

PHARMACOKINETICS IN PREGNANCY; CLINICAL SIGNIFICANCE

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ABSTRACT

In pharmacokinetics drug absorption, distribution, clearance, and bioequivalence are usually considered, but during pregnancy the most important variable is adherence or compliance. Pharmacokinetic changes during pregnancy that may lead to changes in maternal drug use are described through presentation of cases highlighting the relevance of these changes. Non-invasive methods of pharmacokinetic analysis, such as determining concentrations of drug in hair, are now being tested and used.

Pharmacokinetics are important, but one needs to consider the entire pregnant state and its circumstances when treating women. One treats people, not a "volume of distribution" or a drug level. Therapy should be individualized as much as possible, addressing kinetic changes in the context of dynamic alterations and the effects of underlying medical conditions. To ensure that women are not orphaned from advances in drug therapy, much more research is needed into the determinants of pharmacokinetic and pharmacodynamic changes in pregnancy.

Key Words: *Pharmacokinetics, pharmacodynamics, bioequivalence, pregnancy, hair analysis*

Introduction

The objectives of this presentation are to describe pharmacokinetic changes during pregnancy that may lead to changes in maternal drug use, through presentation of cases highlighting the relevance of these changes. In pharmacokinetics one usually considers drug absorption, distribution, clearance, and bioequivalence, but it is my view that during pregnancy the most important variable is adherence, or as it was called previously, compliance.

Adherence

Case Report - A 28-year-old woman with moderate-to-severe asthma was put on montelukast, discovering later that she was at 8 weeks of pregnancy. On learning of her pregnancy, she was herself fearful, and was also frightened by family members and women's magazines that noted drugs may be "bad for the baby". She therefore discontinued taking her medication at 16 weeks' gestation. At 19 weeks, she was brought to Emergency with a severe

asthma attack and died 3 hours later from respiratory failure.

Ever since the thalidomide disaster, there have been high levels of sensitivity regarding teratogenic risks of drugs. In reality, very few drugs have been shown to cause malformations, many others are safe to take during pregnancy, while for quite a few we have insufficient information. Many women, and members of the public in general, believe that to avoid fetal malformations, women should take *nothing* during pregnancy. This leads women to not take medication as prescribed, even for life-threatening conditions. For example, at Motherisk we often counsel women suffering from depression who were told not to take their selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). These women frequently stop their medication, despite being well managed, which often results in deeper depression, hospitalization, and suicide ideation and attempts. Such can be the cost of misperception.

As another example, Motherisk conducts many studies of poor adherence to drug therapy during pregnancy, using vitamins as the target treatment. Women who are keenly interested in participating are recruited and volunteer to participate in these pharmacokinetic/pharmacodynamic studies. Unfortunately, their adherence is quite variable: on average, they take only 53% of their study doses. Factors that can affect adherence during pregnancy can include whether a woman suffers from nausea and vomiting of pregnancy, i.e., not being able to keep down her medications, and medication tolerance: a smaller tablet size will be better tolerated, as will a low iron content in vitamins. Assessment of adherence is critical in evaluating poor response. The biggest variable in kinetics is whether the drug was taken in the first place.

With such poor levels of compliance, it is important for healthcare practitioners to investigate the reasons for them and to assist patients to take their medications. Counselling on the lack of teratogenic and other adverse fetal effects is crucial.

Absorption

These days, with delays in the timing of first pregnancies to a later age, there is a higher potential for mothers to have a chronic illness. The role of the underlying condition needs to be considered. For example, inflammatory bowel disease can be present in up to 5% of women during their productive years. Chronic bowel conditions can result in impaired absorption of nutrients, vitamin B₁₂, and potentially of medications.

In nausea and vomiting of pregnancy, there may be delayed absorption of drugs or incomplete dosing due to vomiting, so drugs may not be absorbed at all or absorbed only partially. Should another dose be given if vomiting occurs soon after the drug is taken? Should the dose be changed? Various disorders and conditions that affect drug absorption have important implications for drug dosing, kinetics, and efficacy.

Distribution

After absorption, a drug is distributed throughout the body into various compartments, depending on the nature of the molecule. A large increase in

body weight can result in a relatively decreased dose per kilogram, and thus a decrease in steady state concentration.

Drug concentration is dependent on the dose per kg and on the clearance rate. In the third trimester there is a physiological decrease in serum albumin. Drugs which are highly albumin bound will then have decreased protein binding, be available to distribute further into other tissues/spaces, and thus have a larger volume of distribution; furthermore, more free drug will be available for elimination. Some may believe that an increased dose would then be required, given the larger volume of distribution, however, both the disease state and the pregnancy state need to be considered when adjusting drug dosing.

Elimination - Clearance Rate

Drug elimination in pregnancy has been an active area of study in the last two decades. It is acknowledged that there is increased activity of several CYP450 enzymes in late pregnancy (third trimester). This means that the elimination of drugs which are substrates to these enzymes will increase, and their steady state levels will therefore decrease. Below are some examples of the CYP450 isozymes and the drugs they affect.

CYP3A4 - is involved in the metabolism of protease inhibitors and midazolam. A woman receiving protease inhibitors before pregnancy for treatment of HIV/AIDS will require anywhere from 2 to 3 times the dose during pregnancy. Midazolam dosing may also need to be increased.

CYP2D6 - activity is increased, so that fluoxetine and other SSRIs/SNRIs will be more highly metabolized. However, dose changes may not be required for sertraline, which is an example of a drug that is metabolized to an active compound.

CYP2A6 - has nicotine as a substrate, and its metabolism is increased in late pregnancy. Smokers may find their habit or addiction worsened as their nicotine blood levels decrease. Women treated for smoking cessation with a nicotine patch may require higher doses in late pregnancy.

The activity of the cytochrome enzyme family is not generalizable in pregnancy, as some isozymes may have increased activity, while

others will have decreased activity. The production of active metabolites must also be kept in mind (e.g., sertraline, venlafaxine).

Examples of enzymes that have decreased activity in pregnancy are CYP1A2, involved in the metabolism of theophylline and caffeine, and CYP2C19, for which phenytoin is a substrate. These drugs will be eliminated more slowly during pregnancy, thus patients should be monitored for higher drug levels.

Besides these metabolic changes, for which the mechanisms remain unknown, there are changes in glomerular filtration rate (GFR) and hepatic blood flow. In late pregnancy, there is an increase of up to 50% in GFR. This results in increased clearance of renally eliminated drugs, such as lithium, digoxin, aminoglycosides. In addition, there is increased active renal tubular secretion. For example, p-glycoprotein, responsible for digoxin renal secretion and is the most studied renal transporter, is another clearance mechanism increased in late pregnancy.

There is also the situation where active metabolites are more highly renally eliminated, resulting in lowered drug effect. This is the case with morphine. It is metabolized to an active glucuronidated metabolite that is more highly cleared in late pregnancy, causing a lowered analgesic effect for the same drug dose.

Two groups of researchers recently published study results on oseltamivir kinetics in pregnancy.^{1,2} Beigi and colleagues compared disposition of the drug in pregnant vs. non-pregnant women and found no changes in the area under the curve (AUC) of oseltamivir, but found a significant decrease in oseltamivir carboxylate, the active metabolite.¹ The active metabolite was cleared more quickly during pregnancy. Greer et al. compared three groups of pregnant women, 10 in each trimester.² They found no differences in AUC or in clearance of the active metabolite among the three subject groups and among the trimesters of pregnancy. Unfortunately, these results, although interesting, need further study, and the studies may require a power calculation to determine whether the number of subjects was sufficient to show significance.

Overall, the pregnant patient needs to be aware that in late pregnancy she could need higher doses of her medication(s). This may be counter-intuitive to her attempt to use fewer drugs or

lower doses. Where drug levels can be monitored, this should be done to determine appropriate dosing changes. For drugs which are not managed using drug levels, then clinical effects and adverse effects should be monitored and doses adjusted as needed—for example, in cases where symptoms are increased (drug effect is diminished), this may be due to increased drug clearance, whether that is due to pregnancy-related metabolic changes or to underlying genetic polymorphism. The minimum instructions to the patient would be to have her seek attention if she is experiencing toxicity or is having symptoms that are not being controlled.

Novel Methods to Study Metabolic Changes in Pregnancy

It is unrealistic to have a pregnant woman be admitted to hospital for the express purpose of monitoring her drug levels by our traditional method of taking repeated blood samples. Hair analysis, on the other hand, is non-invasive and can provide a history of drug and metabolite levels. Hair assay can provide the drug:metabolite ratio of specific drugs. Hair grows approximately 1 cm per month, and can therefore provide long-term information. This method of analysis has been the domain of forensic scientists, and we are learning from their research. Below are a couple of examples from our own studies.

Nicotine - We conducted a study to analyze the hair content of nicotine and of cotinine, its metabolite, in pregnant women who smoked throughout their pregnancy.³ The hair was collected at the time of delivery and sectioned into segments representing the three trimesters. It was found that during pregnancy, nicotine had decreasing levels, whereas cotinine levels remained consistent: the cotinine to nicotine ratio being greater in late pregnancy. The lower levels of nicotine equated to a 50-75% increase in clearance. This may explain the failure of regular nicotine patch doses as an aid for smoking cessation in late pregnancy.

Venlafaxine - Venlafaxine has become a drug of choice for the treatment of depression in pregnancy. We found that in late pregnancy there was an increased production of the active metabolite.⁴ Table 1 shows the results of a single patient, who took the same dose of drug

throughout her pregnancy and volunteered to have her blood levels drawn. This woman's blood levels in the third trimester fell to almost half of the first trimester levels, the trend for which was the same as for the AUC results. Given that she was compliant with taking her doses, this change could indicate either decreased absorption or increased clearance. The ratio of metabolite to parent drug

was the reverse, with about double the blood level of metabolite to parent drug in the third trimester.

This subject's hair analysis results are shown in Table 2. From the 3rd month of pregnancy to the 9th month, there was a rise in metabolite:parent drug ratio, similar to what was found in the blood results. Hence, this method of analysis may replace the use of blood levels.

TABLE 1 Pharmacokinetics of Venlafaxine in Blood for A Sample Patient

Parameter	1 st Trimester	3 rd Trimester
C _{max} (ng/mL)	422	270
AUC (ng.h/mL)	3357	1965
Metabolite:Parent Drug Ratio	0.9	1.96

TABLE 2 Pharmacokinetics of Venlafaxine in Hair for A Sample Patient

Month of Pregnancy	Metabolite: Parent Drug Ratio
3	0.44
6	1.47
9	1.69
3 months post partum	0.74

Again, hair analysis is non-invasive. It can be used to determine population kinetics as well. Testing the hair of many women can serve to determine not only the change in drug concentrations over the term of pregnancy, but also the degree of change among different women. These changes could further be correlated to genotype.

Bioequivalence

Case Example - A company wishes to introduce a generic form of a drug for the treatment of pregnancy-induced biliary cholestasis. They compare their drug to the marketed compound by recruiting 20 men and studying bioequivalence. They claim that "although men may have different absorption or clearance - the comparison of 2 drugs in the same man is valid for women, because gender variability in bioequivalence is similar." But is the variability in both men and women truly the same?

Chen et al. showed that for many drugs gender variability may indeed be similar, but in others this may not be the case.⁵ In their review of bioequivalence studies, 35% of drugs had differences in peak levels between men and women, and 13% showed differences in AUC. Overall, they reported that 28% of the data sets had a statistically significant difference between genders. It is clear that differences between men and women exist in the pharmacokinetics of some drugs. If variability may be different between women and men, then the results could be different depending on your volunteer group's ratio of males to females (e.g., 50:50 vs. 30:70). On top of this, we then need to consider that some drugs are indicated for use specifically in pregnancy.... Are the pharmacokinetic studies for these agents performed in pregnant women, in healthy non-pregnant female volunteers, in healthy male volunteers, or in a combination of male and female volunteers?

Pharmacodynamics

Assumptions for treatment, based on non-pregnant women, may not be valid. For example, during pregnancy we find:

- lower immunity in late pregnancy after a viral infection (e.g., varicella);
- lower protein binding;
- higher sensitivity to nausea and vomiting;
- more depression during the first trimester (due to morning sickness);⁶
- higher glucose levels due to corticosteroid hormones; and
- higher cardiac output, leading to more risk for heart failure in women with existing heart disease.

Furthermore, we need to be aware of the combination of pregnancy-related changes, metabolic changes *plus* genetic polymorphism, such as in the case of increased activity of CYP2D6 in late pregnancy, which will lead to different changes among ultrametabolizers, extensive metabolizers and slow metabolizers. There are also the interactions between a condition induced by pregnancy and an underlying disorder, as in the case of women with nausea and vomiting of pregnancy exacerbated by their underlying reflux disease.

CONCLUSION

We need to consider the entire person and their circumstances when we treat them. We treat people, not a volume of distribution or a drug level. Therapy should be individualized as much as possible, addressing kinetic changes in the context of dynamic alterations due to underlying medical conditions.

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