PK Studies During Pregnancy May Be Essential, But Use Caution, FDA Says

MARTIN BERMAN-GORVINE m.berman-gorvine@elsevier.com

Drug developers often need to gather clinical data on the pharmacokinetic effects of their drugs in pregnant women or women who may become pregnant, but FDA is advising that firms generally should not use healthy, pregnant volunteers and should usually avoid these studies if the drug is going to be used rarely.

However, "there are exceptions to everything," Karen Feibus, medical team leader on the Maternal Health Team at FDA's Office of New Drugs, said during a May 17 symposium the agency sponsored on pregnancy and prescription drug use.

Population PK study designs can help ensure that missed clinic visits or time limitations don't affect study integrity.

In the case of rarely used drugs, a PK study might be appropriate if the medication has a very narrow therapeutic range or is used in very serious conditions, such that the safety and efficacy consequences of under- or overdosing are great. An example is cancer chemotherapy drugs.

Broadly speaking, PK studies may be needed in pregnant women because the physiological changes that come with pregnancy can affect the body's metabolism and clearance of drugs, in turn affecting the dosing.

Examples of drugs that may require PK studies during pregnancy include, according to Feibus, "drugs that are primarily cleared by the kidney, are known substrates of CYP450 isoenzymes in the liver, or that undergo phase 2 metabolic pathways in the liver, such as N-acetyltransferase and glucoronidation."

But before any PK study is done on pregnant women, sponsors should examine the established safety database in non-pregnant women for any relevant safety signals.

"This is really important, not only for deciding whether and how to do the study, but also how to write your informed consent. And you want to design the study in a way that really minimizes the risk for the mother and the fetus and still allows you to achieve the objectives of the research," Feibus said.

PK studies "are a little bit of a bridge for us between post-marketing studies and pre-marketing studies, because there are scenarios where it may be appropriate to do them in either setting," she said.

In the setting of a pre-marketing clinical trial or observational cohort study, investigators can ethically collect blood samples for PK assessments from pregnant women for whom the study drug holds out the prospect of direct benefit for themselves or the fetus. "This would be like a nested study within the clinical trial," Feibus said.

Ideally, the protocol should specify that the PK data collection begins early on, so that the dose can be adjusted if necessary for additional pregnant women who enroll later, and to ensure adequate systemic exposure to achieve efficacy.

Post-Marketing PK Studies

In the post-marketing setting, sponsors can identify pregnant women who are using the drug and obtain their serum levels. Three such studies were presented during the symposium, examining the pharmacokinetics of the antidepressant sertraline (**Pfizer**'s *Zoloft* and generics), the hypertension drug labetalol (**Prometheus Labs**' *Trandate* and generics) and the antibiotic azithromycin.

Sertraline's pharmacokinetics during pregnancy and postpartum were the subject of the Maternal Antidepressant Research and Evaluation (MADRE) study. Results of the OWH-sponsored study, which enrolled patients already taking sertraline, were published in the Journal of Clinical Psychopharmacology in 2008.

Among the six subjects who completed two evaluations, there was an increase in oral clearance of sertraline by 17.4% plus or minus 7% from the second to the third trimester, lead investigator Marlene Freeman, Harvard Medical School, said. In five of the six, there were decreases in the sertraline total area under the plasma concentration versus time curve (AUC) and maximum plasma concentration (Cmax) during the third trimester, which was consistent with results from other studies of antidepressant pharmacokinetics during pregnancy.

The labetalol study was larger, enrolling 57 subjects taking the hypertension drug. Pregnancy significantly influenced labetalol pharmacokinetics, leading to higher oral clearance (CL/F) and apparent central and steady-state distribution volumes, with increased hepatic intrinsic clearance the likely mechanism, according to James Fischer, University of Illinois at Chicago. "Wide individual variability for CL/F precludes providing specific dosage recommendations," he said. "Lean body weight provides a more useful guide for adjusting labetalol doses in pregnant women than total body weight."

Fischer also presented the study on azithromycin pharmacokinetics in pregnancy. This was a pilot study designed to enroll 12 healthy adult women of childbearing age. It found that ethnicity influences the effect of pregnancy on azithromycin clearance, in that "compared to non-pregnant women, azithromycin CL/F during pregnancy is unchanged in African American women and 40% lower in non-African Americans."

Concurrent oral contraceptive use also reduced oral clearance of azithromycin, which suggests in turn that estrogen or progesterone mediates the effects of pregnancy and oral contraceptives on azithromycin clearance.

Fischer and Freeman offered several tips gleaned from these PK studies in pregnant women:

- Collaboration with obstetricians and primary physicians is key in subject recruitment;
- The burdens on pregnant patients of participating in a clinical trial are significant. Thus, Fischer said, it can help to use a population PK study design, since then "missed clinic visits or time limitations have no impact on study integrity";
- IRBs need education about the issue. Fischer suggested requesting a "pre-review" with IRB staff, and being prepared for additional scrutiny;
- It's important to emphasize to IRBs that treatment decisions will be separate from research decisions; and
- The public needs more education on treatment issues related to pregancy, both to improve the prospects for valuable research and to decrease the stigma experienced by women who need treatment for psychiatric disorders, Freeman said.