

IMPACT OF PREGNANCY ON PHARMACOKINETICS OF MEDICATIONS

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ABSTRACT

Pregnancy is associated with significant physiological changes that alter the pharmacokinetics and pharmacodynamics of medications during pregnancy. This overview describes the effects of pregnancy on kidney filtration, drug transport, drug metabolism, protein binding, and their clinical implications for drug therapy.

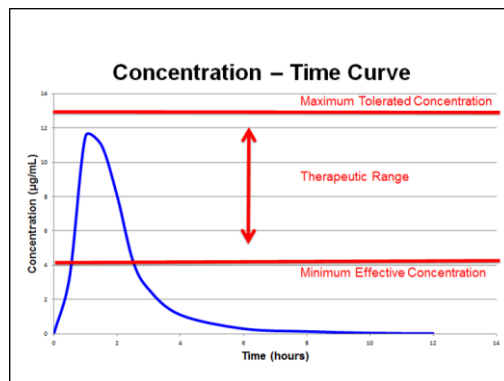
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Pregnancy is associated with significant physiologic changes that have the potential to alter medication selection and dosage.¹⁻⁶ Understanding the effects of pregnancy on total drug exposure is often the first step in understanding a drug's pharmacokinetics. Figure 1 represents a stereotypical oral drug concentration-time profile.⁷ As an oral drug is absorbed, the blood concentrations rise and then peak. As the

drug finishes distribution and is eliminated, the concentrations fall off. The ideal situation is to maintain concentrations for medications above the minimum effective concentration, but less than the maximum tolerated concentration. Many disease states, drug interactions, and some conditions, such as pregnancy, can alter the drug concentration-time curve resulting in sub-therapeutic concentrations, as can be seen in Figure 2.⁷

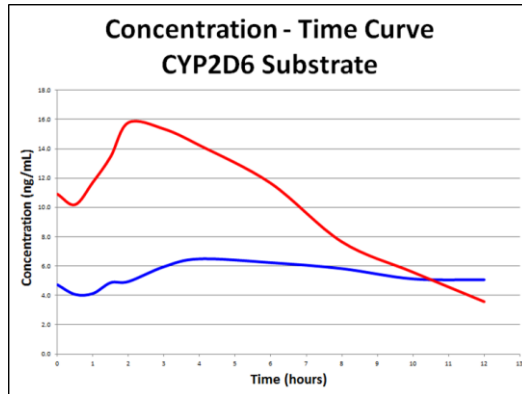
FIG. 1 Stereotypical oral concentration-time curve.

The upper horizontal solid line represents the maximum tolerated concentration and the lower horizontal solid line represents the minimum effective concentration. The therapeutic range for this drug, represented by the vertical double-sided arrow, includes all the concentrations between the minimum effective concentration and the maximum tolerated concentration.



(Hebert MF. Impact of Pregnancy on Maternal Pharmacokinetics of Medications, chapter in *Clinical Pharmacology During Pregnancy*, San Diego: Elsevier; 2013.⁷)

FIG. 2 Concentration-time curves for a CYP2D6 substrate during pregnancy represented by the blue line and in the same subject 3 months postpartum represented by the red line.

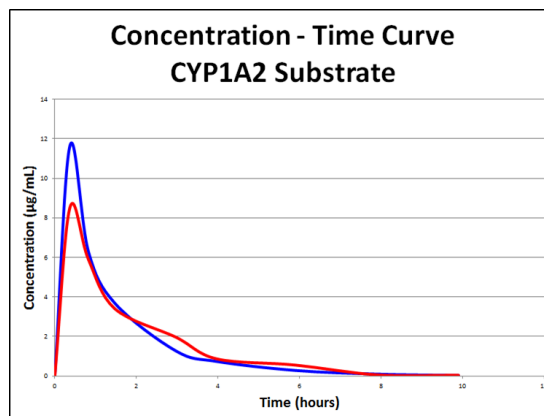


(Hebert MF. Impact of Pregnancy on Maternal Pharmacokinetics of Medications, chapter in Clinical Pharmacology During Pregnancy, San Diego: Elsevier; 2013.⁷)

In pregnancy, when drug concentrations are much lower than expected, the concern is not only for the mother, who is taking a drug that has no chance for benefit and who risks complications from uncontrolled disease, but also for the fetus, that is unnecessarily exposed to the drug and may also suffer potential complications from an inadequately treated maternal disease. In contrast, pregnancy can sometimes result in elevated drug concentrations and increase the risk for toxicity, as can be seen in Figure 3.⁷ In this case, both the mother and fetus are unnecessarily put at risk for

intolerable side effects. Typically, when concentrations are either higher or lower than needed, dosage regimens are modified in order to achieve similar concentrations as in the population in which the drug has been approved. This overview describes the effects of pregnancy on kidney filtration, drug transport, drug metabolism, protein binding, and their clinical implications. The examples presented should be considered off label use, either because the indication for use or dosage differences in pregnancy are not included in product labelling.

FIG. 3 Concentration-time curves for a CYP1A2 substrate during pregnancy represented by the blue line and in the same subject 10 days postpartum represented by the red line.



(Hebert MF. Impact of Pregnancy on Maternal Pharmacokinetics of Medications, chapter in Clinical Pharmacology During Pregnancy, San Diego: Elsevier; 2013.⁷)

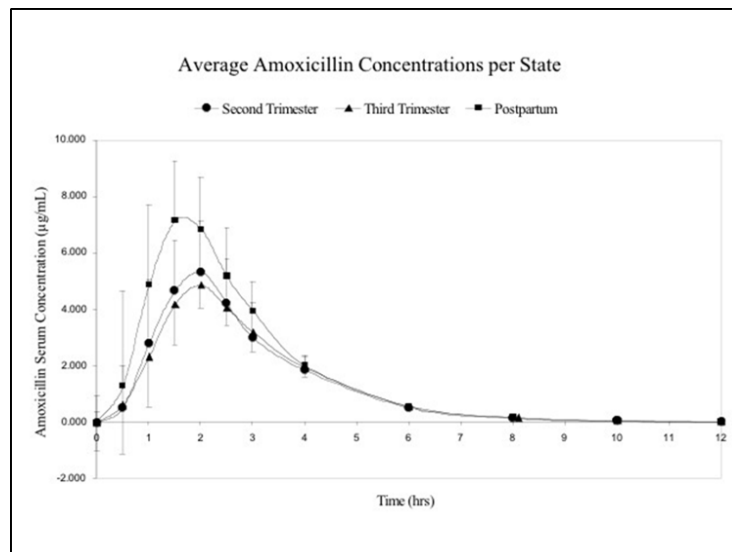
Kidney Filtration and Transport

About one-third of medications used clinically are eliminated by the kidneys. Renal filtration, as measured by creatinine clearance, increases starting in the first trimester (T1) of pregnancy. It peaks sometime during mid-second trimester (mid-T2), and begins to fall off during the last few weeks of pregnancy in some individuals.^{8,9} Pregnancy-induced changes in creatinine clearance occur in both obese (BMI > 30 kg/m²) and non-obese (BMI < 30 kg/m²) women.¹ Furthermore, the changes seen in creatinine clearance during pregnancy correlate well with the renal clearance of drugs such as atenolol and digoxin.^{2,4} Taking atenolol as an example, creatinine clearance and atenolol renal clearance are strongly correlated during pregnancy and postpartum ($r = 0.8$).² This correlation holds true for creatinine clearances as low as ~50 mL/min to as high as almost 400 mL/min, as can be seen in obese pregnant women.¹

Another example of a renally eliminated drug is amoxicillin. Figure 4 illustrates that amoxicillin serum concentrations are substantially lower in the second and third trimesters of pregnancy as compared to 3 months postpartum.³

Since amoxicillin is most commonly used in the treatment of uncomplicated urinary tract infections and amoxicillin is excreted almost entirely unchanged in the urine, these changes in systemic concentrations have not been particularly important. However, for organisms such as *Bacillus anthracis*, which does not have a post-antibiotic effect and therefore requires sustained systemic concentrations, attention to the pharmacokinetic changes seen during pregnancy is essential. Although recommendations for prophylaxis in the setting of inhalation anthrax exposure for pregnant women has been amoxicillin 500 mg 3 times a day for 60 days, these dosage guidelines are inadequate to maintain trough concentrations above the minimum inhibitory concentration for sensitive anthrax isolates and might result in the development of resistant organisms.^{3,10,11} In order to maintain concentrations of amoxicillin above the minimum inhibitory concentration for susceptible anthrax isolates (MIC = 0.12 mcg/mL), amoxicillin would need to be administered every 4 hours.³ Unfortunately, adhering to a regimen with a four-hour dosing interval for 60 days would be extremely challenging, if not impossible.

FIG. 4 Average amoxicillin concentration-time profiles for 16 subjects during the second trimester (18-22 weeks gestation, closed circles), third trimester (30-34 weeks gestation, closed triangles) and postpartum (3 months ± 2 weeks, closed squares). Error bars represent standard deviations.



(From Andrew MA, et al. Clin Pharmacol Ther. 2007;81(4):547-556.³)

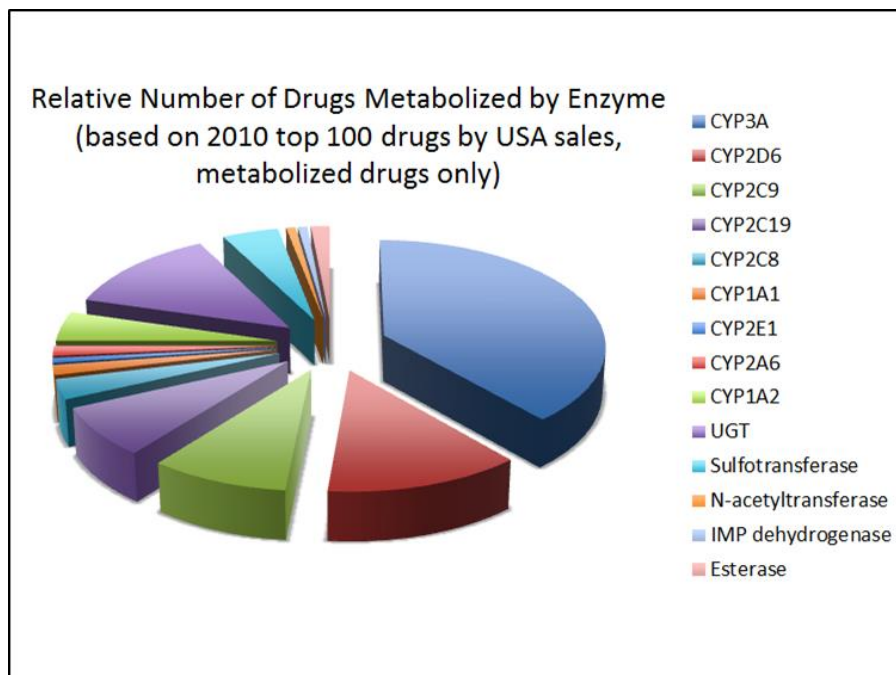
In addition to changes in renal filtration during pregnancy, notable changes have been observed in the active transport of drugs by the kidneys, resulting in an increase in the net renal secretion of medications such as digoxin, amoxicillin and metformin.³⁻⁵ The secretion of these drugs involves multiple transporters. Digoxin has been used as the gold standard probe for p-glycoprotein. During the 3rd trimester of pregnancy, compared to 6-10 weeks postpartum, the net renal secretion of digoxin is doubled.⁴ Amoxicillin is known to be actively secreted by organic anion transporter (OAT) and reabsorbed by oligopeptide transporters, hPepT1 and hPepT2. In both the second and third trimesters of pregnancy, the net renal secretion of amoxicillin increases by ~100 mL/min.³ Similarly, the net renal secretion of metformin, a substrate for organic cation transporter 2 (OCT2), increases by ~100 mL/min in both the second and third trimesters of pregnancy as compared to 3 months postpartum.⁵ For metformin, which is an

intermediate extraction ratio drug, the increase in secretion is dependent on both active transport and renal blood flow, both of which may be altered by pregnancy.

Metabolism

The metabolism of drugs takes place primarily in the liver and intestines, although it can also occur in other places, such as the blood, lungs and kidneys, depending on the drug. Figure 5 depicts the relative number of drugs metabolized by Phase 1 and Phase 2 enzymes (based on metabolized drugs from the 2010 top 200 drug list¹²). Cytochrome P450 3A (CYP3A) is responsible for the metabolism of more drugs than any of the other enzymes. Other enzymes involved in the metabolism of many drugs include CYP2D6, CYP2C9, CYP2C19, UDP glucuronyltransferases (UGT) and sulfotransferases. Pregnancy has differing effects on the apparent activity of the various enzymes.^{4,13-16}

FIG. 5 Pie chart representing the relative number of drugs metabolized by each of the Phase 1 and Phase 2 enzymes. Data based on metabolized drugs from the 2010 top 100 drug list.



CYP1A2

Tracy et al. studied the effects of pregnancy on CYP1A2 activity at 14-18 weeks, 24-28 weeks and 36-40 weeks gestation, utilizing caffeine as a probe substrate. Over the course of gestation, they found a ~30-65% decrease in CYP1A2 activity.¹³ This apparent decrease in enzyme activity may result in higher concentrations of CYP1A2 substrates and potentially increased risk of toxicity during pregnancy.

CYP2C19

Similarly, CYP2C19 activity appears to be decreased in pregnancy. Utilizing the ratio of proguanil to cycloguanil, McGready et al. demonstrated lower CYP2C19 activity during pregnancy compared to 2 months postpartum in CYP2C19 extensive metabolizers. No significant differences were seen in CYP2C19 poor metabolizers.¹⁴

CYP2D6

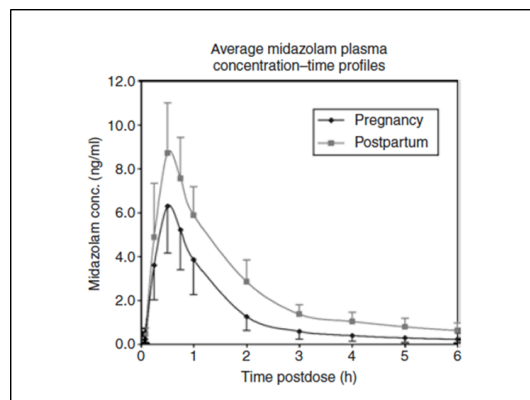
In contrast to CYP1A2 and CYP2C19, CYP2D6 activity appears to be increased in pregnancy. Utilizing metoprolol, the gold standard probe for CYP2D6, Högstedt et al. found a markedly increased clearance during pregnancy, in a small number of subjects (n=5).¹⁵ Consistent with these findings, Tracy et al. utilizing dextromethorphan as a CYP2D6 probe reported ~25-50% increase in CYP2D6 activity during early-, mid- and late-pregnancy as compared to postpartum.¹³ Although dextromethorphan is not the ideal probe for CYP2D6, given the involvement of other enzymes in its metabolism, such as CYP3A, the results provide

supportive evidence that CYP2D6 activity is increased during pregnancy.

CYP3A

There is also evidence of increased activity of CYP3A during pregnancy. Utilizing midazolam as a probe, we found a marked increase in CYP3A activity during pregnancy.⁴ Figure 6 demonstrates the impact of pregnancy on midazolam concentrations in women 28-32 weeks gestation as compared to 6-10 weeks postpartum.⁴ Total midazolam drug exposure ($AUC_{0 \rightarrow \infty}$) during pregnancy was about half of postpartum exposure. Consistent with this, midazolam apparent oral clearance was more than doubled, as was the 1'OH-midazolam formation clearance. Protein binding differences were very small and did not contribute to the marked changes in midazolam pharmacokinetics during pregnancy. These large changes in CYP3A activity seen during pregnancy are of particular concern given the large number of drugs metabolized by CYP3A. One clinical example of the impact of changes in CYP3A activity is highlighted by a study reported by Unadkat et al.⁶ Concentrations during pregnancy of indinavir, a substrate for CYP3A and P-glycoprotein, are approximately 1/3 of those in women 6-10 weeks postpartum.⁶ Since indinavir is used for the treatment of HIV, these lower concentrations are of great concern. When HIV is exposed to subtherapeutic concentrations of antiviral agents, resistance develops. This is not only a problem for the mother, but also increases the potential for transmission of resistant virus to the baby.

FIG. 6 Mean midazolam plasma concentration-time curves during pregnancy and postpartum. Error bars represent SD.



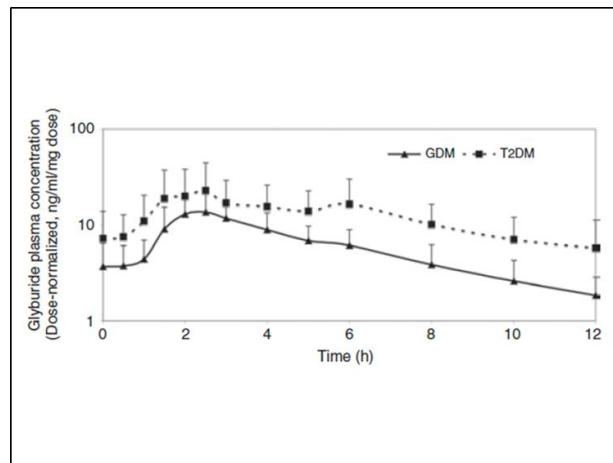
(Hebert MF, Easterling TR, Kirby B, Carr DB, Buchanan ML, Rutherford T, Thummel KE, Fishbein DP, Unadkat JD. Effects of pregnancy on CYP3A and P-glycoprotein activities as measured by disposition of midazolam and digoxin: a UW SCOR study. Clin Pharmacol Ther. 2008;84:248-253.⁴)

CYP2C9

Apparent CYP2C9 activity is also increased during pregnancy. Yerby et al. showed that unbound phenytoin (CYP2C9 substrate) clearance is significantly greater during all three trimesters of pregnancy as compared to the pre-pregnancy state.¹⁶ In addition, glyburide is a substrate for CYP2C9 as well as CYP3A and CYP2C19. With CYP2C9 and CYP3A activity being increased in pregnancy but CYP2C19 activity being decreased, we evaluated glyburide pharmacokinetics in women with gestational diabetes mellitus in their third trimester of pregnancy as compared to non-pregnant women with type 2 diabetes mellitus.

Plasma concentrations of glyburide were markedly lower in pregnancy (Figure 7).¹⁷ Utilizing modelling and simulations, we estimated that maximum dosage would need to be more than doubled to achieve the same concentrations of glyburide in pregnancy as in the non-pregnant state.¹⁷ Caution is advised when considering higher dosage during pregnancy because glyburide does cross the placenta. Safety data currently available during pregnancy are limited to maximum doses of 10 mg twice daily. In addition, given that pregnancy is a state of insulin resistance and hyperinsulinemia, response to therapy is likely to be different than in non-pregnant individuals.¹⁸

FIG. 7 Dose-normalized, steady state, mean glyburide plasma concentration-time curves in women with gestational diabetes mellitus during pregnancy (n=40) and non-pregnant women with type 2 diabetes mellitus (n=25). Error bars represent SD.



(Hebert MF, Ma X, Narahariseti SB, Krudys KM, Umans JG, Hankins GDV, Caritis SN, Miodovnik M, Mattison DR, Unadkat JD, Kelly EJ, Blough D, Cobelli C, Ahmed MS, Snodgrass WR, Carr DB, Easterling TR, Vicini P for the Obstetric-Fetal Pharmacology Research Unit Network. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. Clin Pharmacol Ther. 2009;85:607-614.¹⁶)

UGT1A4

UGT1A4 is yet another enzyme whose activity increases during pregnancy. Lamotrigine undergoes Phase 2 metabolism by UGT1A4. de Haan et al. reported increased seizure activity in a

small cohort of pregnant women on monotherapy with lamotrigine.¹⁹ Consistent with this was their finding that the ratio of lamotrigine serum concentration to dose dropped over the course of pregnancy.

Disposition

Pregnancy can also alter drug disposition. Increased body weight over the course of pregnancy is one factor affecting drug disposition. Body weight changes do not return to baseline immediately post-delivery and some women continue to gain weight at 3 months postpartum and beyond.²

Drug binding also changes during pregnancy. Decreases in serum albumin, hemoglobin, and alpha 1-acid glycoprotein are expected during normal pregnancy. These changes can affect the binding of some drugs. For example, the free fraction of phenytoin is significantly increased during the second and third trimesters of pregnancy, as well as during labor and delivery.¹⁶ Tacrolimus is another drug with altered binding during pregnancy. Tacrolimus is a lipophilic drug that concentrates in erythrocytes and also binds to plasma albumin and alpha-1-acid glycoprotein.²⁰ We found that dose adjustments of tacrolimus in response to lower whole blood levels during pregnancy resulted in increased unbound concentrations in pregnant women.²¹ Changes in hemoglobin, as well as the lower serum albumin and alpha-1-acid glycoprotein in this population, affect how we can interpret drug concentrations in pregnancy.²⁰ Although clinical laboratories are routinely able to measure free phenytoin concentrations, the ability to assay free tacrolimus concentrations is challenging and is largely limited to the research arena.

SUMMARY

Although pregnancy appears to increase the activity of some enzymes (CYP3A, CYP2D6, CYP2C9 and UGT), other enzymes (CYP1A2 and CYP2C19) seem to have decreased activity. Renal filtration and active transport also appear to be increased during pregnancy. In addition, changes in protein binding can occur, particularly for highly bound drugs. Understanding the protein binding changes during pregnancy is critical to the clinical interpretation of drug concentrations. This presentation was intended to provide an overview of some of the physiological changes occurring during pregnancy and how these changes can have significant clinical implications for drug therapy.

Although changes in pharmacokinetics occur during pregnancy, it is essential to recognize that the potential also exists for changes in pharmacodynamics. One needs to account for both pharmacokinetic and pharmacodynamic differences to optimize medication selection and dosing during pregnancy. Limited work has been done in the area of obstetric-fetal pharmacology, yet a critical mass of investigators is still needed to expand our understanding of the pharmacokinetics and pharmacodynamics of drugs in pregnancy and to help resolve issues in the treatment of this special patient population.

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