OPINION

Evidence-Based Antimicrobial Therapy in Pregnancy: Long Overdue

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Little evidence exists to guide the clinician caring for pregnant patients with infectious morbidities. The already-small pool of evidence shrinks rapidly as the pathogen becomes more exotic, making therapeutic decisions increasingly speculative when emerging infectious diseases appear in the pregnant patient. The current drug approval mechanisms, legal environment, and profit-driven drug pipeline have combined to exclude pregnant women from clinical trials, paradoxically resulting in a dangerous situation for pregnant women around the world.

Because of concerns for fetal well-being, most drugs are never formally evaluated for use during pregnancy, and nearly every clinical trial of a new compound lists pregnancy and breastfeeding under the exclusion criteria. In compliance with guidelines from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, most trials go further to require that female enrollees of childbearing age commit to using two effective methods of contraception for the duration of the study.[1] Thus, during the drug discovery and approval process, compounds not specifically developed for use during pregnancy are never administered to pregnant women. Exposures that do occur are generally accidental and limited to the early weeks of gestation before the pregnancy is discovered and during which the fetus is most susceptible to teratogens. Although these regulations are in place to protect women and their fetuses from teratogenic effects of medications, they also result in a critical shortage of information about the safety of drugs that may be needed for treatment of pregnant patients during infectious disease outbreaks or bioterrorism attacks.

Use of antimicrobial drugs during pregnancy is common, and the incidence and severity of some infectious illnesses, including cystitis and pyelonephritis, increase during gestation. The impact of chronic maternal infection on the fetus, as is the case with HIV and malaria, may also drive the use of antimicrobial medications not specifically approved or intended for use in pregnancy. Often such interventions are undertaken with few supporting data about safety or appropriate dosing. Pharmacokinetic parameters during pregnancy may vary greatly from baseline, and this may change with gestational age. Because both volume of distribution and glomerular filtration rate increase during pregnancy, using dosages intended for nonpregnant persons may result in critically low drug concentrations in the pregnant patient. Changes in hepatic enzyme activity and serum protein concentrations may also change pharmacokinetics in unpredictable ways. In settings where drug levels cannot be measured, or when using drugs for which levels are not commonly monitored, inappropriate dosing will often go undetected and may even be mistaken for lack of efficacy.[2] Recognizing that the current categorical labeling system presents clinicians with few data and high liability, the US Food and Drug Administration (FDA) has initiatives under way to change safety labeling to better reflect known risks of drugs administered during pregnancy and lactation.

Pharmaceutical companies have little incentive to investigate the safety of drugs in pregnant women, given that all current studies of compounds not targeted specifically for use in pregnancy occur after marketing. Such studies add unnecessary expense and liability while having little or no financial payoff, because pregnant women make up a small percentage of the population likely to use a given medication. It is much easier and less expensive to simply label a medication as contraindicated in pregnancy than to systematically investigate its safety, efficacy, and pharmacokinetics. By forgoing formal studies, the current drug approval system forces physicians to use

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medications off label for pregnant patients, risking toxicity and uncertain therapeutic value. Because there is little incentive or perceived obligation for the pharmaceutical industry to fill this information void, postmarketing studies to evaluate drugs used during pregnancy are chiefly funded and undertaken by private and governmental organizations.

Whereas common antimicrobial agents are often used during pregnancy despite little supporting evidence, use of less commonly prescribed agents presents more clinical challenges. For example, during the severe acute respiratory syndrome (SARS) epidemic in 2003, patients were treated with ribavirin because it was the drug most likely to inhibit replication of the SARS coronavirus. However, ribavirin carries a pregnancy category X designation from the FDA. This designation is based on evidence of teratogenicity in animal models, with no studies in humans to support or refute the animal data. Because of the severity of SARS, ribavirin was administered off label to infected pregnant women in Hong Kong during the 2003 epidemic. Pregnant women with SARS had worse disease outcomes than nonpregnant controls, and their pregnancies were complicated by fetal loss and preterm labor. It is not clear whether the use of ribavirin in these women resulted in any differences in maternal or fetal outcomes compared with controls (reviewed in ref. 3). What is clear is that the possibility of maternal benefit in the face of severe illness led to off-label administration of a category X drug to pregnant patients during a public health emergency and that no data were available to help physicians weigh the risks and benefits of this decision.

Ribavirin is also of particular interest because of its use in treating hepatitis C. Many patients with chronic hepatitis C are women of reproductive age, and inadvertent early pregnancy exposure to ribavirin is not uncommon in these patients. Hepatitis C is also a common problem throughout pregnancy, with maternal–fetal transmission rates of approximately 5% and no effective antiviral therapies approved or recommended for use during any trimester of pregnancy. Data collection is ongoing for a pregnancy registry that will describe outcomes of inadvertent ribavirin exposure during early pregnancy.[4] Data from the registry may help delineate the risks of early pregnancy exposure in terms of human teratogenesis but is unlikely to provide information about risk and/or benefit in the second and third trimester, because treatment is generally terminated at the time of pregnancy discovery. Because of the pregnancy category X designation, ribavirin administration is contraindicated in all trimesters. Thus, despite a complete lack of evidence that its administration causes harm after the first trimester, we have little hope of assessing whether ribavirin administration later in pregnancy could prevent congenital hepatitis C transmission. Under the current labeling system, we can only hope that the pregnancy registry (which concludes enrollment in 2010) reveals little teratogenic risk after first-trimester exposure, allowing for subsequent prospective studies of safety and efficacy later in gestation.

A similar but larger-scale problem has prompted action to investigate the safety, efficacy, and pharmacokinetics of antimalarial drugs used during pregnancy. Because of the prevalence and severity of malaria in pregnancy, multiple antimalarial drugs were used despite the scant evidence to guide therapeutic decisions.[2] Large numbers of women were treated with antimalarials, the potential therapeutic benefits having already been deemed to outweigh any teratogenic risks. Thus, systematic study of these exposures to generate efficacy data and dosing information became ethically and economically feasible. A recent search of the National Institutes of Health clinical trials database (http://www.clinicaltrials.gov) using the terms "malaria" and "pregnancy" returned information regarding 20 ongoing studies of malaria therapy and prophylaxis in pregnant women.[1] Drugs being studied include chloroquine (FDA pregnancy C), amodiaquine, artesunate, sulfadoxine-pyrimethamine (FDA pregnancy C), artemether, lumefantrine, mefloquine (FDA pregnancy C), and cotrimoxazole. Many of these drugs are not marketed or approved in the United States and thus have no FDA pregnancy category assigned. Perhaps because antimalarials generate little profit, or because studying pregnant women exposes investigators to unnecessary liability, these trials are funded primarily by government agencies and charitable organizations.

As exemplified by the current swine flu outbreak,[5] a pandemic or a bioterrorist attack does not allow sufficient time to prospectively collect and analyze data before administering prophylactic and therapeutic medications and vaccines to large populations of pregnant women. For purposes of pandemic preparedness, the time to collect data is now. Nearly all antimicrobials, drugs, and vaccines are either knowingly or inadvertently prescribed to pregnant patients with varying frequency. We can continue to weigh the risks and benefits of these exposures individually and without supporting data, or we can commit the resources to systematically capture and analyze them. Doing so requires acknowledging that a regulatory system designed to protect pregnant women and their fetuses has instead created a situation in which drugs are frequently dispensed to pregnant women off label and without supporting data.

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CONFLICT OF INTEREST

The author declared no conflict of interest.

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