New Zealand needs guidelines for the safe and responsible inclusion of pregnant women in medical research

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ABSTRACT

Pregnancy is a crucial window of time that influences long-term population health. As a matter of justice, pregnant women are entitled to high quality, evidenced-based care. As a matter of population health, we need to better understand foetal development, particularly the impact of lifestyle, stress, chronic conditions and clinical treatment during pregnancy. Pregnancy continues to be dominated by the precautionary principle, advocating for the routine exclusion of pregnant women from medical research, particularly intervention studies, on the grounds of foetal vulnerability. But this stance simply shifts the risk into the community. Due to a lack of evidence-based data, many pregnant women are refused medically important drugs, are subject to dangerous delays in getting drugs, or are prescribed drugs that are thought ‘safe’, despite evidence of possible teratogenicity. I argue that New Zealand needs to shift to a default position of inclusion of pregnant women in research; and to develop guidelines to facilitate their safe and responsible inclusion. The uniqueness of pregnancy gives rise to specific questions regarding research ethics. These questions warrant focused debate and the answers cannot simply be deduced from the general principles of research ethics we currently have in New Zealand.

Clinical research with pregnant women is limited; and that which does occur tends to focus on obstetric practice, and foetal safety. We need to broaden the research agenda to include a much wider range of health conditions, and study both short and long-term maternal and foetal outcomes. For example, this could include research on mental health, asthma, oral health and hypertension during pregnancy.

Pregnancy is a crucial window of time that influences long-term population health. Optimising health during pregnancy benefits the pregnant woman and her child, and can moderate future levels of chronic disease. During foetal development epigenetic programming occurs. This can have significant and long-lasting effects on mental and physical health through the course of the child’s life. For example, domestic violence triggers stress in pregnant women that changes the cortisol receptors of offspring observed during adolescence. Epigenetic effects can extend across generations through impact on germ cells.

Significant advances have been made in the last century in understanding what constitutes best health during pregnancy, resulting in vast improvements in both maternal and infant mortality and morbidity in developed countries such as New Zealand. Despite these advances, pregnant women remain one of the most underserved populations in clinical research. Much healthcare for pregnant women, especially drug prescription, is not evidence-based because pregnant women are routinely excluded from participating in clinical trials. Some pregnant women face serious medical conditions, such as heart disease, diabetes, lupus, and cancer.
But medicines for these conditions are prescribed off-label for pregnant women. There are only 12 medicines approved by the FDA for use in pregnancy, and those are used to prevent premature labour or treat labour pains. There is no equivalent empirical research regarding prescribing during pregnancy in New Zealand.

The use of medication during pregnancy and lactation is one of the least-developed areas of clinical pharmacology and drug research. Due to a lack of evidence-based data, many pregnant women are refused medically important drugs, are subject to dangerous delays in getting drugs, or are prescribed drugs that are thought ‘safe’, despite evidence of possible teratogenicity. Correct drug dosage, changes in pharmacokinetics during pregnancy, and compliance during pregnancy are not well understood. The teratogenic risk in pregnancy is unknown for 91% of medications. Research shows that pregnant women continue to be prescribed drugs despite the lack of clinical research. The most common drugs provided to pregnant women are antiasthmatics, antibiotics, NSAIDS, anxiolytics, antidepressants and (inadvertently) oral contraceptives. In Scotland, 85% of pregnant women are prescribed drugs via primary care services: many of the drugs are classified as high-risk, with one-fifth of women using FDA category C, D and X drugs during their pregnancy. One study at Liverpool Women’s Hospital in the UK found that 10% of total prescriptions for pregnant women were high-risk, off-label medicines. In the US, 64% of pregnant women are prescribed one or more medications for the management of chronic or acute illness during pregnancy. Adherence to treatment for chronic conditions (cardiovascular, rheumatic and bowel disorders, diabetes and epilepsy) during pregnancy remains low in Europe, North America and Australia; with women's views about the safety of drugs affecting their adherence. We have a situation where the drugs are not tested, the risks are not well understood, drugs continue to be prescribed, and many pregnant women do not adhere to regimes—where all of these factors are related.

The exclusion of pregnant women from research is driven by liability concerns on the part of the manufacturer; restrictive regulatory environments; researchers’ concerns about the vulnerability of pregnant women and their foetuses; ethical guidelines stating that research that can be undertaken in other populations should not be done in vulnerable populations; reluctance of health care providers to recruit pregnant women; and the risk aversion of pregnant women (and their families, and communities).

**Vulnerability and dangerous research**

The split between research ethics and clinical ethics was driven by public outrage at cases of unethical research by clinicians. For example, in the US, the Tuskegee study prompted the National Research Act 1974, the establishment of institutional review boards, and the Belmont Report in 1979. In New Zealand, the research ethics framework is based on Judge Cartwright’s 1988 recommendations following investigation of cervical cancer research conducted at National Women’s Hospital in Auckland. As a result of this history, the field of research ethics is pervaded with a sense that research is dangerous rather than a social good.

Research ethics guidelines have historically advocated for the protection of vulnerable groups from the potential harms of research. Vulnerable groups are generally deemed by international and national research ethics regulation to include: children, women of reproductive age, pregnant women, people in prison, people with cognitive impairment, and those highly dependent upon medical care. Pregnant women and their foetuses are physiologically vulnerable, and pregnant women may also be subject to social, cultural and economic pressures that constrain their freedoms and options. But exclusion from research is not a simple answer to supposed vulnerability. Protective policies may have been motivated by concerns for the wellbeing of pregnant women and their foetuses, but the effect is unjust because the consequence of such exclusion is that pregnant women lack information about treatment options that would ordinarily be available to other non-pregnant patients.

The widespread exclusion of so called vulnerable groups from medical research
has resulted in a disproportionate body of evidence regarding the health of middle-aged white men. Some clinical guidelines continue to be based on research that under-represents women, rather than actively selecting for studies that are more representative. The last 40 years have seen a progressive effort to rebalance this perspective and to recognise that research participation is of value to both the individual and the population they represent. Recent policies have advocated for more medical research with women, children, and prisoners. But pregnant women remain one of the last groups to be routinely excluded from research. Why is this?

The precautionary principle and pregnancy

Pregnancy care is dominated by the precautionary principle, which advocates action to reduce potential threats, before there is strong evidence of harm, in cases where the potential harm is serious or irreversible. Two seminal cases of drug use during pregnancy changed the way we perceive risk and pregnancy. Ten thousand foetuses were affected by exposure to thalidomide, prescribed for morning sickness during the 1950s. And the daughters of women prescribed diethylstilbestrol (DES) were subsequently found to have a 40-fold increase in the risk of cancer later in life.

The problem with the precautionary principle in relation to research is that it simply shifts the risk from the environment of a carefully controlled and monitored study, to inconsistent use of untested treatments and medicines off-label in the community. In other words, it is precautionary about one sort of risk, and blind to the other sort of risk that it itself thereby causes. The danger to pregnant women and their foetuses arises primarily from the lack of evidence about medical treatment during pregnancy, not from research itself. Untreated and under-treated disease can be dangerous for the foetus, and off-label prescription of untested drugs can be dangerous. A philosophy of absolute risk aversion may appear superficially lofty, but is actually impractical; it does not take account of the complex trade-offs that women make daily throughout their pregnancy. If we are to take precautionality seriously—rather than myopically focusing on only one source of risk—we have to assess the risks and potential benefits of research versus treatment to determine which approach would be overall most precautionary. In some cases, this will call for the careful inclusion of pregnant women in well-designed studies.

International trends

Research ethics guidelines have a role to play in defining whether the default position is to include or exclude pregnant women from research. International guidelines tend to support inclusion. The Declaration of Helsinki, Item 5, notes that: “Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.”

The Council for International Organizations of Medical Sciences (CIOMS) Guideline 17 asserts, “Pregnant women should be presumed to be eligible for participation in biomedical research.” The CIOMS guidelines are currently under revision and it is anticipated that the section on pregnant women will be significantly updated and revised.

In some jurisdictions, guidelines now advocate for limited and careful inclusion of pregnant women in research, subject to extra safeguards. In the US, pregnant women and their foetuses are categorised as a vulnerable research population and regulated under Subpart B of the Code of Federal Regulations (45 CFR 46). These regulations are now thought to be overly restrictive and the categorisation of vulnerability is in tension with the views of the National Institutes of Health, which argue that pregnant women should be reconceptualised as ‘complex’ rather than ‘vulnerable’. The Australian National Statement on Ethical Conduct in Human Research has a chapter devoted to “Ethical considerations specific to participants”. 
which contains a section on pregnant women, along with other groups usually considered vulnerable. The National Statement requires that all research with pregnant women (including, for example, a questionnaire of dietary habits) is scrutinised by full Human Research Ethics Committee (HREC) review, rather than any expedited or alternative review pathways. Under these guidelines, interventional research with pregnant women must be limited to “therapeutic research”.33

New Zealand guidelines

New Zealand does not have any research ethics regulation regarding the safe and responsible participation of pregnant women in research. In general terms, National Ethics Advisory Committee (NEAC) Ethical Guidelines for Interventional Studies state:

5.26 Investigators may not exclude participants on the basis of sex, ethnicity, national origin, religion, education or socioeconomic status, except where such exclusion or inclusion is essential to the purposes of the study.

5.27 Inclusion and exclusion of participants affect the extent to which study findings can be generalised. To contribute to an equitable distribution of study benefits and burdens, investigators should, when practicable, consider including all those who may benefit from the study findings.34

These general statements may be read to support the inclusion of pregnant women, because to routinely exclude them is not essential for the purposes of the research and discriminates against groups who could benefit from the knowledge gained from the research.

Paragraph 5.28 of the Guidelines identifies the following classes of vulnerable groups: children and young people, people with a mental illness, people with serious intellectual disability, people with English as a second language and/or a different cultural background to the investigators, people whose freedom to make independent choices is restricted (eg, prisoners, employees of a sponsoring company, or students) and people with serious illness.34 From this list, the appendices include specific advice for research involving children, persons with an intellectual disability, unconscious patients, terminally ill patients, and older persons. Various sections of the guidelines discuss the need for special care to ensure that vulnerable participants are not subject to discrimination, abuse, undue inducement, coercion or exploitation.

One might assume that the general tone of New Zealand guidelines facilitates reasonable inclusion of pregnant women in New Zealand health research simply because they do not prescribe any specific limits on research with pregnant women (By New Zealand health research I mean research conducted with New Zealand residents in New Zealand, regardless of whether the sponsor is from New Zealand or overseas). In my experience, this is not the case. I have served on the Central Ethics Committee for 3 years, and in my view pregnant women are still routinely excluded from research without any justification. Often it is the case that pregnant women are excluded from studies for conditions known to affect them, where there is a high likelihood that they will be receiving treatment in the community off-label. Researchers rarely offer any justification for exclusion.

Specific guidelines

Health and Disability Ethics Committees, and researchers in New Zealand, need specific guidance about when and how to ethically include pregnant women in research. During pregnancy an entity of indeterminate moral status, with the potential to become a separate human being with legal identity and rights, exists inside a competent autonomous adult. The moral status of the foetus, and whether it is entitled to moral rights, is hotly contested. However, it is widely accepted, and reasonably so, that a wanted foetus which is likely to be carried to term, is a morally valuable entity worthy of care and protection. It is plausible to assume that the community has some duty of care to prevent irresponsible and unnecessary harm to the foetus. Does this duty extend to excluding pregnant women from trials that are relevant to their own health needs,
solely on the basis of potential risk to the foetus? Or would this unreasonably impede on the autonomy of the pregnant women?

Nor is pregnancy equivalent to the state of parenthood. A child is not located inside the mother, and its physiological health is not integrally linked to the health of the mother. The courts can independently assess the best interests of the child. During pregnancy, is it often difficult to disentangle the interests of the mother and the foetus, because the well-being and health of each is inter-dependent. We cannot therefore extrapolate from the research ethics guidelines regarding the inclusion of children in research. The uniqueness of pregnancy gives rise to specific questions regarding research ethics. These questions warrant focused debate, and the answers cannot simply be deduced from the general principles of research ethics we currently have in New Zealand. Research with children, unconscious patients, patients with a terminal illness, and prisoners also raise specific ethical issues, and all these populations receive focused attention and research related advice from NEAC. Pregnancy is mentioned nowhere in the NEAC guidelines for interventional or observational research or in the Operating Standards for ethics committees.

The US guidelines are generally thought to be overly restrictive. The Australian and CIOMS guidelines are currently under review, and the inclusion of pregnant women is expected to receive greater attention. In New Zealand, NEAC is reviewing their research ethics guidance in 2016–2017 and so this is a timely point to consider research ethics and pregnancy.

Questions for debate:
Research ethics guidance should include advice on the following topics:

- Should the foetus be conceived of as a separate patient or research participant?
- Who should assess the balance of risks versus potential benefits on behalf of the foetus? For example, should ethics committees reject applications on the grounds that they are too risky to the foetus, even if they represent some benefit to the woman? Or should the ethics committee's role be limited to ensuring that the risks and potential benefits are clearly explained in the informed consent process, leaving pregnant women to make the risk/potential benefit assessment themselves?
- Should the consent of the father or other nominated parent be required for research during pregnancy?
- Should the consent of the father or other nominated parent be required for the child’s continued participation in the research or follow-up after birth?
- When assessing the risks of research, should ethics committees consider the relative risks to pregnant women of not participating in research (for example, undergoing untested ‘treatment’ in the community or remaining untreated)?
- Should pregnant women be classed as a separate sub-category of research participants within the study, subject to distinct data collection, safety monitoring and grounds for stopping the pregnancy-related arm of the trial?
- What rules should govern research in cases when the woman intends to abort the foetus?

Conclusion
For some, these questions may seem obscure, academic and uncomfortable. The default routine exclusion of pregnant women from research may appear safer and easier. We must remember that pregnancy is not simply a 9-month window; it is a crucial period affecting the long-term health of the future person. As a community we need to better understand health, disease, and medical treatment during pregnancy, and we can only achieve this by including pregnant women in health research. We have an ethical obligation to determine how to achieve this safely and responsibly.
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