CHAPTER 16

DRUGS IN PREGNANCY

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Evidence of drug safety in pregnancy

Unfortunately, there is very little information in the literature to support practise in an area as complex as prescribing during pregnancy. Because newer antimicrobials are tested without pregnant women for risk reasons, prescribers must rely on post-marketing surveillance data. This takes the form of a formal registry for some medications (for example, the antiretroviral pregnancy registry). Although prospective safety data from Phase I/II clinical trials is preferable, registry data provides some reassurance in the absence of this. Older antibiotics, on the other hand, may have a long history of use to suggest their safety, but there is little solid scientific evidence to back up their use.

Evidence of treatment efficacy in pregnancy

There are no large prospective trials of treatment in pregnancy in the literature. A number of Cochrane reviews have been published on various topics related to the treatment of infections in pregnancy, ranging from asymptomatic bacteriuria to bacterial vaginosis. All of the reviews have very diverse primary articles in common, as well as cautious recommendations based on a lack of data. Antibiotics are generally effective at treating the infection in question, but studies on optimal therapy or foetal safety are underpowered.

Infection and pregnancy

Immune tolerance' in pregnancy is a controversial topic, and some evidence suggests that pregnant women are at a slightly higher risk of contracting infections (including poliomyelitis, smallpox, hepatitis A and falciparum malaria). Some infections also increase the risk of severe disease and death. During the 2009 influenza pandemic, pregnant women had a relative risk of admission for influenza of 4.3. As with other (non-infectious) medical conditions, severe infections increase the risk of miscarriage or foetal death. This can happen through direct foetal infection, placental infection, which causes placental insufficiency, or effects on the mother's health, which increases the risk of miscarriage.

Regardless of pregnancy, urinary tract infections and asymptomatic bacteriuria are common in women. Except in the case of pregnancy, guidelines advise against treating asymptomatic bacteriuria. Asymptomatic bacteriuria is no more common in pregnant women than in non-pregnant women, but the consequences are more severe. It's more likely to develop into pyelonephritis, which can lead to preterm labour. Changes in smooth muscle tone and ureteric mobility are thought to play a role in infection susceptibility. A Cochrane review found that treating asymptomatic

bacteriuria reduces perinatal mortality, though the data on the best drug and duration is mixed. 8 Five days of antibiotics are enough for uncomplicated cystitis or asymptomatic bacteriuria.

Pregnancy and antibiotics

The physiologic changes that occur during pregnancy cause changes in drug pharmacokinetics, which may affect antibiotic plasma levels. Increased plasma volume causes an increase in distribution volume, which lowers plasma levels, and increased renal blood flow causes increased clearance of drugs excreted through the kidneys. There are few formal studies of plasma antimicrobial levels, aside from limited data for amoxicillin. Therapeutic drug monitoring can be used in cases where long-term treatment is required, though this is rarely practical for short courses of antibiotics or outside of major teaching hospitals. In most cases, the recommended treatment duration for infections in pregnancy errs on the conservative side of the spectrum, such as five days for cystitis or bacteriuria versus three days in non-pregnant women.This is based on expert opinion rather than scientific evidence that these infections require long-term 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 (cefaclor, cephalexin, cephradrine)
  - 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
- Floroquinolones:
  - Pregnancy Category C
  - Not recommended in pregnancy
  - Cartilage damage in animal
  - 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, topramycin).
  - Pregnancy Categories B/C/B
  - Cross the placenta in low amounts
  - Limited data with azithromycin and clarithromycin
  - Lactation
  - Erythromycin compatible
  - Others probably compatible

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- 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 1St trimester if possible
  - Lactation – hold feeds for 12-24 hrs afterward
- Nitrofurantoin
  - Pregnancy Category B, possible hemolytic anemia with use at term

Classification of Drugs

Medications are currently divided into five different pregnancy-risk categories by the Food and Drug Administration (FDA). Based on human and animal studies, drugs are classified into different risk categories (See Table 1). The first step in determining the safety of drugs during pregnancy is to identify a pregnancy-risk category. There are resources available to help health care providers by listing drugs in their potential risk categories. However, using pregnancy-risk categories has its limitations. First, until December 1983, drugs on the market were not required to have a risk category assigned to them; as a result, many drugs are not rated by the manufacturer. Second, results from animal studies cannot be assumed to be comparable to human results. Drugs that fall into those categories for which only animal data is available should be used with caution (Categories B and C). If a drug does not have a pregnancy risk classification, primary literature should be retrieved and evaluated for pregnancy safety.

Table 17.1: Classification of Drugs

Category	Definition
A	Controlled studies in women have failed to show a risk to the foetus in the first trimester, and foetal harm appears unlikely.
B	Either animal studies show no risk to the foetus and no controlled studies in pregnant women exist, or animal studies show foetal risk but controlled studies in pregnant women fail to show a risk.
C	Either animal studies show no risk to the foetus and no controlled studies in pregnant women exist, or animal studies show foetal risk but controlled studies in pregnant women fail to show a risk.
D	Although there is evidence of foetal risk, there may be circumstances where the benefit outweighs the risk (life-threatening or serious diseases where other drugs are ineffective or carry a greater risk).
X	Based on animal or human studies or personal experience, there is a clear foetal risk, and the risk clearly outweighs any benefit in pregnant women.

General Considerations

The risk to the foetus versus the benefits to the mother is known as the pregnancy risk to benefit ratio. 1) Mother and foetus genotypes, 2) embryonic stage at

exposure, 3) dose, and 4) exposure to other drugs or environmental agents that may increase or decrease potential abnormalities are all factors in this ratio. The timing of exposure is linked to the greatest risk of teratogenic effects (s). The stage of foetal development at which the drug is consumed is referred to as exposure timing. As the foetus grows, the risk of teratogenicity of the drug decreases.

The embryo may be aborted if the foetus is exposed during conception and implantation. The embryo may be capable of survival as the foetus progresses through the first 12 to 15 days because the cells are totipotent (meaning that if one cell is damaged, another cell can take over). Because this is the critical stage of physical development, the risk of physical malformations increases during the first three months of growth.

Because the central nervous system continues to grow and develop throughout pregnancy, the risk of functional and behavioural abnormalities increases.

Product Selection

Drugs that fall into categories A, D, or X make drug selection easier. The problem arises with medications in categories B and C, where adequate research is lacking to make a definitive decision. The next best steps in selecting an appropriate drug are to consider risk versus benefit, as well as some of the drug's characteristics. When it comes to drug selection, there are four factors to consider. The molecular weight, ionisation, lipophilicity, and degree of protein binding are among these characteristics. The smaller the molecule, the better its chances of passing through the placenta. The majority of medications on the market have a molecular weight of between 250 and 400 daltons, making them highly likely to enter the foetal circulation. In drugs that cross the placenta, ionisation and lipophilicity are also important factors. Drugs that are more ionised and less lipophilic cross the placenta more easily than those that are unionised and highly lipophilic. Finally, the quantity of protein binding is important. The less likely a drug is to cross the placenta, the more protein bound it is.

DRUG SELECTION IN SELECTED DISEASE STATES

Nausea and Vomiting

Between 60 and 70 percent of pregnant women experience nausea and vomiting. The majority of women do not require treatment, but a small percentage (0.5-10 per thousand) do in order to avoid negative pregnancy outcomes (such as malnutrition, weight loss, and dehydration). Nonpharmacologic options should be tried first. Avoiding foods that may cause nausea and vomiting (e.g., spicy, fatty, or fried

foods), eating when nausea is less severe, and avoiding the smell of food are just a few of them. Additionally, iron-containing supplements can cause nausea and vomiting in some women. Women who are unable to keep themselves hydrated should be admitted to the hospital for IV fluid and electrolyte replacement. Women who do not respond to IV replacement are given antiemetics, which are considered third-line therapy. There is little clinical evidence to support the safety and efficacy of these drugs, so they should be used with caution. See Table-17.2

There are currently no approved medications for the treatment of nausea and vomiting in pregnant women. Another option is to take antihistamines first thing in the morning to prevent nausea and vomiting. If hyperemesis does not respond to conventional treatment, ondansetron or corticosteroids may be used.

Table 17.2: Drug Risk Classification during Pregnancy

Drug Pregnancy	**Risk Category**
Metoclopramide (Reglan®)	B
Cyclizine (Marezine®)	B
Ondansetron (Zofran®)	**B**
Promethazine (Phenergan®)	C
Prochlorperazine (Compazine®)	C
Chlorpromazine (Thorazine®)	C

Hypertension

Chronic hypertension in pregnancy is high blood pressure that existed prior to pregnancy or was diagnosed before the 20th week of pregnancy. Women with a diastolic pressure of 100 mm Hg or higher (lower if end organ damage or renal disease is present) and women with acute hypertension with pressures greater than 105 mm Hg are treated with antihypertensive drugs. 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) (Category X). Chronic abnormalities (e.g., renal insufficiency requiring dialysis, growth retardation, and cranial malformations) and even foetal death have been linked to ACE inhibitors. Methyldopa is the drug of choice for high blood pressure diagnosed during pregnancy. Methyldopa has been extensively researched and found to

be well tolerated in this population. Hydralazine is an effective alternative to parenteral therapy when it is required (See Table 17.3).

Table 17.3: Pregnancy Risk Category as per Drug Class

Drug Class	**Example**	**Pregnancy Risk Category**	**Comment**
Central ŏ-agonist	(Aldomet®)	C	Drug of choice by the NHBPEP* Working Group
α-Blockers	Atenolol (Tenormin®)	C	
	Metoprolol (Lopressor®)	C	
	Labetolol(ŏ)®)		
Calcium antagonists	Diltiazem (Cardizem® CD, Dilacor®XR, Trizac® Verapamil (Calan®, Covera-HS®, Verelan®)	C C	Potential synergism with magnesium sulfate may lead to precipitous hypotension
ACE inhibitors	ACE inhibitors Captopril (Capoten®)	D	Fetal abnormalities including death, can be caused, and should not be used in pregnancy
Angiotensin IIReceptor blockers	Enalapril(Vasotec®) Lisinopril (Prinivil, Zestril®) Losarten (Cozaar®) Valsarten(Diovan®)	D D D D	
Diuretics	Bumetanide (Bumex®)	DCCBBDB	Recommended for chronic hypertension if prescribed before gestation or if patients

	Frosemide (Lasix®) Hydrochlorothiazide (HydroDIURIL®) Indapamide (Lozol®		are saltsensitive. Not recommended in preclampsia

Drugs Considered Safe in Pregnancy:

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

Drugs Contraindicated in Pregnancy: Some drugs in scheduled X that are contraindicated in pregnancy, following are the effects on the foetus:

Vitamin A and its derivatives: Accutane (Isotretinoin), Acitretin, Etretinate - 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: Statins may harm the foetus because cholesterol is required for foetal growth.

Finasteride: Though finasteride is not usually prescribed to women, pregnant women should avoid handling broken or crushed tablets because it can be absorbed through the skin and affect the male foetus' sex organ development..

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

The following are some known drug side effects during pregnancy:

Tetracyclines: Deposit in foetal bones, slowing their growth; also affect teeth, discolouring and deforming them.

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chloramphenicol: Gray baby syndrome

Isoniazid: causes foetal neuropthy and seizures, as well as liver damage in the mother.

Sodium Valproate: causes nervous system defects; ACE inhibitors cause growth retardation, birth defects, and foetal death.

Lithium: Affects the foetal thyroid and heart, among other things.

Phenytoin: causes cleft lip and palate, as well as other deformities.

Anticonvulsants: such as trimethadione, valproic acid, and carbamazepine have been linked to numerous birth defects.

Androgens: Multiple defects.

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