Optimizing Participation of Pregnant Women in Clinical Trials: Factors Influencing Decisions About Participation in Medication and Vaccine Trials

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Abstract

Objective: To obtain information on women's attitudes and opinions about participation in vaccine and medication trials during pregnancy.

Methods: A quantitative, cross-sectional survey was administered to 110 consenting women over a four-week period in the waiting room of an ambulatory obstetrics and gynaecology clinic in Ontario.

Results: The final response rate was 74.8%, with the majority of participants agreeing with statements about the importance of obtaining safety data about products in pregnancy and the importance of a woman having the ability to choose whether to participate in such research. Of all participants, 16.3% indicated they would consider participating in vaccine research during pregnancy and 20.0% would consider participating in medication research during pregnancy. Factors relating to maternal or fetal/child health were the most frequently cited factors influencing willingness to participate, with lack of trust in researchers and pharmaceutical companies as factors that would discourage participation.

Conclusion: A minority of pregnant women were willing to consider participating in medication or vaccine research during pregnancy. Optimizing participation requires providing women (and if appropriate, their partners) with detailed, multidisciplinary education about the maternal and fetal benefits and risks of such trials. Education about the principles of research ethics, including the limits of involvement of pharmaceutical companies, would be beneficial.

Résumé

Objectif : Obtenir de l'information sur les attitudes et les opinions des femmes quant à leur participation aux essais de vaccins et de médicaments pendant la grossesse.

Méthodes : Une enquête transversale quantitative a été réalisée auprès de 110 femmes consentantes sur une période de quatre semaines dans la salle d'attente d'une unité ontarienne de soins ambulatoires en obstétrique-gynécologie.

Résultats : Le taux de réponse final a été de 74,8 p. cent. La majorité de participantes étaient d'accord avec les énoncés concernant l'importance d'obtenir des données sur la sûreté des produits employés pendant la grossesse, ainsi que sur l'importance pour chaque femme de pouvoir décider si elle désire ou non participer à de telles recherches. Dans l'ensemble, 16,3 p. cent des participantes ont indiqué qu'elles envisageraient de participer à un essai de vaccin pendant leur grossesse, alors que ce chiffre s'élevait à 20,0 p. cent pour ce qui est de la participation à des essais de médicaments durant la grossesse. Les facteurs les plus fréquemment cités comme ayant une influence sur le désir de participer à de tels essais étaient ceux liés à la santé de la mère, du fœtus ou de l'enfant. En ce qui a trait aux facteurs pouvant décourager les femmes de participer, le manque de confiance envers les scientifiques ou les entreprises pharmaceutiques ont été les plus mentionnés.

Conclusion : Une minorité de femmes enceintes étaient prêtes à envisager de participer à des recherches sur des vaccins ou des médicaments pendant leur grossesse. Afin de maximiser la participation des femmes, il est nécessaire de leur fournir (ainsi qu'à leurs conjoints, le cas échéant) de l'information pluridisciplinaire détaillée au sujet des bienfaits et des risques des essais de ce genre pour la mère et pour le fœtus. Il serait bon de les éduquer sur les principes d'éthique en recherche scientifique, notamment sur les limites à l'implication des entreprises pharmaceutiques.

Key Words: Women's health, pregnancy, ethics, research, vaccines, drug therapy

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INTRODUCTION

Pregnancy is frequently an absolute exclusion criterion for an individual to participate in a clinical trial, and strict standards for informed consent in research often prevent the testing of pharmaceuticals during labour and

delivery. The strictness of these regulations reflects fears of teratogenicity and other harmful effects of pharmaceutical products, untested in pregnancy, on a developing embryo or fetus. Historical examples of adverse effects from medication use in pregnancy, such as the use of thalidomide and diethylstilbestrol, clearly show that great caution is required when using pharmaceuticals in pregnancy. The individual and societal effects of teratogenicity and developmental toxicity can be devastating. While ideally the use of medications in pregnancy is minimized whenever possible, women with pre-existing medical conditions may wish to become pregnant, and some women will develop significant illness during pregnancy. More than one half of pregnant women in Canada and the United States take at least one prescription drug during their pregnancy because of either a pre-existing illness or an illness that develops during pregnancy.[1,2] Furthermore, some vaccinations are recommended in pregnancy as a preventative health measure for both mother and infant, including the inactivated influenza vaccine and, in certain jurisdictions or circumstances, the tetanus, diphtheria, and pertussis vaccine.[3] The maternal immunologic response to the vaccine provides the neonate with passive immunity via transplacental transfer of maternal antibodies. Yet because the physiological changes of pregnancy may alter the pharmacokinetic and pharmacodynamic properties of drugs, extrapolation of findings in non-pregnant women to pregnant women must be cautious.[4] Pregnancy-mediated physiologic changes to the maternal immune system may also result in differences in the degree of protective immunogenic reaction produced in response to vaccination during pregnancy.[5]

Ironically, current regulations limiting research in pregnancy may have the unintended consequence of exposing a greater number of pregnant women to harm through the off label use of unproven therapies in clinical practice.[6] Additionally, the systematic exclusion of pregnant women from pharmaceutical research studies has had identifiable negative effects on maternal and perinatal morbidity and mortality. Multiple recent studies have focused on H1N1 influenza and its association with disproportionate maternal and perinatal morbidity and mortality.[7–12] Although pregnant women and infants are at greater risk of influenza-related morbidity and mortality than the general population, population-level public health studies have shown that common strategies to prevent, identify, and treat influenza infection in pregnant women are not optimally employed because of hesitancy on the part of both physicians and pregnant patients to use and accept interventions such as the influenza vaccine and antiviral influenza medications in pregnancy.[9,10] A lack of basic research into the safety, pharmacokinetics, and pharmacodynamics of these products in pregnancy leaves physicians and patients having to extrapolate their effect in non-pregnant populations to pregnant women or to rely on interpretations of a drug's safety from retrospective analyses. This provides a lower quality of evidence than could be obtained from a prospectively conducted controlled trial. A study of 468 drugs approved by the Food and Drug Administration in the United States between 1980 and 2000 showed that it took an average of 27 years for drugs with "undetermined" pregnancy risk to be assigned a more precise estimate of risk based on post-marketing surveillance.[13] Unfortunately, in addition to this lack of information resulting in delay or avoidance of necessary medical intervention in pregnancy, women who have been exposed to pharmaceuticals with unclear teratogenic risk may choose to terminate an otherwise wanted pregnancy.[14] Ultimately, research conducted in pregnancy is necessary to obtain timely and sufficiently accurate information about the safety and efficacy of pharmaceutical products used in pregnancy.

Recognizing that a lack of safety and efficacy data for medications and vaccines in pregnant populations affects maternal and perinatal health outcomes in measurable ways, influential medical and scientific journals including *Nature*,[15] *The Lancet*,[16] and the *New England Journal of Medicine*[17] have published editorials over the past few years that call for the broader inclusion of pregnant women in clinical trials. Furthermore, in November 2015 a committee opinion on the ethical inclusion of women, including pregnant women, as research participants was published by the American College of Obstetricians and Gynecologists (ACOG), with endorsement from the American Society for Reproductive Medicine, the Society for Maternal-Fetal Medicine, and the American Academy of Pediatrics.[18] This committee opinion recommended that pregnant women be classified as a scientifically complex population, rather than a vulnerable population, and that enrolment in research trials of women who are pregnant or could become pregnant should be individualized after careful consideration of potential risks and benefits to a woman and her pregnancy (or possible pregnancy). Describing a recent H1N1 vaccine trial which did include pregnant women through a careful, staged, study design, the ACOG committee noted that ethical inclusion of pregnant women in research represents a paradigm shift—a move towards protecting populations through research instead of from research.[18] Proposed criteria and study design protocols for the ethical inclusion of pregnant women in medical research have been described in detail elsewhere.[19–21]