Clinical Research Enrolling Pregnant Women: A Workshop Summary

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Abstract

Clinical research investigates mechanisms of human disease, interventions, or new technologies, but pregnant women are often excluded from clinical studies. Few studies, beyond research on pregnancy, are designed to address questions relevant to pregnant women. A recent National Institutes of Health workshop considered the barriers and opportunities in conducting clinical research studies enrolling pregnant women.

Introduction

THE LACK OF EVIDENCE addressing the treatment of medical conditions concurrent with a pregnancy recently has garnered much needed attention.¹⁻⁴ The long-standing focus on protection of the fetus as the overriding concern is being reevaluated.⁵ Clinical research investigates mechanisms of human disease and tests therapeutic interventions for use with various populations, yet pregnant women usually are excluded from clinical studies. Few studies are specifically designed to address health concerns and questions relevant to pregnant women. As a result, there is meager evidence to inform healthcare and treatment decisions during pregnancy.

The responsible inclusion of pregnant women in research was the focus of the Second Wave Initiative begun at Georgetown University in 2009.⁶ That initiative addressed why it is necessary to move forward to include pregnant women in clinical research beyond research on pregnancy: pregnant women need safe and effective treatment. In October 2010, the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) convened a workshop, "Clinical Research Enrolling Pregnant Women," to discuss the current paradigm for clinical research addressing the healthcare needs of pregnant women. The presentations addressed ethical, regulatory, and practical issues in conducting studies in pregnant women. Successful approaches to enrolling pregnant women based on recent experience in clinical research studies were discussed, as were the remaining challenges to enrolling. This report briefly summarizes these presentations and discussions.

Reconsideration of the Ethics of Clinical Research in Pregnant Women

The rallying cry at the NIH workshop on enrolling pregnant women was that pregnant women should be thought of as complex rather than as vulnerable and that issues relevant to their health should be the focus of clinical research. Pregnant women need safe and effective treatment with adequate pharmacokinetic details to identify the appropriate therapeutic dose across each of the trimesters of pregnancy and to quantify the risks of exposure of the fetus. Reticence to treat pregnant women's health needs because of concern about lack of evidence of safety for the fetus has its own risks, as is often seen in undertreated or untreated asthma, depression, diabetes, and cancer.

Pregnancy may be the last remaining condition for the application of the precautionary principle even when a clinical practice or policy could be updated. A National Academies report on HIV prevention trials suggests that "although the current policy of excluding pregnant women from biomedical HIV prevention and other trials stems from an historically protectionist orientation adopted by regulators, the principles of research ethics neither mandate nor preclude use of the product by pregnant women."⁷ The Institute of Medicine (IOM) Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Research recommended that pregnant women be "presumed eligible for participation in clinical studies."⁸

Using the language of justice, it is recognized that exclusion of groups from clinical research may result in an unfair denial

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of the benefits of participation in research for individuals in the group, as well as inadequate evidence of the safety and efficacy of interventions for that group. The situation for pregnant women is similar to patterns of inclusion of all women in clinical research before the 1993 NIH Revitalization Act. Pregnant women may be the most underrepresented group in the entire clinical research process. The essence of social justice is to treat others as dignified beings deserving of equal moral concern and to view others as independent sources of moral worth and dignity. By that standard, the current state of clinical research is disrespectful of pregnant women. The health concerns and the treatment decisions of pregnant women should be afforded the same attention, rigorous research, and opportunity to improve health status as any other group.

A further injustice to pregnant women occurs when they are considered merely as wombs or vessels, ignoring the person behind the intrauterine environment.⁹ The outcomes to the fetus and the mother are not independent; the fetus depends on the maternal environment. Often, however, the risks are more heavily weighed than are the benefits. When women are not viewed as independent individuals in clinical research, they are disrespected and their health interests are ignored. The clinical research enterprise should demonstrate respect for all research participants.

Regulations That Apply to Research in Pregnant Women

Pregnant women are therapeutic "orphans" relative to information about the safety of medications during pregnancy,¹⁰ yet in a retrospective study of administrative databases, approximately two thirds of pregnant women in the United States had taken at least one prescription medication during pregnancy,¹¹ and similar percentages were reported for pregnant women in European countries.^{12,13} This continues to be an unaddressed problem because pregnant women are different from other participants in the drug safety, pharmacokinetics, and dose-finding research. Often, they respond differently to treatments. Pregnant women have increased cardiac output and plasma volume, decreased gastric emptying and intestinal transport, and increased renal excretion. All of these factors can impact drug metabolism. Pharmacokinetics in pregnant women has not been adequately studied. There is limited evidence on how most drugs for nonpregnant indications work in pregnant women.

Recognizing the importance of understanding how drugs work differently in pregnant women and although there is little known about the appropriate dosage and frequency of administration during pregnancy, regulatory authorities have provided guidance on pharmacokinetics¹⁴ and pharmacovigilance¹⁵ studies during pregnancy. Registries of exposures to medications during pregnancy are encouraged.¹⁶ Such registries can measure incidence and record follow-up information on adverse events or other outcomes. In the absence of a comparison group, however, these registries cannot provide evidence of association between exposures and outcomes. Also advocated at this meeting were opportunistic pharmacokinetic studies in pregnant women already prescribed the drug of interest, in which the study-required blood sampling would be the only additional risk.¹⁷

Federal regulations detail additional protections for certain vulnerable groups. Protections that apply to pregnant women

are specified in subpart B of the U.S. Federal regulations.¹⁸ According to subpart B, pregnant women are excluded from participation in clinical research unless "(1) the purpose of the activity is to meet the health needs of the mother, and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal."¹⁸ At the workshop, it was pointed out that the language of minimal risk relative to the fetus is unclear and that it would be helpful to define minimal risk to minimize the ambiguity. It was also suggested that a proactive approach to including pregnant women in clinical research rather than an exclusionary one may be more appropriate in order to develop evidence about safe and effective ways to intervene in illnesses experienced by pregnant women.

The International Ethical Guidelines for Clinical Research of the Council for International Organizations of Medical Sciences (CIOMS)¹⁹ adopted the presumption that pregnant women should be eligible for participation in clinical research and goes on to say that "Research should be performed only if relevant to the particular health needs of a pregnant women or her fetus, or to the health needs of pregnant women in general."¹⁹

Studies Enrolling Pregnant Women and Practical Considerations

At the workshop, both ongoing and completed studies enrolling pregnant women were presented as examples of clinical research addressing healthcare issues relevant to pregnant women and of the successful enrollment of pregnant women in clinical research. Methodologically, these studies included randomized, blinded intervention trials, epidemiologic studies, and specialized registries. They addressed prevention trials of H1N1 influenza,^{20,21} pharmacokinetics of malaria treatments,²² a pharmacokinetics and safety study of a vaginal microbicide,²³ a randomized trial of treatment of opioid-dependency in pregnant women,²⁴ treatment of depression in pregnant women,²⁵ epidemiologic investigations of the risk of hyperglycemia in pregnancy,²⁶ and registries of pregnant cancer patients.²⁷ Certain insights gained from these experiences of clinical research involving pregnant women and reported at the workshop are summarized here.

The U.S. Department of Health and Human Services (DHHS) recognized that approximately 3.5 million pregnant women annually were among their tier 1 (highest) vaccine priority groups in the 2005 DHHS Pandemic Influenza Plan. The rationale was that in past epidemics and in seasonal influenza, pregnant women were at high risk for complications from influenza, and vaccination of the pregnant woman would also protect the fetus, who could not be vaccinated. In 2009, it became clear that the risk of morbidity and mortality from H1N1 was higher in pregnant women than in most other groups. The focus of new studies by the pharmaceutical industry and by the NIH Network of Vaccine and Treatment Evaluation Units became the issues of optimal dosing for pregnant women with the H1N1 vaccine. Those studies showed that pregnant women had immunogenic responses that were equivalent to those of the general population.

In another example discussed at the workshop, pharmacokinetic studies, particularly those conducted in underdeveloped countries,²⁴ have logistical challenges and put additional requirements on study participants. Participants

who live in remote areas, have household responsibilities including child care, have otherwise fragile health due to co-infections or chronic conditions, or have difficulty with the blood volumes or required hospital stays may be unable to participate. In order to reduce the burdens while maintaining scientific integrity and data quality, researchers in these contexts can undertake creative solutions, such as ultralow volume blood analytic methods, mobile clinics, and flexible scheduling. Although these burdens may apply to any study participant, pregnant women may have lower thresholds for accepting the additional requirements to participate in a research study.

Randomized trials in pregnant women also pose unique challenges, but the results of such trials are essential for progress in caring for pregnant women and for supplanting the existing standard of care. These trials must be conducted within a thoughtful ethical framework that synthesizes the benefits and risks of both the mother and the fetus. Lessons learned from randomized trials presented at the workshop include ensuring that the sites selected will provide sufficient numbers of subjects to meet the target sample size and consistent screening and eligibility practices. An example of inconsistencies in existing clinical practices was presented based on experiences from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study,²⁶ where some sites offered no gestational diabetes screening, other sites routinely screened with a glucose tolerance test at 75 g of glucose, and still others screened at 100 g. Although such inconsistencies differentially impacted the site-specific recruitment success, once those inconsistencies were standardized, the HAPO study recruited, enrolled, and reported results on over 23,000 pregnant women from nine countries.

Observational studies in pregnant women also have their challenges. One example²⁵ of a study of treatment of depression had the requirements that (1) no mention of the study name or of the pregnancy be in any materials sent to the participant, (2) no pregnant women below the age of 18 be enrolled despite emancipation status changing after delivery, and (3) no questions about contraceptive history. Researchers presented examples of working proactively with Institutional Review Boards to vet difficult issues in advance.

Registries provided another source of information on pregnant women. For pregnant women surprised and shocked by a diagnosis of cancer, participation in a cancer registry²⁷ provided an opportunity to benefit others by contributing to the very limited information on cancer and pregnancy.

These are examples of overcoming the rationalizations for excluding pregnant women from clinical research—they are physiologically complicated, they will complicate our research, and they would be difficult to recruit. The studies presented as examples have overcome these challenges and have had a direct impact on clinical practice informing clinical guidelines and improving patient outcomes.

Conclusions

There is much to be learned about how to treat pregnant women with health problems effectively and safely and how to prevent poor pregnancy outcomes. This is the type of useful knowledge that clinical research should provide, yet there remains an unhealthy reluctance to involve pregnant women

in clinical trials, a legacy of decades. There remains a need for more regulatory clarity, for example, what is minimal risk to the fetus. The legal liability concerns continue to challenge the clinical research efforts, yet the clinical research examples presented at the workshop demonstrate efforts to ensure that pregnant women benefit from clinical research so that ultimately we have the knowledge needed to help pregnant women be healthy and to ensure that healthy fetuses and healthy babies have healthy mothers.

The purpose of clinical research is to generate useful knowledge related to human health and illness and to solve or resolve uncertainties in a responsible and rigorous way, with respect for the individuals involved. The NIH workshop was intended to help guide the development of a new research agenda, to enrich interactions with local Institutional Review Boards, to enhance the formulation of recruitment plans, and to facilitate the conduct of clinical research in pregnant women. Workshop presenters emphasized the importance of asking the right research questions both in studies focused exclusively on pregnant women and in studies that include pregnant women among the eligible participants.

Clinical research needs to address the health of pregnant women both within individual research studies and in overall research portfolios. When women are enrolled in a given study, the analyses and reporting of that study should address the overall impact of treatment decisions made during pregnancy on women's health.

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Disclosure Statement

The authors declare that they have no competing financial interests.

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