is based on case reports, post-marketing surveys and drug registries, as well as on animal studies. Hopefully, future studies will provide better information. Meanwhile, most accurate and correct information can be obtained through online reproductive toxicity services such as Reprotox and TERIS.

Resources

Information from the U.S. FDA, product labels, peer-reviewed medical literature, online drug information and online reproductive toxicity services was reviewed concerning the use of various drugs in pregnancy and their safety profiles. The main references have been listed here.

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