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Pregnancy and the Drug Dilemma

By Michelle Meadows

Jennifer, 25, of Baltimore wishes she only had to deal with the basics of pre-pregnancy planning, like going for a routine checkup and taking prenatal vitamins. "I get discouraged when I think of how much more I have to consider before trying to conceive," says Jennifer, who has taken the antidepressant Zoloft (sertraline) for three years.

She and her husband plan to try for a baby soon, but the questions feel overwhelming. Should Jennifer stop taking the antidepressant? Before conceiving or only after? For the first trimester or the whole pregnancy? What if she stops taking the medication and can't cope? Why aren't there definitive answers about the medicine's effect on babies, especially long-term? And what about breast-feeding? The couple has set up appointments with Jennifer's psychiatrist and an obstetrician in hopes of finding answers.

Unfortunately, there are times when such questions not only rattle the nerves of patients, but also of doctors. For example, there are no definitive answers about the long-term effects of Zoloft and many other medications on babies. Experts say that while they have certainly learned some useful information for successful drug treatment in pregnancy, their knowledge is limited for the most part. That goes for information in the literature and on the labels doctors use to make clinical decisions, says Beth Conover, a genetic counselor who coordinates the Teratogen Information Service at the University of Nebraska Medical Center. "Teratogen" is a term that refers to any substance with the potential to cause birth defects.

Conover says advising patients and doctors about medication use in pregnancy is like working in shades of gray. "Parents want someone to assure them their babies will be OK, and of course that's what we want to do," she says. "But it's very hard to prove absolute safety. We would need extensive, long-term studies to do that, and we don't have them in many cases."

The reality, of course, is that pregnant women get sick, whether it's with pneumonia or

cancer. Or like Jennifer, they come to pregnancy with chronic conditions that require treatment. So despite some areas of uncertainty, health professionals must look to the resources they do have to make clinical decisions.

Dianne Kennedy, a regulatory health project manager with the Food and Drug Administration's Center for Drug Evaluation and Research (CDER), says withholding all medication during pregnancy is not the answer. Too many conditions pose more of a health risk if left untreated, she adds (see "The Danger of Untreated Disease"). In fact, medication use in pregnancy is common, and the number of prescriptions tends to rise with the mother's age. "We use the safest, best drugs we can so women can receive the treatment they need," Conover says.

The FDA has taken several steps to improve doctors' ability to give pregnant women safe and effective drug treatments. For example, the FDA regularly trains its reviewers in translating reproductive studies in animals into health risks for humans. The agency has also drafted a guidance document for industry on establishing pregnancy registries. Sponsored mostly by pharmaceutical companies, these studies identify women using certain drugs and then observe pregnancy outcomes.

In addition to general questions about safety, almost no information is available to help doctors know what the best dose of a particular medicine is for pregnant women. Changes in the body's physiology during pregnancy have the potential to require that doses be increased or decreased. In December 2000, the FDA and the National Institute of Child Health and Human Development held a meeting in Washington, D.C., on clinical pharmacology in pregnancy. Experts discussed the need for more and better data to assess the rational dosing of drugs that are often used to treat pregnant women, ethical issues in research, and ways to share data more effectively with health professionals through labeling and other education.

Challenges in Clinical Research

For Jennifer and her husband, the answers they'll find about Zoloft's effects in pregnancy will be "relatively reassuring," says Conover. Data from animal studies and small studies in humans suggest that use of Zoloft during pregnancy does not pose a high risk of birth defects, she explains, but the data are insufficient to state that there is no risk.

Zoloft's product labeling indicates that there are no well-controlled studies on the drug in pregnant women, that the effect of Zoloft on labor and delivery in humans is unknown, and that it also isn't known whether, or in what amount, the drug is excreted in human milk.

Unless research focuses on a pregnancy-related condition such as labor induction, drugs typically aren't studied in pregnant women because of the fear of exposing the woman to

an experimental drug and harming the fetus. Catherine Stika, M.D., assistant professor of obstetrics and gynecology at Northwestern University School of Medicine, says the research approach for pregnant women has to be different than that for non-pregnant people who consent to participate in clinical trials.

Drugs are first studied in animals to make sure they are sufficiently safe to test in non-pregnant people. Human safety is evaluated from results of clinical trials, in which patients are observed for adverse events. To be well-controlled, a study needs to involve an adequate number of patients and have a control group--patients who are similar to the group being studied but who are receiving a different treatment regimen. Sometimes, the different treatment is another drug already approved to treat the disease; other times, it may be an inactive pill (placebo).

The limitations that go with conducting research on pregnant women don't mean we shouldn't do any research, Stika says. "We have to improve education for researchers about other ways to do clinical studies in pregnancy."

According to Maria Palmisano, M.D., director of clinical pharmacology-experimental medicine at Bristol-Myers Squibb Co., the natural population to recruit for research is pregnant women already needing to take a drug. But we need to first know a drug is safe in the general population and that it works before heading in that direction, she says.

Drugs enter the market based on clinical trials of several thousand people, and sometimes adverse events aren't revealed until later, after the drug is used in greater numbers in the general population. So the difficult part is determining when it is safe enough, Palmisano says. "There are some crucial mileposts in determining when a drug should be tested in pregnant women," she says. "Chief among them are establishing a drug's safety and effectiveness in the general population and knowing when a disease occurs in childbearing years."

Yvonne Maddox, deputy director of the National Institute of Child Health and Human Development, says she is putting together a consortium of experts to focus on advancing clinical research in pregnant women. "We want to try to find at least a couple of drug companies willing to take on what many have said is too risky," she says. "Academicians are asking why research in pregnant women should be any more risky than other high risk/high payoff research areas. But this type of research makes pharmaceutical companies worry more about financial loss from lawsuits."

Knowledge Gaps

For now, what we have is a significant lack of adequate information on medications that sometimes must be used in pregnancy, such as antibiotics, and drugs to treat seizure

disorders, hypertension, and psychiatric conditions, according to Sandra Kweder, M.D., co-chair of the FDA's Pregnancy Labeling Task Force. The FDA established the task force in 1996 to ensure pregnancy labeling of medical products is based on sound, scientific information.

More research has been done on hypertension, depression, and other conditions that commonly occur in women of childbearing age, but no areas could be considered well studied in pregnancy, Kweder says. "Hypertension is one of the number one problems women bring to pregnancy or develop during pregnancy," she says. "Yet the number of pregnant women who have been in clinical trials for hypertension is only several hundred."

This limits treatment options, says Stika. "We'll prescribe an older hypertension drug because its long history hasn't turned up serious safety concerns," she explains. "There may be other drugs that are more effective and better tolerated, but we don't use them because we don't know about their safety. Nor do we always know the appropriate dose for use in pregnancy."

Most people think that determining whether a drug causes birth defects is the major concern, but the knowledge gap doesn't stop there. "We also need more research on basic science and physiology in pregnancy," Stika says. There is a lot to be learned about how a pregnant woman's body changes from one trimester to the next, which can affect drug levels. Pharmacokinetic (PK) studies are needed to help determine accurate dosing, she adds. PK studies show how our bodies absorb, distribute, metabolize, and excrete drugs.

Pregnant women have increased blood volume, which forces the heart and kidneys to work harder. Drugs may be cleared through a pregnant woman's kidneys faster than normal. "In an effort to protect the baby, some doctors may err on the side of caution by giving pregnant women a lower dose than for non-pregnant patients," says the FDA's Kennedy. "But because of the physiological changes that occur in pregnancy, there may be times when pregnant women need a higher dose."

Making Treatment Decisions

So in the absence of adequate human studies, how do health-care professionals make decisions about drug treatment? "Generally, we use medicine when we have to and try to do the best we can," says Conover. "That means looking carefully at the data we do have."

Animal studies look for possible adverse reproductive effects in humans by giving animals higher doses of a drug. Experts also consider how a drug works and its likely effects, reported experiences with similar drugs, and adverse event reports.

Additionally, pregnancy registries have grown over the years. These registries follow

women taking a certain drug until their pregnancy ends, allowing researchers to use the results to assess risks to mothers and their babies. According to a review of pregnancy registries published in the November/December 1999 issue of the *Journal of the American Pharmaceutical Association*, eight were recruiting patients as of October 1999, including the Antiepileptic Drug Pregnancy Registry run by Massachusetts General Hospital and the Organization of Teratology Information Services' (OTIS) Asthma Medications and Pregnancy Project.

The stage of pregnancy also influences clinical decisions. For example, after 24 weeks of pregnancy, the antibiotic tetracycline can cause permanent staining of a baby's teeth. And ACE (angiotensin converting enzyme) inhibitors, a group of drugs that treat high blood pressure, can damage a baby's kidneys in the second and third trimesters of pregnancy.

Depending on the risks, doctors may adapt treatment by switching a pregnant woman to a similar drug that is safer or prescribing medicine only during a certain portion of the pregnancy. "For example, if a depressed woman is taking lithium, she may be able to briefly discontinue the medication during the period of the baby's heart formation," Conover says. "Lithium use in pregnancy carries a small risk of fetal heart defects."

Revamping Pregnancy Labeling

Revamping pregnancy labeling is at the core of the FDA's efforts to better guide health-care professionals in making treatment decisions. Since 1975, the FDA has required drug labeling to include a subsection on a drug's ability to cause birth defects and other effects on reproduction and pregnancy. Products also must be classified under one of five letter categories--A, B, C, D, and X (see the chart "Current Categories for Drug Use in Pregnancy").

A public hearing in 1997 revealed that while this category system is a start, it's confusing and leads to oversimplification. "The letters imply a gradation of risk that doesn't necessarily exist," says the FDA's Kweder. People falsely assume that drugs labeled as category X pose the most risk in pregnancy and drugs labeled as A pose the least. But X reflects a benefit-risk judgment, and drugs in that category may be no more toxic than drugs called C or D.

Some drugs, such as oral contraceptives, land in Category X simply because there is no reason to use them in pregnancy. And a drug can fall into Category C because there is some medium level of risk based on animal studies, or because no animal studies have been conducted.

Since 1997, the FDA has been developing a new regulation that will revamp the pregnancy labeling system. The proposed regulation would replace the letter categories with more

detailed, narrative descriptions. Information on fertility, pregnancy, and breast-feeding would be included.

Pooling Data

Enhancing data collection is critical for making a new labeling system meaningful for health-care professionals, says Kweder. As part of a large, new safety reporting regulation that the FDA is developing, drug manufacturers would be required to provide periodic reports on positive and negative experiences in women who are pregnant or breast-feeding.

"In the past, we've waited for spontaneous reports of bad outcomes," she explains. "This rule would require a proactive approach--looking for data from different sources and trying to understand how they enhance our understanding of a given drug's safety profile."

The FDA is also working with the Centers for Disease Control and Prevention (CDC) on strategies for more comprehensive data collection. "CDC has birth defects surveillance, FDA has spontaneous event reports, some companies conduct pregnancy registries, and clinicians are seeing their own cases," Kweder says. "But there is no way yet that we can systematically bring all of this together, and that's the direction we need to go."

Pre-Pregnancy Planning

Imagine finding out you're two months pregnant, and then you remember all the cough medicine and aspirin you took over the last few weeks, not to mention the herbal teas you drank. That's when the panic usually sets in.

The risk of adverse effects on a fetus is greatest in the first several weeks of pregnancy when major organs are developing. Pre-pregnancy planning increases the likelihood of having a healthy baby.

Half of all pregnancies in the United States--more than 3 million a year--are unplanned, which means the potential for accidental exposure to medication is high.

- -M.M.

Over-the-Counter Concerns

While many over-the-counter (OTC) drugs can be used during pregnancy under a physician's supervision, some are known to be unsafe. As indicated on product labels, women who are pregnant, who may be pregnant, or who are nursing should consult a doctor before taking OTC medication.

Aspirin is one OTC drug that should be avoided in the last three months of pregnancy. In 1990, the FDA issued a warning that it is especially important not to use aspirin during the last trimester of pregnancy unless specifically directed to do so by a physician because it may cause problems in the unborn child or complications during delivery. OTC non-steroidal anti-inflammatory drugs such as ibuprofen also carry the same warning about use during the third trimester.

Experts stress that we don't know enough about the effects of herbs and dietary supplements on a growing fetus to determine whether they are safe to use during pregnancy. Don't assume a product is safe during pregnancy because it is sold over-the-counter and labeled as "natural."

- -M.M.

Current Categories for Drug Use in Pregnancy

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women. **or** Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.

C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. **or** No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

The Danger of Untreated Disease

Fear of taking medication in pregnancy is understandable, but there are times when under-treating or not treating a condition can be dangerous, or even life-threatening. For example, a parasitic infection called toxoplasmosis, which you can get from cat feces or eating infected meat or soil, can infect infants and cause problems with the brain, eyes, heart, and other organs. The infection requires antibiotic treatment.

For all pregnant women infected with HIV, the CDC recommends the drug zidovudine (AZT). Research has shown that the drug decreased by two-thirds an HIV-positive mother's risk of passing the infection on to her baby, and neither mothers nor babies had significant side effects other than mild anemia. Uncontrolled diabetes increases the risk of miscarriage and stillbirth.

Uncontrolled asthma can decrease oxygen in the fetal blood, possibly impairing fetal growth and survival. And uncontrolled high blood pressure increases the risks of placental problems and fetal growth retardation.

Melissa Moore-Sumter, 28, of Temple Hills, Md., was diagnosed with lupus in 1991, and says her doctor monitored her closely throughout her pregnancies. She needed various medications, including a drug for high blood pressure when she was pregnant with her daughter Sade, now 8. "I didn't want to be on any medication," Melissa says, "but I knew I needed it." It's important to talk with your doctor about whether the potential benefit of taking a medication outweighs the risk for you and your baby.

For More Information

Motherisk
Hospital for Sick Children
Toronto, Ontario, Canada
http://www.motherisk.org/

Organization of Teratogenic Information Services
1-888-285-3410
http://www.otispregnancy.org/

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