

Wanted: Inclusive Guidelines for Research Involving Pregnant Women

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Abstract

The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS) was first issued in 1998. At that time, the inappropriate exclusion of women from clinical trials was a serious problem. Currently, the TCPS is undergoing a comprehensive review and it is expected that new research guidelines will be issued in 2010. One of the problems with the current draft of the revised TCPS is that it fails to properly address the routine exclusion of pregnant women from research. We illustrate the negative ethical implications of excluding pregnant women from research and argue for changes to the research guidelines that would address these negative implications.

Résumé

L'Énoncé de politique des trois Conseils : Éthique de la recherche avec des êtres humains (EPTC) a été émis pour la première fois en 1998. À l'époque, l'exclusion inappropriée des femmes dans le cadre des essais cliniques constituait un grave problème. À l'heure actuelle, l'EPTC fait l'objet d'une analyse exhaustive et l'on s'attend à ce que de nouvelles lignes directrices concernant la recherche soient émises en 2010. L'un des problèmes de l'ébauche actuelle de l'EPTC révisé, c'est qu'elle ne parvient pas à traiter adéquatement de l'exclusion systématique des femmes enceintes dans le cadre de la recherche. Nous illustrons les conséquences éthiques négatives de l'exclusion des femmes enceintes de la recherche et plaidons en faveur de l'apport de modifications aux lignes directrices concernant la recherche qui traiteraient de ces conséquences négatives.

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In Canada, all research involving humans that is funded by, or conducted in an institution that receives funding from, one of the three federal granting agencies must be in compliance with the TCPS.¹ The federal granting agencies are the CIHR, the SSHRC, and the NSERC. The TCPS is currently being revised by the Interagency Panel on Research Ethics (hereafter the Panel), which is responsible for its development, interpretation and implementation.² The Panel released a draft second edition of the TCPS for public consultation in December 2008; a year later, in December 2009, a revised draft second edition was published. The Panel plans to submit a final draft of the revised research guidelines to the three granting agencies in the spring of 2010.³

When the TCPS was first published in 1998 (following a public consultation process that began in 1994), the exclusion of women from clinical trials was common practice.⁴⁻⁶ For example, important research studies in the late 1980s and early 1990s investigating heart disease, diet and cholesterol, aging, and AIDS routinely excluded women as research participants, despite the fact that these health issues clearly affected both women and men.⁴ During the four year consultation period, many commentators insisted that the TCPS address a range of ethical issues relevant to research involving women.⁷⁻⁹ Perseverance and politics paid off, insofar as the first edition of the TCPS included the following stipulation: "Women shall not automatically be excluded from research solely on the basis of sex or reproductive capacity."¹

Today the inclusion of women in health research is no longer the problem it was 15 or 20 years ago. While there is no official monitoring of the inclusion of women in research in Canada,¹⁰ there is reason to believe that our enrolment practices are similar to those in the United States. In the United States the NIH reports that over 50% of the participants in NIH-funded research are women.¹¹ But while the overall representation of women in research is no longer a problem, important ethical challenges remain, one of which is

Clinical Scenario

Ms F. is 24 years old and 6 weeks pregnant. Although unplanned, the pregnancy is a happy event. Ms F. is concerned about her baby's health, however, because of the medication she is using to manage her hypertension. She remembers that when her physician prescribed benazepril he had asked her if she was pregnant or planning to become pregnant, because the drug was known to be harmful to the developing fetus.

Ms F. calls her physician: "Doctor, should I stop this medication? I don't want to do anything to harm my baby." Dr E. advises her to stop the benazepril immediately, and arranges for her to start a different antihypertensive agent. Ms F. is extremely worried that she may have harmed her baby, and an appointment is made with a specialist obstetrician for counselling.

Following this call, Dr E. sits back and remembers how just a few years ago he would have given his patient different advice. Until 2006, physicians (including himself) knew that ACE inhibitors were dangerous when used during the second and third trimester, but they believed that these agents were safe to use during the first trimester.^{12,13} Follow-up data, however, eventually showed that this drug was also dangerous when used in the first trimester, resulting in an increased risk of cardiac or central nervous system malformations.¹⁴ To this day, Dr E. regrets that many infants were harmed by the use of ACE inhibitors. He is also frustrated by the knowledge that some of this harm could have been avoided had there been well-designed clinical trials. He knows that drug research in pregnant women is potentially risky for the developing fetus, but no more risky than clinical treatment without the benefit of clinical trial data. He estimates that more fetuses are harmed by the current practice of prescribing drugs not approved for use in pregnant women and waiting for clinical experience (documented in case reports and case studies) to accumulate than would ever be at risk of harm in a randomized control trial.

the routine exclusion of pregnant women from clinical research.

The exclusion of pregnant women from research is a serious ethical problem because of the harms that women and their fetuses may experience as a result of our lack of knowledge about the pharmaceuticals, nutraceuticals, natural health products, and vaccines that women take while pregnant.¹⁵ Previously healthy pregnant women can become sick during their pregnancy and require treatment. As well, women with underlying health conditions such as diabetes, hypertension, depression, epilepsy,

and HIV infection require continued treatment when they are pregnant. According to US data, approximately 4% of all pregnant women are affected by diabetes, and another 4% are affected by hypertension.¹⁶ The drugs commonly used to treat these illnesses are not approved for use in pregnancy.¹⁷ The same is true for many vaccines; research involving their use in pregnant women is challenging. As an example, clinical trials of the H1N1 vaccine that include pregnant women are only now being undertaken in the United States and Canada.¹⁸

More generally, data suggest that during pregnancy and labour two out of three women use four to five medications.¹⁹ Despite this, according to Health Canada, "there are few prescription drugs labelled for use in pregnancy and only limited numbers of drugs under development for this purpose."²⁰ For the great majority of drugs used in pregnancy, there is insufficient evidence regarding appropriate dosing levels for pregnant women, efficacy in pregnancy, and safety for the fetus and the pregnant woman.

This lack of research knowledge about the effects of drugs and biologics in pregnancy forces pregnant women and

ABBREVIATIONS

CIHR	Canadian Institutes of Health Research
NIH	National Institutes of Health
NSERC	Natural Sciences and Engineering Research Council of Canada
SSHRC	Social Sciences and Humanities Research Council of Canada
TCPS	Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans

clinicians into an unconscionable dilemma. If a clinician treats a pregnant woman with a drug or biologic that has not been studied in pregnancy, he or she must do so without the benefit of robust clinical trial data about appropriate dosing or the potential effects of treatment on the fetus.¹⁷ On the other hand, if the clinician doesn't treat the pregnant woman, then she (or her fetus) must bear the burden of illness, which may be harmful to her and to her fetus.¹⁷

There are at least four reasons for promoting the responsible inclusion of pregnant women in research¹⁷:

1. Ensuring the safety and efficacy of treatment for pregnant women requires research data.
2. Research data are required to assess the fetal safety profile of the drugs and biologics that pregnant women require for treatment and vaccination.
3. The decision to forego treatment or vaccination during pregnancy because the risks are unknown can have serious health implications for the pregnant woman and fetus.
4. Participation in research can sometimes give direct benefits, and pregnant women are denied the opportunity to realize these benefits if they are excluded from research.

Despite these compelling reasons for including pregnant women in research, researchers and research ethics boards are simply directed in both the first edition and revised draft second edition of the TCPS to “take into account potential harms and benefits for the woman and her embryo, fetus or infant” when considering research involving pregnant women.^{1,2} This is not bad advice. But it fails to ensure the just and appropriate inclusion of pregnant women in research. To achieve this goal it is imperative that we shift the burden of justification for the exclusion of pregnant women from research. The starting assumption should not be that pregnant women should be excluded from research, but rather that pregnant women should be included in research unless a sound justification for their exclusion is provided by the researcher and accepted by the research ethics board. An example of a sound justification for the exclusion of pregnant women from research would be a clinical trial that involves a category X drug that is contraindicated in pregnancy, such as isotretinoin to treat cystic acne.

The fear associated with conducting research within pregnant women derives from the fear of exposing fetuses to substances of unknown teratogenicity. But there are responsible ways of reducing this risk, just as there are responsible ways of reducing the risks of research involving other populations, such as children or others incapable

of providing consent. Including pregnant women in research coincides with the overall goal of research involving any population, which is “to take responsible, limited, and calculated risks in order to garner evidence, lest we visit more risk on more people in the future.”¹⁷

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