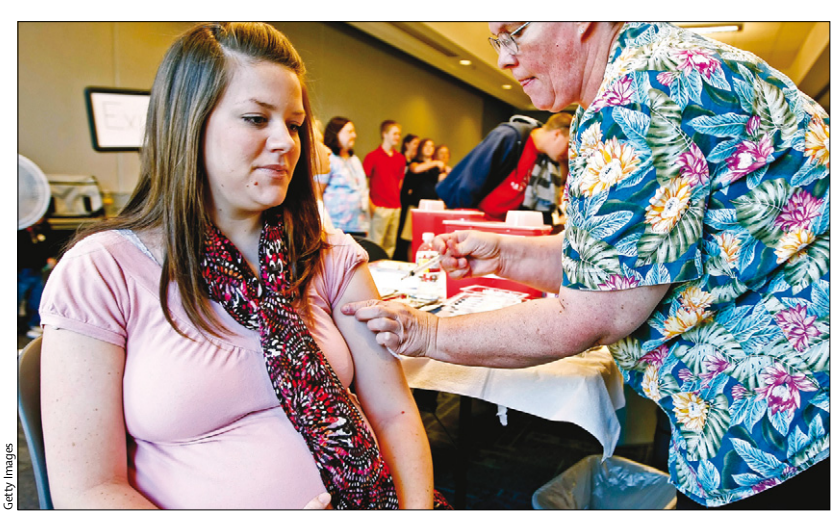
The art of medicine

Enrolling pregnant women in biomedical research

The long history of excluding pregnant women from biomedical research is beginning to witness some overdue rethinking and possible reversal. Perceptions of what is ethically permissible or necessary often change over time. We have only to think of the evolution of informed consent in both the clinical and research settings to remind us that past practice can change for ethical reasons. Mere decades ago, it was more common for physicians to withhold a diagnosis of cancer than to reveal it to their patients. Fewer than 20 years ago, the US Food and Drug Administration (FDA) still had a policy of excluding women "of childbearing potential" from enrolling in drug research. To exclude any group or population from participating in medical research results in a lack of knowledge about the risks and potential benefits of products that will be available for their use once on the market. Whether it is respect for the autonomy of patients or justice in the selection of participants for research, an evolution in ethical thinking has undeniably occurred.

Although no one questions the importance of preventing pregnant women, their fetuses, and their future children from avoidable harms that could be caused by experimental drugs, several reasons can justify the inclusion of pregnant women in a greater number of biomedical studies than current practice allows. The most compelling reason is the need for evidence gathered under rigorous scientific conditions, in which fewer women and their fetuses would be placed at risk than the much larger number who are exposed to medications once they come to market.

The thalidomide tragedy in the late 1950s and early 1960s led to the FDA's expansion of the category of exclusion from that of pregnant women to "women of childbearing potential". It was not until 1993 that the FDA reversed this policy on grounds that the exclusion of the majority of women from most clinical trials had resulted in a lack of scientific data on the risks and benefits to women of drugs that had been studied exclusively in men. Today, the FDA Office of Women's Health actively promotes the participation of women in clinical trials. Yet the FDA remains extremely cautious about the inclusion of pregnant women. The agency did, however, adopt the view that when a clinical trial is the only way pregnant women with a life-threatening condition could have access to the only possible beneficial treatment that is still under investigation, then it is essential to include them. Since that condition was true for HIV/AIDS in the early 1990s, and remains true today, the FDA advocated early testing of new treatments in HIV-infected pregnant women.



Getty Images

But the overall reluctance to include pregnant women in clinical trials remains. Possibly the wrong message was taken from the thalidomide episode, in which about 10 000 babies around the world (many in western Europe) were born with severely deformed limbs because their mothers had taken the medication when they were pregnant. Never having been tested in pregnant women, the drug came to market and was readily available for morning sickness, a relatively mild indication. Had the drug been tested in very few women in a phase I or phase II clinical trial, the mutagenic effect would most likely have been discovered and the number of babies born with deformities would have been much smaller. This is a simple utilitarian calculation, an appropriate method for decision making when the intention is to decrease the number of individuals exposed to potential harm.

Recognising the need for information about the effects of drugs during pregnancy, in 2005 the European Medicines Agency (EMEA) adopted its *Guideline on the Exposure to Medicinal Products During Pregnancy*, which proposed active surveillance for collecting postauthorisation data in pregnancy for newly marketed drugs and recommended a similar plan for established products and "old products", for which reliable data in animals are lacking and experience in human beings is poorly documented. It was not until the end of 2009 that the FDA embarked on a systematic study of the outcomes of pregnancy in women who had taken prescription drugs during pregnancy. These surveillance activities may have considerable value, but they lack the rigor of the scientific gold standard: a prospective, randomised clinical trial in which pregnant women are enrolled.

The various ethical guidelines that address research in human beings reveals a mixed picture. Some guidance documents do not mention research involving pregnant women, and at least one guidance point clearly recommends the inclusion of pregnant women. The Declaration of Helskinki omits any mention of research in pregnancy. The 2002 *International Ethical Guidelines for Biomedical Research*

Involving Human Subjects of the Council for International Organizations of Medical Sciences (CIOMS) contains a guideline specifically addressed to research involving pregnant women. Guideline 17 states:

> "Pregnant women should be presumed to be eligible for participation in biomedical research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the foetus and their subsequent offspring, and to their fertility.
>
> Research in this population should be performed only if it is relevant to the particular health needs of a pregnant woman or her foetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity."

The guideline states a presumption of eligibility, but the second paragraph is hard to interpret. Does "the particular health needs of a pregnant woman…or the health needs of pregnant women in general" mean only those health needs that are unique to pregnancy? Or does it mean health needs that any woman might have, but in this case when a woman is pregnant? Clearly, the first interpretation is much narrower than the second. Also puzzling is the phrase "if appropriate" with regard to prior animal studies. Not only is it always appropriate, but it is ethically necessary to have data from animal studies. Regulatory agencies require reproductive and developmental safety testing in animals before studies in pregnant women can be initiated, and the EMEA, FDA, and International Conference on Harmonisation (ICH) have detailed specifications of the required animal studies. The problem, of course, is that in some cases animal models may not accurately predict results in human beings.

The clearest and most liberal guidance for participation of pregnant women in research is in the UNAIDS/WHO ethical guidance for HIV prevention trials. Unlike the CIOMS guidelines, this does not have a separate guidance point for pregnant women. UNAIDS/WHO Guidance Point 9 on women says: "Researchers and trial sponsors should include women in clinical trials in order to verify safety and efficacy from their standpoint, including immunogenicity in the case of vaccine trials, since women throughout the life span, including those who are sexually active and may become pregnant, be pregnant or be breastfeeding, should be recipients of future safe and effective biomedical HIV prevention interventions." Since vaccines, microbicides, and drugs for HIV treatment are preventive methods to be used by healthy women, these products have not been considered to be urgent in life-threatening conditions as the FDA had determined for therapeutic drugs for AIDS back in the early 1990s. Nevertheless, an effective method to prevent acquisition of HIV is just as urgent for healthy pregnant women as it is for everyone else at high risk of this disease. The UNAIDS/WHO guidance is a step in the right ethical direction.

An even bolder step goes beyond ethical guidance and into implementation of the guidance. An ongoing microbicide trial marks a change not only in the long-standing practice of withdrawing women who become pregnant in the course of biomedical research, but actually enrols women who are already pregnant. This study, conducted by the Microbicide Trials Network (MTN) and researchers from the University of Pittsburgh, has enrolled participants who are healthy, pregnant HIV-negative women. As a phase I study, it is not designed to test the efficacy of the microbicide gel. But it is a pioneering effort, particularly because it involves pregnant women in the earliest stage of a drug trial.

Needless to say, researchers must make concerted efforts when enrolling pregnant women to ensure that the informed consent process meets the highest standards. Women must be informed of potential hazards to the fetus, as well as risks to their own health. It is likely, however, that the quality of informed consent will be better in the research setting than in the clinic when physicians prescribe a medication that has never been tested in pregnant women. Research ethics committees will surely pay special attention to their review of the informed consent document, but ultimately the responsibility falls to the investigators to ensure that all relevant information is presented and understood.

Many questions remain to be explored. Should enrolment of pregnant women be delayed until a new product is tested in non-pregnant women? For how long should follow-up be continued for infants born of women who took part in clinical trials while pregnant? It is not only that information is sorely needed with regard to the risks and benefits of preventive and therapeutic products for women who are pregnant. The same information is critical for the health and safety of the fetus and future child. The typical practice has been to remove women from a clinical trial once they become pregnant and follow them to obtain outcome data. That is a faulty way of doing science. Harm to a fetus can occur at any gestational age, not only in the first trimester when pregnancy is normally detected and women are withdrawn from clinical trials. If fetal safety is a concern, as well it should be, the time to study drugs and biologicals is not only in the early stage of pregnancy but throughout the pregnancy. Only then can appropriate data be obtained for the safety of products before they are marketed and used by millions of pregnant women worldwide. The postmarketing surveillance by the EMEA and the similar study proposed by the FDA show an ethically enhanced recognition of the need to acquire information about the effects of drugs in pregnancy, but they do not go quite far enough. The next logical—and ethical—step is the enrolment and retention of pregnant women in clinical trials.

Ruth Macklin
Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY 10461, USA
ruth.macklin@einstein.yu.edu

Further reading

Lyerly AD, Little MO, Faden RR. The national children's study: a golden opportunity to advance the health of pregnant women. *Am J Public Health* 2009; **99:** 1742–45.

Lyerly AD, Little MO, Faden RR. Pregnancy and clinical research. *Hastings Center Report* 2008; **38:** c3.

Mastroianni A, Faden R, Federman D, eds. Women and health research: ethical and legal issues of including women in clinical studies. Washington, DC: National Academy Press, 1994.

Merkatz RB, Temple R, Sobel S, Feiden K, Kessler DA, for The Working Group on Women in Clinical Trials. Women in clinical trials of new drugs—a change in food and drug administration policy. *N Engl J Med* 1993; **329:** 292–96.

UNAIDS/WHO. Ethical considerations for biomedical HIV prevention trials: guidance document. Geneva: Joint United Nations Programme on HIV/AIDS, 2007.

Microbicide Trials Network. Phase I study of the maternal single-dose pharmacokinetics and placental transfer of tenofovir 1% vaginal gel among healthy term gravidas. http://www.mtnstopshiv.org/node/66 (accessed Feb 9, 2010).