

# DRUGS IN PREGNANCY

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## **Evidence of drug safety in pregnancy**

For an area as complex as prescribing in pregnancy, unfortunately, there is very little information in the literature to support practice. Newer antimicrobials are trialled excluding pregnant women for reasons of risk-avoidance and, therefore, prescribers must rely on post-marketing surveillance data. For some medications, this takes the form of a formal registry (for example, the antiretroviral pregnancy registry). Obviously, prospective safety data from Phase I/II clinical trials is preferable, but in the absence of this, registry data provides some reassurance. Older antibiotics, on the other hand, may have many years of practical experience to suggest their safety, but little robust scientific evidence to support their safe use.

## **Evidence of treatment efficacy in pregnancy**

Large prospective trials of treatment in pregnancy are conspicuously absent from the literature. There have been a number of Cochrane reviews on different topics in the treatment of infections in pregnancy – from asymptomatic bacteriuria to bacterial vaginosis. All of the reviews have in common very heterogeneous primary articles and cautious recommendations based on lack of data. In general, antibiotics are effective at treating the infection in question, but studies are underpowered to provide information on optimum therapy or fetal safety.

## **Infection and pregnancy**

Immune tolerance' in pregnancy is widely discussed and there are some data to suggest that pregnant women are at slightly higher risk of developing disease from some infections (including poliomyelitis, smallpox, hepatitis A and falciparum malaria). Also, the risk of severe disease and death are increased for some infections. During the 2009 influenza pandemic, the relative risk of admission for influenza in pregnant women was 4.3.

Severe infections, as with other (non-infectious) medical conditions do pose an increase risk of miscarriage or fetal death. This may be either through direct fetal infection; placental infection, resulting in placental insufficiency; or through effects on the mother's health, resulting in increased risk of miscarriage.

Urinary tract infections are common in women irrespective of pregnancy, as is asymptomatic bacteriuria. Guidelines recommend against treatment of asymptomatic bacteriuria, except in the setting of pregnancy. Pregnant women are no more likely to have asymptomatic bacteriuria than non-pregnant women, although the consequences are more severe. It is more likely to progress to pyelonephritis and can precipitate preterm labour. The predisposition to infection is thought to be related to changes in smooth muscle tone and altered ureteric mobility. Treatment of asymptomatic bacteriuria has been shown in a Cochrane review to reduce perinatal mortality, although the data about ideal drug and duration is conflicting.<sup>8</sup> For uncomplicated cystitis or asymptomatic bacteriuria, five days of antibiotics is sufficient.

## Pregnancy and antibiotics

The physiologic changes in pregnancy result in changes in drug pharmacokinetics that may affect plasma levels of antibiotics. Increased plasma volume results in an increase volume of distribution that lowers plasma levels and increased renal blood flow results in increased clearance of renally excreted drugs. Other than limited data for amoxicillin, there are few formal studies of plasma antimicrobial levels. In cases where long-term treatment is required, therapeutic drug monitoring can be performed, although this is rarely practical for short courses of antibiotics or outside of major teaching hospitals.

The recommended duration of treatment for infections in pregnancy generally errs to the more conservative end of the spectrum, for example, five days for cystitis or bacteriuria as opposed to three days in non-pregnant women. This is based on expert opinion rather than solid evidence of these infections requiring prolonged treatment.

- Penicillins :

- Category B in pregnancy

- Cross the placenta easily and rapidly
    - Concentrations equal maternal levels
  - Lactation
    - Crosses in low concentrations
    - Compatible with breastfeeding

- Cephalosporins :

- Category B in pregnancy

- Cross the placenta during pregnancy
    - Some reports of increased anomalies with specific cephalosporins (cefactor, cephalexin, cephadrine)
    - Primarily cardiac and oral cleft defects
  - Lactation
    - Excreted into breastmilk in low concentrations
    - Considered compatible with breastfeeding

- Carbapenems :
  - Category B/C/B in pregnancy
    - Likely cross the placenta
    - Very little human data
  - Lactation
    - Excreted into breastmilk in low amounts
    - Unknown effects but likely low clinical significance
- Fluroquinolones :
  - Pregnancy Category C
    - Not recommended in pregnancy
    - Cartilage damage in animals
    - Safer alternatives usually exist
  - Lactation
    - Excreted into breastmilk
    - Limited human data
    - AAP says compatible with breastfeeding
- Macrolides :
  - Pregnancy Categories B/C/B
    - Cross the placenta in low amounts
    - Limited data with azithromycin and clarithromycin
  - Lactation
    - Erythromycin compatible
    - Others probably compatible
- Aminoglycosides (amikacin , gentamicin, tobramycin).
  - Pregnancy Categories B/C/B
    - Cross the placenta in low amounts
    - Limited data with azithromycin and clarithromycin
  - Lactation
    - Erythromycin compatible
    - Others probably compatible

- Sulfonamides:

Pregnancy Category C

- Readily cross the placenta
- Concerns of use at term

Lactation

- Excreted into breastmilk in low levels
- Use should be avoided in premature infants

- Tetracyclines :

- Pregnancy Category C

- Readily cross the placenta
- Concerns of use at term

- Lactation

- Excreted into breastmilk in low levels
- Use should be avoided in premature infants

- Aztreonam

- Pregnancy Category B, likely safe in pregnancy, little human data
- Lactation – Compatible per AAP

- Clindamycin

- Pregnancy Category B, commonly used
- Lactation – Compatible per AAP

- Linezolid

- Pregnancy Category C, no human data available
- Lactation – unknown, myelosuppression in animals

- Metronidazole

- Pregnancy Category B, carcinogenic in animals, avoid in 1<sup>st</sup> trimester if possible
- Lactation – hold feeds for 12-24hrs afterward

- Nitrofurantoin

- Pregnancy Category B, possible hemolytic anemia with use at term

- Lactation – Compatible, avoid with G-6-PD deficiency
- Trimethoprim
  - Pregnancy Category C, potentially problematic early in pregnancy
  - Lactation – Compatible as combination drug
- Vancomycin
  - Pregnancy Category B, compatible
  - Lactation – likely compatible, not absorbed

### **Classification of Drugs**

The Food and Drug Administration (FDA) currently divides medications into five different pregnancy-risk categories. Drugs are placed in different risk categories based on available studies in humans and animals (**See Table 1**). Locating a pregnancy-risk category is the first step in evaluating the safety of drugs in pregnancy. There are resources that assist health care professionals by listing drugs in their prospective risk categories. However, there are limitations to using pregnancy-risk categories. First, drugs on the market were not required to have an assigned risk category until after December 1983; therefore, many drugs are not rated by the manufacturer. Second, it cannot be assumed that outcomes from animal studies are similar to outcomes found in humans. Caution should be advised in the use of drugs that fall under those categories for which only animal data is available (Categories B and C). If a drug does not have a pregnancy-risk classification, primary literature should be retrieved and assessed for safety in pregnancy information.

**Table 1: Pregnancy-Risk Categories**

| Category | Definition   |
|----------|--|
| A        | Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester, and the possibility of fetal harm appears remote.  |
| B        | Either animal studies do not indicate a risk to the fetus and there are no controlled studies in pregnant women, or animal studies have indicated fetal risk, but controlled studies in pregnant women failed to demonstrate a risk. |
| C        | Either animal studies indicate a fetal risk and there are no controlled studies in women, or there are no available studies in women or animals.   |
| D        | There is positive evidence of fetal risk, but there may be certain situations where the benefit might outweigh the risk (life-threatening or serious diseases where other drugs are ineffective or carry a greater risk).            |
| X        | There is definite fetal risk based on studies in animals or humans or based on human experience, and the risk clearly outweighs any benefit in pregnant women.   |

### **General Considerations**

The pregnancy risk to benefit ratio is defined as the risk to the fetus compared to the benefits to the mother. Components of this ratio are the 1) genotype of mother and fetus, 2) embryonic stage at exposure, 3) dose, and 4) exposure to other drugs or environmental agents that may increase or decrease potential abnormalities. The timing of exposure is associated with the most potential for teratogenic effect(s). Timing of exposure is defined as the stage of fetal development when the drug is consumed. In general the risk of teratogenicity of the drug decreases as growth of the fetus progresses.

If the fetus is exposed at the time of conception and implantation, the embryo may be aborted. As the fetus progresses through the first 12 to 15 days, the cells are still totipotent (i.e., if one cell is damaged another cell can assume its function) and the embryo may be capable of survival. During the first 3 months of growth, the chance of physical malformations is increased because this is the critical stage of physical development. Later in gestation, risk of functional and behavioral abnormalities increases because of the continuous growth and development of the central nervous system.

### **Product Selection**

Drug selection is easier when drugs fall under the categories A, D, or X. The dilemma is with medications that fall under the categories B and C where adequate studies are not available to make a definitive judgement. Risk versus benefit, as well as some of the drug characteristics, are the next best steps to take in selecting an appropriate drug. There are four characteristics to evaluate in drug selection. These characteristics are molecular weight, ionization, lipophilicity, and degree of protein binding. The less the molecule weighs, the more likely it will be able to pass through the placenta. Most of the medications on the market fall between 250 and 400 daltons and, therefore, the likelihood for crossing into the fetal circulation is high. Ionization and lipophilicity are also important determinants in drugs crossing the placenta. More ionized and less lipophilic drugs tend to cross the placenta more readily than unionized and highly lipophilic drugs. Finally, the amount of protein binding plays a role. The more protein bound a drug, the less likely it is to cross the placenta.

### **Drug Selection in Selected Disease States**

#### **Nausea and Vomiting**

Nausea and vomiting affect between 60 and 70% of women who become pregnant. Most women do not require treatment, though there are women (0.5-10 in a thousand) who require treatment to avoid adverse consequences (e.g., malnutrition, weight loss, dehydration) during pregnancy. First, nonpharmacologic options should be attempted. Some of these include avoiding foods that may trigger episodes of nausea and vomiting (e.g., spicy, fatty, or fried foods), eating when nausea is less severe, and avoiding of the smell of food. Additionally, supplements containing iron can be a source of nausea and vomiting in certain women. Women who are unable to maintain adequate hydration should be

admitted to the hospital for intravenous (IV) fluid and electrolyte replacement. Antiemetics, which are generally third-line therapy, are given to women who do not respond to IV replacement. Clinical data to support the safety and efficacy of these drugs are minimal and use of the following medications should still be exercised with caution (**See Table 2**). Currently, no medications are approved for the treatment of nausea and vomiting in pregnant women. One other suggested therapy involves giving antihistamines in the morning to prevent nausea and vomiting. If hyperemesis is resistant to conventional treatment, then the use of ondansetron or corticosteroids may be considered.

Table 2: Drugs Used in the Management of Nausea and Vomiting During Pregnancy

| Drug                                       | Pregnancy Risk Category |
|--|-------------------------|
| Metoclopramide (Reglan <sup>®</sup> )      | B                       |
| Cyclizine (Marezine <sup>®</sup> )         | B                       |
| Ondansetron (Zofran <sup>®</sup> )         | B                       |
| Promethazine (Phenergan <sup>®</sup> )     | C                       |
| Prochlorperazine (Compazine <sup>®</sup> ) | C                       |
| Chlorpromazine (Thorazine <sup>®</sup> )   | C                       |

Adapted from: Nelson-Piercy C. Treatment of Nausea and Vomiting in Pregnancy: When Should It Be Treated and What Can Be Safely Taken? *Drug Saf* 1998; 19(2): 155-64

## Hypertension

Chronic hypertension in pregnancy is defined as high blood pressure that is present before pregnancy or diagnosed before the 20<sup>th</sup> week of gestation. Antihypertensive agents are used in women with a diastolic pressure of 100 mm Hg or higher (lower if end organ damage or renal disease is present) and in women with acute hypertension when pressures are greater than 105 mm Hg. According to the JNC VI guidelines, pregnant women can be continued on most antihypertensive medications with the exception of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (Category X). ACE inhibitors are associated with chronic abnormalities (e.g., renal insufficiency requiring dialysis, growth retardation, and cranial malformations) and even death of the fetus. The drug of choice for high blood pressure diagnosed during pregnancy is methyldopa. Methyldopa has been studied extensively and is well tolerated in this population. When parenteral therapy is required, hydralazine is an effective alternative. (See Table 3).

**Table 3: Drugs Used for the Management of Hypertension During Pregnancy**

| Drug Class                | Example                              | Pregnancy Risk Category | Comment                                     |
|---------------------------|--------------------------------------|-------------------------|---|
| Central $\alpha$ -agonist | (Aldomet <sup>®</sup> )              | C                       | Drug of choice by the NHBPEP* Working Group |
| $\alpha$ -Blockers        | Atenolol (Tenormin <sup>®</sup> )    | C                       |   |
|                           | Metoprolol (Lopressor <sup>®</sup> ) | C                       |   |
|                           | Labetolol( $\alpha$ ) <sup>®</sup>   | C                       |   |

|                                  |  |         |   |
|----------------------------------|--|---------|---|
| Calcium antagonists              | Diltiazem (Cardizem <sup>®</sup> CD, Dilacor <sup>®</sup> XR, Trizac <sup>®</sup> )  | C       | Potential synergism with magnesium sulfate may lead to precipitous hypotension  |
|                                  | Verapamil (Calan <sup>®</sup> , Covera-HS <sup>®</sup> , Verelan <sup>®</sup> )  | C       |   |
| ACE inhibitors                   | Captopril (Capoten <sup>®</sup> )  | D       | Fetal abnormalities including death, can be caused, and should not be used in pregnancy   |
| Angiotensin II Receptor blockers | Enalapril (Vasotec <sup>®</sup> )  | D       |   |
|                                  | Lisinopril (Prinivil, Zestril <sup>®</sup> )   | D       |   |
|                                  | Losarten (Cozaar <sup>®</sup> )  | D       |   |
|                                  | Valsarten (Diovan <sup>®</sup> )   | D       |   |
| Diuretics                        | Bumetanide (Bumex <sup>®</sup> )<br>Frosemide (Lasix <sup>®</sup> )<br>Hydrochlorothiazide (HydroDIURIL <sup>®</sup> )<br>Indapamide (Lozol <sup>®</sup> ) | DCCBBDB | Recommended for chronic hypertension if prescribed before gestation or if patients are salt-sensitive. Not recommended in preclampsia |

|  |   |   |   |
|--|---|---|---|
|  | Spironolactone<br>(Aldactone <sup>®</sup> ) |   |   |
|  | Triamterine<br>(Dyrenium <sup>®</sup> )     |   |   |
| Direct vasodilators  | Hydralazine<br>(Apresoline <sup>®</sup> )   | C | Hydralazine is parenteral drug of choice based on its long history of safety and efficacy |
|  | Minoxidil (Loniten <sup>®</sup> )           | C |   |
| * NHBPEP: National High Blood Pressure Education Program   |   |   |   |
| Adapted from: The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The sixth report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997; 157: 2413-46. |   |   |   |

## Migraine

The drug of choice for migraine headaches during pregnancy is acetaminophen. There appears to be no effect on the fetus as well as minimal effects on platelet function. It can be given in doses up to 1000 mg per dose. Other typical medications used in migraine treatment are not recommended during pregnancy (**See Table 4**), which include the selective serotonin agonists (e.g., sumatriptan, naratriptan, zolmitriptan, and rizatriptan). Although they have not been proven to be harmful to humans, there have been no well-controlled studies to validate their use. Nonsteroidal anti-inflammatory drugs (NSAIDs) should also be avoided in pregnancy because of their ability to prolong pregnancy and labour. Ergotamine and dihydroergotamine are contraindicated in pregnancy because of their uterotonic effects.

**Table 4: Drugs Used in the Treatment of Migraines during Pregnancy**

| <b>Drug</b>                                  | <b>Pregnancy Risk Category</b> |
|--|--------------------------------|
| Acetaminophen (Tylenol <sup>®</sup> )        | B                              |
| Ibuprofen (Motrin <sup>®</sup> )             | B                              |
| Ergotamine tartrate (Ergorate <sup>®</sup> ) | D                              |
| Dihydroergotamine (Migranal <sup>®</sup> )   | X                              |
| Prochlorperazine (Compazine <sup>®</sup> )   | C                              |
| Sumatriptan (Imitrex <sup>®</sup> )          | C                              |
| Naratriptan (Amerge <sup>®</sup> )           | C                              |
| Zolmitriptan (Zomig <sup>®</sup> )           | C                              |

### **Drugs Considered Safe in Pregnancy:**

- ❖ Some antibiotics namely Amoxycillin, Ampicillin, Cephalosporins, Erythromycin (not estolate)
- ❖ Levothyroxine
- ❖ Acetaminophen
- ❖ Folic Acid and Vitamin B6
- ❖ Methyl dopa, and hydralazine
- ❖ Insulin
- ❖ Heparin

**Drugs Contraindicated in Pregnancy:** Some drugs in **category X** that are contraindicated in pregnancy and their effects on the fetus are listed below:

- ❖ Vitamin A and its derivatives - Accutane(Isotretinoin), Acitretin, Etreinate - Birth defects, miscarriage
- ❖ Thalidomide – Seal like limbs and other defects
- ❖ Diethylstilbestrol – Causes cancer of the vagina or cervix in female children during their teenage years
- ❖ Warfarin – Causes multiple birth defects
- ❖ Danazol – Causes malformations in sex organs of female fetus
- ❖ Simvastatin and other statins – Cholesterol is needed for fetal growth and its reduction by statins could harm the fetus
- ❖ Finasteride – Though finasteride is normally not prescribed to women, pregnant women should not handle broken or crushed tablets since it can get absorbed through the skin and affect the sex organ development of the male fetus.
- ❖ Testosterone - Can cause birth defects
- ❖ Oral contraceptives- Can cause birth defects
- ❖ Dutasteride - Affects the sex organ development of the male fetus.
- ❖ Methotrexate – Causes cleft palate along with multiple defects

**Some known side effects of drugs during pregnancy are listed below:**

- ❖ Tetracyclines - Get deposited in fetal bones and retard their growth, also affect teeth causing them to be discolored and deformed
- ❖ Chloramphenicol – Gray baby syndrome
- ❖ Isoniazid - Neurophy and seizures in fetus, liver damage in mother
- ❖ Sodium Valproate – Defects of the nervous system
- ❖ ACE inhibitors – Growth retardation, birth defects, fetal death
- ❖ Lithium – Affects fetal thyroid, heart beside causing other abnormalities
- ❖ Phenytoin – Cleft lip/ palate along with other deformities
- ❖ Anti convulsants - Trimethadione, Valproic acid, Carbamazepine – Multiple birth defects
- ❖ Androgens – Multiple defects.

During the **last 3 months of pregnancy**, drugs crossing the placental barrier may interfere with the vital functions of the fetus E.g.:

- ❖ Morphine - If the mother is given morphine during labor, fetal asphyxia can occur
- ❖ Anti-coagulants - May cause fatal bleeding in the newborn
- ❖ Radioactive iodine therapy - A cretin may be born due to radioactive iodine therapy
- ❖ Anti thyroid drugs - may produce goiter, which can lead to face presentation
- ❖ Sulfonamides – may increase bilirubin levels leading to kernicterus

#### **References :**

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