Antimicrobial use in pregnancy

IDAT week 2018

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What are the antimicrobials of choice?

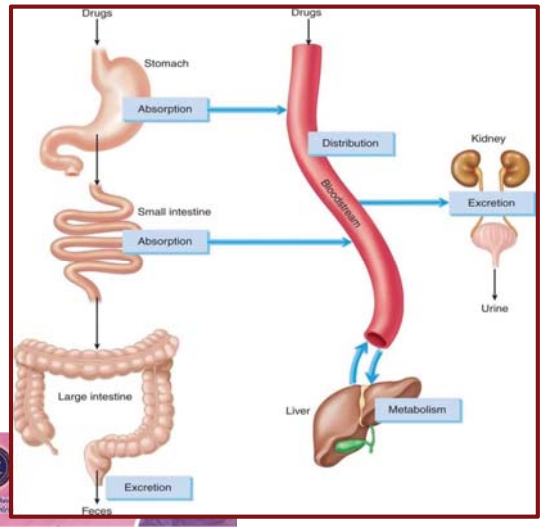
1 27-year-old pregnant woman without symptoms
U/A: no WBC
Urine C/S: *E. coli* >10^5 CFU/ml X 2

2 37-year-old pregnant woman without symptoms
She is allergic to penicillin
VDRL +ve, TPHA +ve

Three factors to be considered

- PK change
- Placental cross
- Drug safety

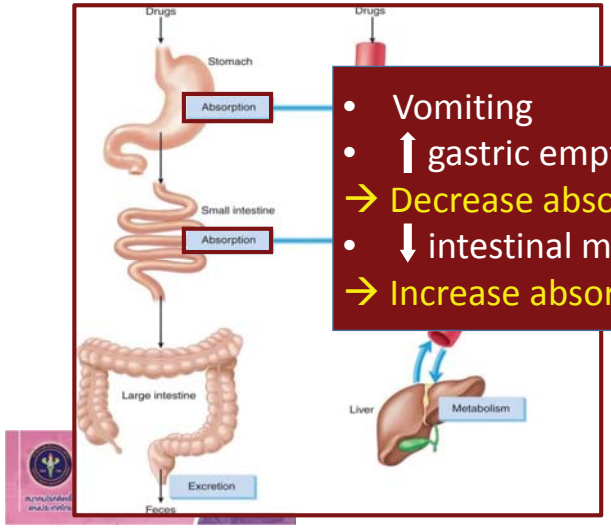
Pharmacokinetics



https://nootropix.com/what-happens-to-drugs-inside-body

ADME
- Absorption
- Distribution
- Metabolism
- Elimination

PK change in pregnancy
Absorption



- Vomiting
- ⬆ gastric emptying time

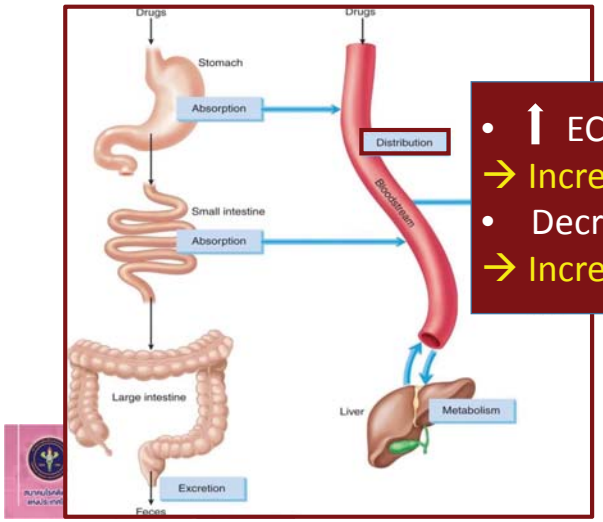
→ Decrease absorption

- ⬇ intestinal motility

→ Increase absorption

Chow AW, et al. Rev Infect Dis 1985;7:287-313
Feghali M, et al. Semin Perinatol 2015;39:512–9

PK change in pregnancy
Distribution



- ⬆ ECF/TBW → ⬆ Vd

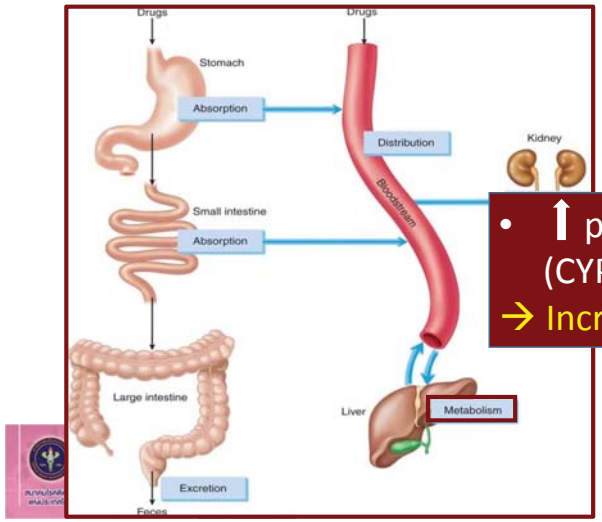
→ Increase distribution

- Decrease albumin

→ Increase free form

Chow AW, et al. Rev Infect Dis 1985;7:287-313
Feghali M, et al. Semin Perinatol 2015;39:512–9

PK change in pregnancy
Metabolism



- ⬆ progesterone (CYP450 inducer)

→ Increase metabolism

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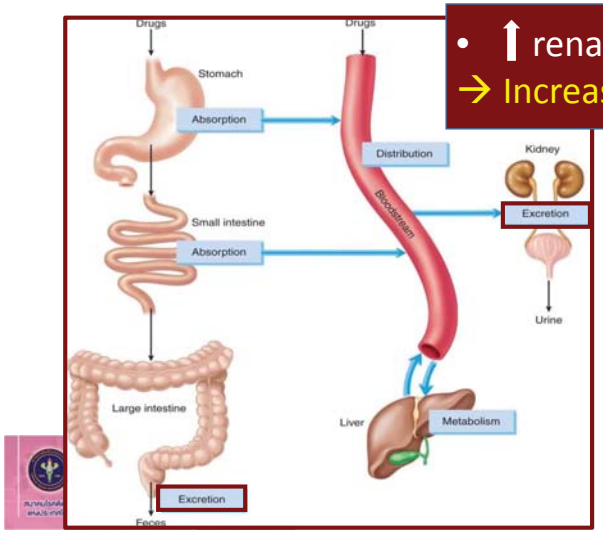
Feghali M, et al. Semin Perinatol 2015;39:512–9

PK change in pregnancy
Elimination



- ⬆ renal blood flow

→ Increase elimination

Chow AW, et al. Rev Infect Dis 1985;7:287-313
Feghali M, et al. Semin Perinatol 2015;39:512–9

PK change in pregnancy

- Decrease absorption
- Increase distribution
- Increase metabolism
- Increase elimination

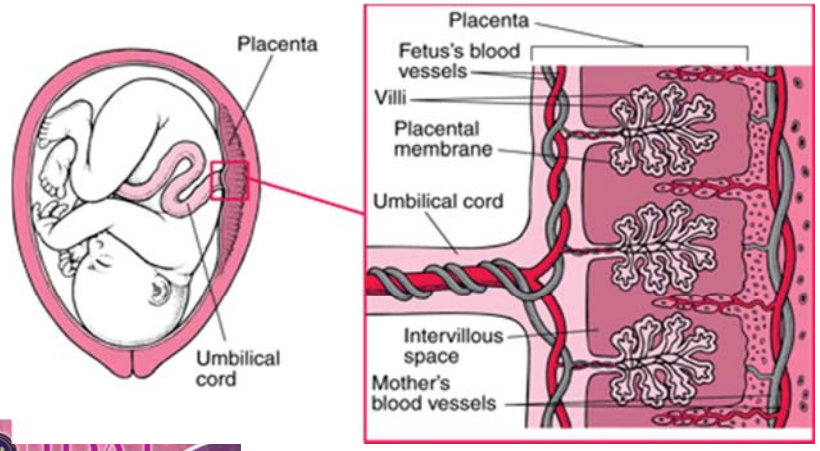
→ Require high dosage

Three factors to be considered

- PK change
- Placental cross
- Drug safety

Placental cross

- ✓ Fat soluble
- ✓ Non-ionized
- ✓ Low MW



www.merckmanuals.com/home/women-s-helath-issues/drug-use-during-pregnancy/drug-use-during-pregnancy

Three factors to be considered

- PK change
- Placental cross
- Drug safety

Drug safety

Pregnant woman ←→ Fetus

- Data: case control or cohort study
- Old US FDA: 5 pregnancy category

Category	Level of Evidence
A	No AEs in human pregnancy *Safety established using well-controlled human studies*
B	Presumed safety in human pregnancy *Limited human studies/no AE in animal studies*
C	Uncertain safety *Limited human studies/AE in animal studies*
D	AEs in pregnancy *Benefits may outweigh associated risks*
X	AEs in pregnancy *Risks outweigh possible benefit*

Bookstaver PB, et al. Pharmacotherapy 2015;35:1052-62

Antibacterial agents

Recommend as 1st line

Use only indicated

Avoid use in pregnancy

Antibacterial agents

Recommend as first line agents

- Penicillin (B)
- Cephalosporin (B)
- BL/BI (B)
- Macrolide (B, Clarithro:C)

AVOID *erythromycin estolate*
esp. in 2nd & 3rd trimester
→ hepatotoxicity

Mylonas I. Arch Gynecol Obstet 2011;283:7-18
Lewis JH. Eur J Gastroenterol Hepatol 1991;3:883-91

Antibacterial agents

AVOID use in pregnancy

- Chloramphenicol (D)
- Aminoglycoside (D)
- Tetracycline (D)
- Fluroquinolone (C)

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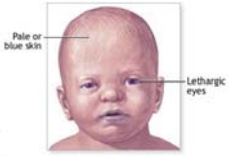
Adam MP, et al. Am J Med Genet 2011;Part C:175-82
Basim I, et al. Therapeutic principles in practice 5th ed
Lamont HF, et al. Expert Opin Drug Saf 2014;12:1569-81
Wenk RE, et al. J Reprod Med 1981;26:135-41
Whalley PJ, et al. Obstet Gynecol 1970;88:27-33
Landers DV, et al. Am J Obstet Gynecol 2004;190:1004-10
Czeizel AE, et al. Eur J Obstet Gynecol Reprod Biol 2000;88:27-33

Antibacterial agents



Chloramphenicol
- Gray baby syndrome

Aminoglycoside
- Irriversible congenital deafness (1st trimester)

Streptomycin
Prefer: Gentamicin

Tetracycline
- Tooth discoloration & limit long bone growth of newborn
- Fatty liver & nephropathies of pregnant woman

Fluoroquinolone
- Abortion in animal model
- Inhibit cartilage & bone growth in animal model

Oflox, levoflox
Prefer: Norflox, ciproflox

Antibacterial agents

Recommend as alternative agents
or use only indicated
- Cotrimoxazole
- Metronidazole & Clindamycin
- Fosfomycin & Nitrofurantoin

ATB for MDR pathogens
- Vancomycin & Linezolid
- Carbapenem & Colistin

Antimycobacterial agents
- IRZE

Antibacterial agents

ATBs	FDA	Caution
Cotrimoxazole	C	Teratogenicity in animal model (1st trimester) Kernicterus (GA > 32 weeks)
Metronidazole	B	Carcinogenicity in animal model Congenital hydrocephalus (intravaginal form)
Clindamycin	B	Antibiotic associated diarrhea
Fosfomycin	B	Use in cystitis only
Nitrofurantoin	B	Use in cystitis only, avoid in G6PD def

Mylonas I. Arch Gynecol Obstet 2011;283:7-18
Bookstaver PB, et al. Pharmacotherapy 2015;35:1052-62
Takayama S, et al. Arzneimittelforschung 1986;36:1244-8
Kazy Z, al. Eur J Obstet Gynecol Reprod Biol 2005;2:174-8
Kinzy BJ, et al. Ann Intern Med 1984;101:565
Brumfitt W, et al. J Infect Dis 1973;128:657-63
Boskovic R, et al. Therapeutic principles in practice 5th ed

Antibacterial agents

ATBs	FDA	Caution
Carbapenem	B C (Imipenem)	Use only indicated
Vancomycin	C	Nephrotoxicity
Linezolid	C	Limited data
Colistin	C	Nephrotoxicity

Mylonas I. Arch Gynecol Obstet 2011;283:7-18
Bookstaver PB, et al. Pharmacotherapy 2015;35:1052-62

Antivirals & Antifungals

Antivirals	FDA
Acyclovir	B
Valacyclovir	C
Cidofovir	C
Oseltamivir	C
Zanamivir	C
Ribavirin	X

Antifungals	FDA
Nystatin	A
Amphotericin B	B
Echinocandins	C
Itraconazole	C
Posaconazole	C
Fluconazole	C (150 mg) D (400-800 mg)
Voriconazole	D

Vlachadis N, et al. N Engl J Med 2013;369:2061
Kochhar DM. Toxicol Appl Pharmacol 1980;52:99-112
Cottreau JM, et al. Pharmacotherapy 2016;36:669-78
Pilmis B, et al. J Antimicrob Chemother 2016;70:14-22
Svensson T, et al. Pharmacopeidemiol Drug Saf 2011;20:1030-4
Tiboni GM. Res Commun Chem Pathol Pharmacol 1993;79:381-4
Wollenhaupt M, et al. Pharmacopeidemiol Drug Saf 2014;23:1035-42

Antimalarials & Antihelminthes

Antimalarials	FDA
Mefloquine	B
Chloroquine	C
Quinine	C
Artesunate*	Unclassified
Primaquine**	Unclassified
Doxycycline	D

Antihelminthes	FDA
Praziquantel	B
Albendazole	C
Mebendazole	C
Ivermectin	C

* Artesunate: Teratogenicity in <u>animal model</u>
Use with caution in 1st trimester

** Primaquine: Acute hemolysis in NB with G6PD deficiency

Yakasi IA, et al. AJSC 2013;2:31-8
Kovacs SD, et al.Drug saf 2015; 38: 165–181
Nosten F, et al. Current Drug Safety 2006;1:1-15

Infection in pregnancy: case 1

27-year-old pregnant woman without symptoms
U/A no WBC but urine C/S: *E. coli* >10^5 CFU/ml X 2

I/C of ATBs: Asymptomatic bacteriuria

✓Reduce incidence of pyelonephritis by 52-86%

Choice of ATBs

✓Nitrofurantoin, coamoxiclav: good efficacy and safety
? Fosfomycin: limited study in pregnancy
? Amoxicillin, cephalexin : high rate of resistance
? Cotrimoxazole: high rate of resistance, caution in 1st and term
X Fluoroquinolone: avoid use in pregnancy

Infection in pregnancy: case 2

37-year-old pregnant woman without symptoms
She is allergic to penicillin
VDRL +ve, TPHA +ve

I/C of ATBs: Latent syphilis

✓ Reduce incidence of congenital syphilis by 68-98%

Choice of ATBs

✓PGS: Good efficacy and adequate placental cross
→ Skin test then desensitization if positive (except SJS/TEN)
X Macrolide: Poor placental cross
X Doxycycline: Fair efficacy but contraindicated in pregnancy

Antimicrobial use in pregnancy

- Use only indicated
- Precounseling
- Use safest drug
- Use well known drug
- Prefer oral agent
- Prefer monotherapy
- Prefer high dosage
- Prefer shortest duration

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