Antimicrobial Use in Pregnancy

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Antimicrobial Use in Pregnancy

- One of the most commonly prescribed medications for pregnant women
  - 9 of the 20 top medications
- Concerns
  - Pharmacokinetic
  - Teratogenic
  - Other toxic effects

Andrade SE, et al. Am J Obstet Gynecol 2004;191:398-407

Pharmacokinetic Considerations During Pregnancy

Absorption
- Gastric emptying delay, dyspepsia, nausea, vomiting
- Can reduce absorption and bioavailability

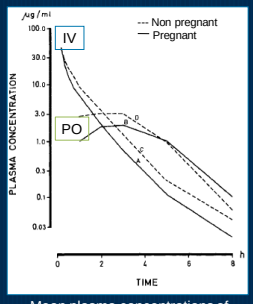
Distribution
- Increased maternal volume of distribution

Metabolism
- Increase in hepatic activity

Elimination
- Increased renal clearance
- May or may not increase half-life

Varies significantly based on trimester

Pharmacokinetics of Ampicillin during Pregnancy

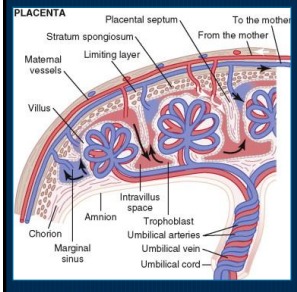


Mean plasma concentrations of 500 mg Ampicillin (IV & PO)

- 26 females
- During and after pregnancy
- Mean gestational age 19.5 (9-33) weeks
- Significant increase in volume of distribution and renal clearance

Philipson A. JID 1977;136:370-76

Drug Transfer Across the Placenta



- Transfer occurs via
  - Passive diffusion
  - Protein transport
- Transfer dependent on
  - Molecular size (< 5kDa)
  - Ionic state
  - Protein binding
  - Lipid solubility
  - pH (weak organic acids)

Picture from Guyton & Hall Textbook of Medical Physiology, 12th ed.

FDA Pregnancy Categories

A
- Adequate well-controlled trials in pregnant women show no increased risk of fetal abnormalities.

B
- Animal studies show no evidence of harm; however no human studies have been conducted.
- Animal studies show adverse events; however human studies have not shown an increased risk of fetal abnormalities.

C
- Animal studies show an adverse effect on the fetus. No adequate studies in humans.
- No animal or human studies have been conducted.

D
- Studies in humans show the drug can cause fetal harm, but the potential benefits may be acceptable despite its potential risks.

X
- Studies in animals or humans demonstrate fetal abnormalities and risk outweighs any possible benefit.

Labeling Requirements

- 2008, FDA proposed new labeling requirements
- Code of Federal Regulations, Title 21, updated April 1, 2010
- Use in special populations
  - Teratogenic effects (Pregnancy category)
  - Non-teratogenic effects
  - Nursing mothers
- The labeling now requires a summary of the risks of using a drug during pregnancy and lactation and a discussion of the data supporting that summary.

Antibiotics Safe in Pregnancy

- Penicillins (B)
- Cephalosporins (B)
- Carbapenems (B)
- Aztreonam (B)
- Clindamycin (B)
- Vancomycin (C)
- Quinupristin/dalfopristin (B)
- Daptomycin (B)
- Fosfomycin (B)

- Safe except near term
  - Nitrofurantoin (B)
  - SMX/TMP (C)

Nitrofurantoin

- Pregnancy Category B
- Crosses the placenta but low concentrations in amniotic fluid
- Consistent safety data in animal and human studies
- Avoid near term (38-42 weeks)
  - Hemolytic anemia

Sulfamethoxazole/Trimethoprim

- Pregnancy Category C
- Crosses the placenta & distributes to amniotic fluid
- Animal studies
  - Cleft palates
- Human studies
  - May increase risk of congenital anomalies
  - Folic acid supplementation may decrease this risk
  - Most studies failed to show an increased risk for congenital malformations
- Avoid near term (38-42 weeks)
  - Kernicterus

Macrolides

Macrolide	Pregnancy Category	Comments
Erythromycin	B	Do NOT use the estolate salt (hepatotoxicity) ?pyloric stenosis Preterm premature rupture of membranes
Clarithromycin	C	Animal studies show increased risk of fetal death and congenital malformations. Prospective study in humans did not show any difference in malformations to matched controls.
Azithromycin	B	No adverse effects in animal studies Recommended for chlamydial infections in pregnancy

Aminoglycosides

- Pregnancy Class D
- Readily crosses the placenta
- Streptomycin use in pregnancy lead to congenital deafness
- Animal studies demonstrated renal toxicity

Tetracyclines & Tigecycline

- Pregnancy Category D
- Cross the placenta and enter fetal circulation
- Maternal hepatic toxicity
- Chelates calcium
  - Abnormalities in bone growth
  - Permanent discoloration of teeth (tetra>doxy)
- Life-threatening infections require weighing risks vs benefits

Fluoroquinolones

- Pregnancy Category C
- Crosses the placenta
- Animal studies show adverse effects on bone and cartilage growth
- Teratogenic effects have not been observed in human studies

Metronidazole

- Pregnancy Category B
- Animal studies in mice showed mutagenic and carcinogenic effects
- Human studies did not reveal any increased incidence of congenital malformations
- Safe for use in 2nd and 3rd trimesters
- Avoid in 1st trimester due to potential mutagenic effects

Linezolid

- Pregnancy Category C
- Animal studies have shown embryonic death, decreased weight, abnormalities in cartilage and ossification
- No adequate studies in humans

Antifungals Safe During Pregnancy

- Amphotericin (B)
- Lipid formulations (B)

Moudgal & Sobel. Expert Opin Drug Saf 2003;2(5):475-83.

Azoles

Azole	Pregnancy Category	Comments
Fluconazole	C	Teratogenic in animal studies – dose dependent Case reports of congenital abnormalities in humans (high-dose for prolonged periods) Low, single dose (150 mg) therapy did not show risk
Itraconazole	C	Dose-related embryotoxicity and teratogenicity in rats Manufacturer recommends contraception Cohort of 229 women exposed showed no risk
Voriconazole	D	Teratogenic and embryotoxic in animal studies at 0.3 times human doses
Posaconazole	C	Teratogenic in animal studies No adequate or well-controlled studies in humans

Moudgal & Sobel. Expert Opin Drug Saf 2003;2(5):475-83.

Echinocandins

- Pregnancy Category C
- Animal studies
  - Visceral teratogenic and abortifacient effects
  - Skeletal abnormalities
  - At doses with similar exposure to human doses
- No adequate well controlled studies in pregnant women
- Use if benefits outweigh risk

Moudgal & Sobel. Expert Opin Drug Saf 2003;2(5):475-83.

Flucytosine

- Pregnancy Category C
- 5-FC metabolized to 5-FU
- Crosses placenta and high concentrations in amniotic fluid and cord blood
- Teratogenic in rats
- Case reports of safe use in humans in 2nd and 3rd trimester

Moudgal & Sobel. Expert Opin Drug Saf 2003;2(5):475-83.

Antivirals Safe During Pregnancy

- Acyclovir (B)
- Valacyclovir (B)
- Famciclovir (B)

Anti-CMV Therapy

Antiviral	Pregnancy Category	Comments
Ganciclovir & Valganciclovir	C	Boxed warning: Animal studies have demonstrated carcinogenic & teratogenic effects, and inhibition of spermatogenesis
Foscarnet	C	Skeletal abnormalities in animal studies at human doses Case report of use during 3rd trimester; no harm
Cidofovir	C	Boxed warning: Animal studies show carcinogenic, teratogenic and embryotoxic effects Hypospermia in animal studies

Lexi-Comp®
Money DM. Obstet Gynecol Clin N Am 2003;30:731-49.

Anti-Influenza Drugs

Antiviral	Pregnancy Category	Comments
Amantadine	C	Teratogenic and embryotoxic at high doses in animals
Rimantadine	C	Embryotoxic in animal studies
Zanamivir	C	Limited systemic absorption
Oseltamivir	C	Animal studies: dose-dependent increase in skeletal abnormalities (did not exceed background rate) Incomplete placental transfer; minimal accumulation Human cohorts: Increased rate of adverse fetal outcomes has NOT been observed CDC recommends for treatment and prophylaxis

Vaccines & Medications in Pregnancy Surveillance System (VAMPSS) (877) 311-8972

Lexi-Comp®

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States

- Regardless of plasma HIV RNA copy number or CD4 cell count, all pregnant HIV-infected women should receive a combination antepartum ARV drug regimen to prevent perinatal transmission (AI)
- http://www.aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0/
- Antiretroviral Pregnancy Registry www.APRegistry.com

Antiretrovirals

- NRTIs
  - Lamivudine (C)*
  - Zidovudine (C)*
  - Tenofovir (B)#
  - Abacavir (C)#
  - Didanosine (B)#
  - Emtricitabine (B)#
  - Stavudine (C)#
- NNRTIs
  - Nevirapine (B)*
  - Efavirenz (D)
  - Etravirine (B)^
  - Rilpivirine (B)^
- Protease Inhibitors
  - Lopinavir/ritonavir (C)*
  - Atazanavir (B)#
  - Saquinavir (B)#
  - Indinavir (C)#
  - Nelfinavir (B)#
  - Darunavir (C)^
  - Fosamprenavir (C)^
  - Tipranavir (C)^
- Enfuvirtide (B)^
- Maraviroc (B)^
- Raltegravir (C)^

* Preferred
# Alternative
^ Insufficient data

http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

Anti-Tubercular Drugs

- CDC recommends:
  - Isoniazid (C)
    - Increased risk of hepatitis & peripheral neuropathy
  - Rifampin (C)
  - Ethambutol (C)
- Total duration: 9 months
- Pyrazinamide, limited safety data, not routinely recommended in the US

Vaccines Recommended in Pregnancy

- Influenza Vaccine
  - Inactived influenza vaccine (IIV) recommended
  - Live attenuated influenza vaccine (LAIV - Flumist®) contraindicated
- Tetanus, diphtheria, acellular pertussis (Tdap)
  - New recommendation for Tdap with every pregnancy
  - Optimally between weeks 27 and 36 gestation

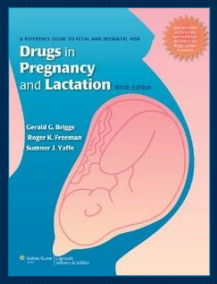
MMWR 2013;62(7):131-5.
http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule.pdf

Vaccines Contraindicated in Pregnancy

- Live vaccines
  - Measles, Mumps, Rubella (MMR)
  - Varicella (Varivax®)
  - Zoster (Zostavax®)
  - Live attenuated influenza vaccine (LAIV - Flumist®)

References

- Briggs, et al. Drugs in Pregnancy and Lactation
- LexiComp®
- Micromedex®



Questions