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How to Pick the Right Drug Doses for Pregnant Women

By Alice Ke, PhD, David Taft, PhD

Most pregnant women are careful about their diets, mindful of their own health and that of their unborn child. But the majority of pregnant women are prescribed a drug during their pregnancy and half of them take four or more.[1] These drugs include antibiotics or antivirals to combat infections, continuing treatment for conditions such as epilepsy or depression, and medications for pregnancy-related conditions such as hypertension or gestational diabetes. However, often little or no information is available about the appropriate dose to prescribe or the potential adverse fetal effects. In fact, according to the Centers for Disease Control and Prevention (CDC), less than 10% of medications approved by the US Food and Drug Administration (FDA) since 1980 have sufficient information to determine their risk for birth defects.[2]

Most drugs are prescribed to pregnant women off-label; the dose used is usually based on the recommended dose for men or non-pregnant women combined with the clinician's judgement. Pregnant women are rarely included in clinical trials for numerous practical, legal and ethical reasons. Consequently, the traditional avenue for determining appropriate dosing is unavailable for this patient population.

Regulatory acceptance

Physiologically-based pharmacokinetic (PBPK) modeling and simulation offers a viable alternative to clinical trials for this vulnerable patient population. Scenarios can be investigated in silico that could never be tested clinically. Global biopharmaceutical companies and regulatory agencies such as the FDA, the European Medicines Agency, and the Japanese Pharmaceuticals and Medical Devices Agency have adopted PBPK modeling and simulation. For example, the Simcyp® Population-based Simulator has informed more than 100 label claims for new drug approvals from FDA in the past few years. These label additions include potential drug-drug interactions (DDIs), dosing regimens, and data about new populations.

FDA also recognizes that clinicians need more information to make appropriate dosing decisions for their pregnant patients. FDA's Pregnancy and Lactation Labeling Rule, which took effect on June 30, 2015, specifies that a drug's labeling "must also contain relevant information, if it is available, to help health care providers make prescribing decisions and counsel women about the use of the drug during pregnancy; this could include information on disease-associated maternal and/or embryo/fetal risk, dose adjustments during pregnancy and the postpartum period, maternal adverse reactions, fetal/neonatal adverse reactions, and/or the effect of the drug on labor or delivery." PBPK modeling and simulation can elucidate that additional dosing information.

Physiological changes during pregnancy

Numerous physiological and absorption, distribution, metabolism and excretion (ADME) changes occur during pregnancy, and they vary by trimester.

For example, delayed gastric emptying and re-

duced intestinal motility can slow drug absorption during pregnancy. Changes in metabolic enzyme activity in the liver or intestine can also alter oral drug bioavailability. Furthermore, increased transporter expression in the intestine, for example Pgp, can reduce drug bioavailability by increasing cellular efflux into the intestinal lumen.

Drug distribution also changes during pregnancy. As the pregnant woman's weight increases, so does her body water, plasma and blood volume, thereby reducing the hematocrit in the blood. This hemodilution, combined with reduced levels of circulating plasma proteins, can increase the fraction of unbound drug. That will tend to increase a drug's volume of distribution, and in many cases can also increase drug clearance.

The activity of many hepatic enzymes – particularly those in the cytochrome P450 (CYP) family – is increased during pregnancy, resulting in increased drug clearance. Conversely, the activity of the drug metabolizing enzyme, CYP1A2, declines during pregnancy.

Moreover, increased cardiac output in pregnant women leads to greater hepatic blood flow and enhanced hepatic clearance for drugs with high extraction ratio. Increased renal blood flow also increases glomerular filtration rates (GFR), which combined with enhanced renal transporter expression, will also increase the renal clearance in pregnant women.

All these physiological changes can affect a drug's pharmacokinetics (PK). As a result, prescribing the standard adult dose to pregnant women has the potential to cause drug toxicity or reduced efficacy.

PBPK modeling & simulation

Certara has developed a whole body simulation methodology that can predict the PK and pharmacodynamics (PD) of small molecule and biological medicines using laboratory-derived data. Its Simcyp Simulator includes unique genetic, physiological and epidemiological databases that facilitate simulating virtual populations with different demographics and ethnicities. The Simcyp Simulator is used to determine first-in-human dose selection, evaluate new drug formulations, and predict DDIs and PK outcomes in clinical populations.

Simcyp's pregnancy model simulates the drug exposure in the pregnant patient, her fetus and placenta. It also considers the physiological and biochemical changes that occur with gestational age. As a result, researchers can run simulations at different weeks of pregnancy, capture those changes, and then determine how they would affect systemic drug exposure.

Oseltamivir case study

David Taft, PhD and his research team at Long Island University developed PBPK models of pregnancy-induced changes for oseltamivir, an antiviral used to treat influenza.[3] This research is particularly important because the CDC recommends that pregnant women with a suspected or confirmed case of influenza be given antiviral therapy.

The team began by researching the literature and obtaining the requisite information about the physiochemical properties of oseltamivir, the key enzymes and transporters involved in its disposition and their kinetic values, and its plasma protein binding properties. These data were used to develop an oseltamivir substrate profile.

Oseltamivir is a pro drug. After oral administration, it is converted by hepatic carboxylesterase enzymes into its active form, oseltamivir carboxylate, which is eliminated from the body by renal excretion.

As both the GFR and expression of OAT1 – an organic anion transporter that takes up oseltamivir carboxylate – may increase during pregnancy, oseltamivir clearance is also likely to increase in pregnant patients.

Then the literature search was expanded to include clinical data on using oseltamivir in healthy volunteers. Those human PK data often take the form of plasma concentration-time profiles for the drug. These data enabled the team to compare its oseltamivir PBPK model's predictions with real-world results and determine its predictive accuracy.

Once the oseltamivir model had been verified in healthy subjects – by comparing the fold error, the ratio of the observed value divided by the model-predicted estimate, for C_{max} and area under the curve (AUC) – it could be included in the Simcyp PBPK pregnancy simulation.

Then the team used the Simulator to run a virtual trial of a single dose of oseltamivir to see how well its model predicted the drug's PK

across four populations representing the different pregnancy trimesters (T1-3) and postpartum. It simulated the systemic exposure curve and then examined the fold error in C_{max} and AUC. In this case, it was able to compare its Simulator results with clinical data on the use of oseltamivir in pregnant women in two published papers.[4,5]

This comparison showed that the disposition of oseltamivir carboxylate was altered during pregnancy but not oseltamivir. As a result, the team focused on modeling the metabolite.

They observed a significant decrease in AUC during pregnancy due to increased drug clearance. They surmised that the increased GFR and potentially increased OAT1 expression during pregnancy were responsible and noted that pregnant women may require an increased dose of oseltamivir.

Modeling CYP enzyme metabolism

As most drugs administered to pregnant women are metabolized by CYP enzymes, Alice Ke, PhD, and her team at Certara examined whether CYP activity profiles determined either from probe data or *in vitro* data could be used to predict drug disposition.

A PBPK model was constructed that incorporated CYP activity profiles for six CYP enzymes. The model was validated using datasets from non-probe drugs that were cleared primarily by the same CYP enzymes.

By assuming 99% induction of hepatic CYP3A during T3 (based on midazolam data), the PBPK model was able to predict accurately T3 changes in the disposition of two other CYP3A-metabolized drugs, nifedipine and indinavir. Using caffeine data from the literature, the team assumed a 65% suppression of hepatic CYP1A2 in T3, and the PBPK model was then able to predict accurately theophylline disposition during that period. The CYP2D6 induction range during T3 was defined as 100%-200% by modeling metoprolol, paroxetine, dextromethorphan, and clonidine disposition during pregnancy.[6]

As no probe-drug study data was available for CYP2B6, they estimated CYP2B6 induction based on *in vitro*–to–*in vivo* extrapolation of estradiol. The resulting PBPK model assumed hepatic CYP2B6 induction of 40% (T2) and 90% (T3); hepatic CYP2C9 induction (based on phenytoin data) of 50% (T2) and 60% (T3); and hepatic CYP2C19 suppression (based on proguanil data) of 62% (T2) and 68% (T3). Using this enhanced model, the team successfully predicted the disposition of methadone (cleared by CYP3A, CYP2B6, and CYP2C19) and glyburide (cleared by CYP3A, CYP2C9, and CYP2C19) during T2 and/or T3.[6]

Future uses

PBPK models can be used to assess the systemic exposure changes that occur for a pregnant woman. However, researchers are now extending this approach and building fetal exposure into their pregnancy PBPK models. Two recent publications examine passive permeability across the placenta[7] and look at different P450 pathways in the context of fetal exposure.[8]

Additional data about maternal and fetal drug exposure during pregnancy is needed to minimize risk to both parties and help to ensure healthy outcomes. PBPK modeling technology provides quantitative results that can be verified and validated when data become available; it's an obvious choice for optimizing treatment of these vulnerable patient populations.

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