PREGNANT WOMEN AND HEALTH RESEARCH: AN ETHICAL IMPERATIVE

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Queen's University May 2013

An Unnecessary Risk

By Françoise Baylis,
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When a clinical trial excludes pregnant women, we have no idea how the drug or vaccine will affect their fetuses.

In Canada, research involving humans is primarily governed
out in the Tri-Council Policy Statement: Ethical Conduct for
Humans. These guidelines are currently being [revised]
(http://pre.ethics.gc.ca/eng/policy-politique/initiatives/revi
revisee/Default/) and the public consultation period ends M

When the policy statement was published in 1998, it address
problem of the day, namely the exclusion of women from res
guidelines stipulated that "women shall not automatically be
research solely on the basis of sex or reproductive capacity."
salutary effect – the number of women research participants
exponentially. However, problems with research involving w

Frequently, women of reproductive capacity (including nuns,
heterosexual women with infertile male partners, and wome
sexual activity) are required to use oral contraceptives as a c
participation. This is ethically offensive.

Another ethical problem is the common practice of excluding
from research. This can harm pregnant women and undermi
example, frequently there are no clinical trial data on which
decisions about treatment or immunization. This can result i

nature
International weekly journal of science

Pregnant women deserve better

Clinical trials routinely exclude expectant mothers. This is unethical and unscientific, and regulators must mandate change, says **Françoise Baylis**, in the second of three related pieces on gender bias in biomedicine.

International ethical guidelines drawn up by the Council for International Organizations of Medical Sciences[1] clearly stipulate that pregnant women are eligible to participate in biomedical research. Yet they are routinely excluded from the vast majority of clinical trials of drugs, vaccines, nutraceuticals, natural health products and medical devices because of the harm the intervention might do to the dev
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women are excluded from clinical studies. New drugs and devices are typically not approved for use in pregnant women as the many physiological changes that women experience during pregnancy — such as increased plasma volume, body weight, body fat, metabolism and hormone levels — make it impossible to calculate dose and safety information by extrapolating from data on men and non-pregnant women.

This means that when a pregnant woman has a health condition that requires treatment, her physician often has insufficient information to make an evidence-based recommendation.

> This is ethically and medically unacceptable for two reasons: pregnant women get sick, and sick women get pregnant. Patients who happen

the same time as phase III efficacy trials in the general population. With this staggered approach, pregnant women and fetuses would not be exposed to any compounds that failed in phase I and II trials. Another option would be to allow pregnant women to join phase III trials once a drug had passed safely through phases I and II. This would need to include enhanced safety monitoring for pregnant women, similar to that done in a stand-alone phase I trial. As researchers and sponsors are unlikely to make such changes of their own volition, regulators will need to make the inclusion of pregnant women in such trials mandatory, and oblige drug companies to conduct follow-up studies to identify any short- or long-term effects of the drugs.

Persuading pregnant women to take part in research can be difficult because of the perception that trials are riskier than taking prescribed medication. Trial organizers should take pains to demonstrate that this is often a false belief, and that it is generally safer for pregnant women to use drugs in a trial under controlled

My starting assumptions

- Physicians should practice evidence-based medicine
  - Individual clinical expertise
  - External clinical evidence
- Pregnant women are capable of autonomous decision-making
  - trial participation
  - treatment
- Pregnant women should have access to sound information and advice on the basis of which to make medical decisions for themselves and their fetuses
- Pregnant women care about fetal well-being

My conclusions

- The automatic exclusion of pregnant women from research potentially harms women and their fetuses.

- The responsible inclusion of pregnant women in research potentially benefits women and their fetuses.

Children

"Children cannot be regarded simply as 'little people' pharmacologically. Their metabolism, enzymatic and excretory systems, skeletal development and so forth differ so markedly from adults' that drug tests for the latter provide inadequate information about dosage, efficacy, toxicity, side effects, and contraindications for children."

Capron A. *Clin Res.* 1973; 21: 141-50.

Women

"Women are not simply 'men with estrogen'. Women differ systematically from men in many ways, including in their genetics, metabolism, behavior, and social determinants of health. Female–male health differences may be due to 'sex' (ie, sex-linked biology), 'gender' (ie, socially-structured relations), or both."

Giacomini M, Baylis F. *Clin Res.* 2003: 3, 12-5.

Pregnant women

"Pregnant women are not just women with bigger bellies. Physiological changes during pregnancy such as increased plasma volume, body weight, body fat, metabolism and hormone levels preclude the extrapolation of data about dosing and safety (from men and non-pregnant women) to pregnant women."

Baylis F. *Nature* 2010;465: 689-90.

Reasons for inclusion

- Develop effective treatment for women during pregnancy
- Promote fetal safety
- Reduce harm from suboptimal care
- Allow access to benefits of research participation

Lyerly, A.D., Little, M.O., and Faden, R.R. *Hastings Center Report* 2008; 8(6)

Outline

- Where are we?
- Where should we be?
- How can we get there?

- Where are we?
- Where should we be?
- How can we get there?

Some facts

- Most drugs are not studied in pregnant women
- Most drugs are not labeled for use during pregnancy
- Most pregnant women (64%) take one or more prescribed medications for chronic medical conditions or acute problems

Goldkind SF, Sahin L, Gallauresi B. 2010 *NEJM 362(24): 2241-43.*
Daw JR, Mintzes B, Law MR, Hanley GE, Morgan SG. 2012 *Clin Ther 34(1): 239-249.*

Drugs: Not for use in pregnancy

- *OTC:* "If pregnant or breast-feeding, ask a health professional before use."
- *Product monograph:* "The effect of pregnancy on the pharmacokinetics and pharmacodynamics of XXX has not been studied."
- *Physicians' Desk Reference*: "Use in pregnancy is not recommended unless the potential benefits justify the potential risks to the fetus."

The problem

- “Physicians caring for pregnant women have very little information to help them decide whether the potential benefits to the mother outweigh the risks to the fetus.”

Koren, Pastuszak, and Ito. NEJM 1998; 338:1128-1137

Exclusion from clinical trials

- Majority of information is from:
  - Animal studies
  - Case reports
  - Registries
  - Retrospective exposure studies
  - Meta-analysis

Diet & Fitness Sexual Health

HEALTHBEAT: More women use medicine in pregnancy, need better info on safety and how to choose

BY LAURAN NEERGAARD, THE ASSOCIATED PRESS MARCH 12, 2013

STORY PHOTOS (1)

This photo taken March 10, 2013 shows non-prescription drugs displayed at a pharmacy in New York. Nearly every woman takes a medication at some point during pregnancy. Yet there's disturbingly little easy-to-understand information about which drugs pose a risk to her baby, and what to do about it. (AP Photo/Seth Wenig)

WASHINGTON - Nearly every woman takes a medication at some point during pregnancy. Yet there's disturbingly little easy-to-understand

MORE ON THIS STORY

- Pregnancy: Body changes
- Govt panel says not yet to test that would diagnose more diabetes during pregnancy
- Scientists say child born with HIV apparently cured, offers clues for fighting pediatric AIDS
- From autism to depression: Largest genetic study shows mental disorders share genetic kinks

STORY TOOLS

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The problem

- "The effort to protect a *small* number of fetuses from research-related risks places a *greater* number of fetuses and women at risk from unstudied clinical interventions, and from lack of therapeutic options."

Goldkind SF, Sahin L, Gallauresi B. 2010 *NEJM* 362(24): 2241-43.

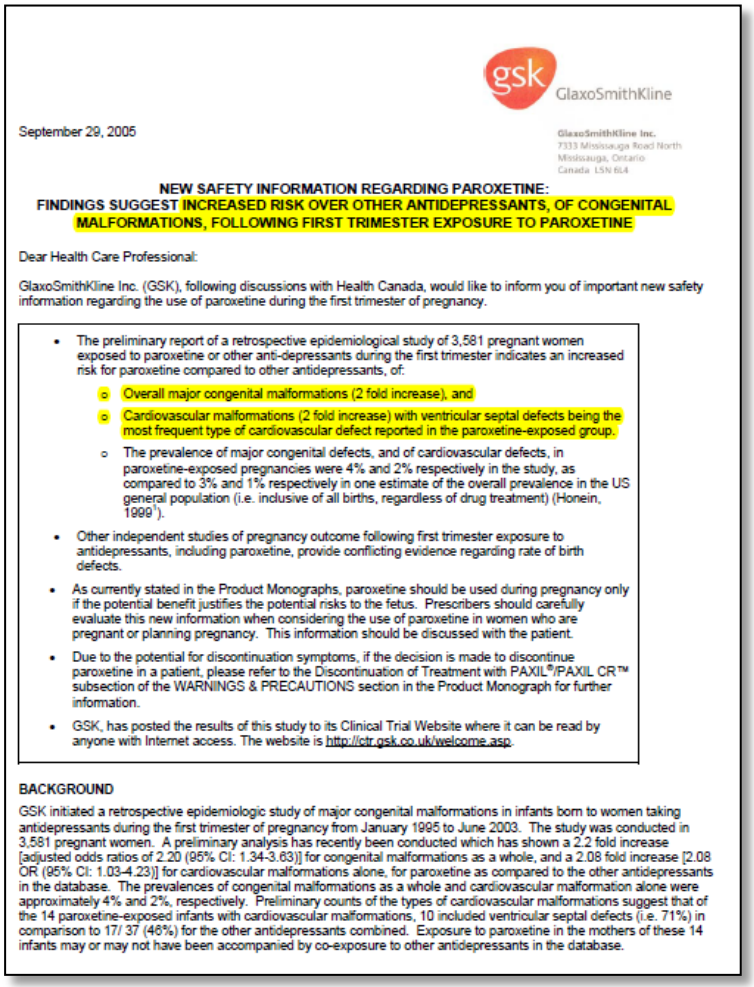
SSRIs during pregnancy

- "The controversy surrounding antidepressants and pregnancy"
  Anne Kingston, April 20, 2013 *Maclean's*

Bartram vs GlaxoSmithKline

- Faith Gibson (Surrey BC) prescribed Paxil (SSRI) in December 2002
- Became pregnant, asked Dr about continuing Paxil during pregnancy; told “100 % safe”
- Daughter, Meah Bartram, born September 2005 with hole in heart
- 2 weeks later, Health Canada and GSK issued advisory: Paroxetine taken in first trimester may pose “an increased risk” of caridovascular defects

Paroxetine



GlaxoSmithKline

September 29, 2005

GlaxoSmithKline Inc.
7333 Mississauga Road North
Mississauga, Ontario
Canada L5N 6L4

NEW SAFETY INFORMATION REGARDING PAROXETINE:
FINDINGS SUGGEST INCREASED RISK OVER OTHER ANTIDEPRESSANTS, OF CONGENITAL MALFORMATIONS, FOLLOWING FIRST TRIMESTER EXPOSURE TO PAROXETINE

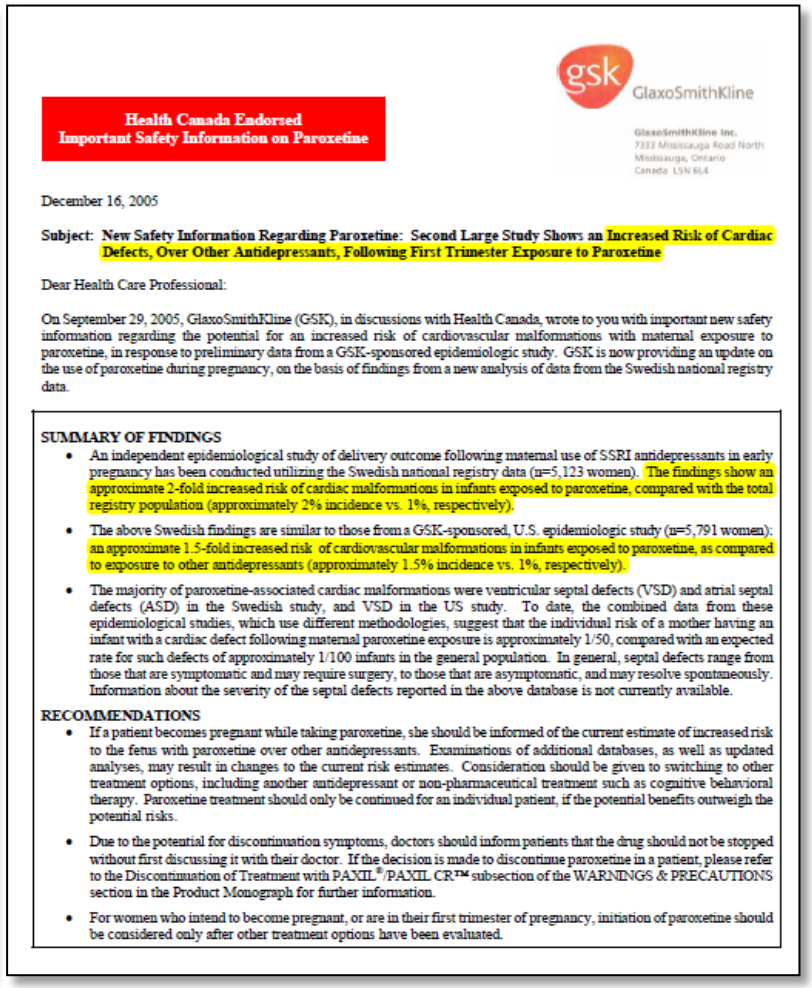
Dear Health Care Professional:

GlaxoSmithKline Inc. (GSK), following discussions with Health Canada, would like to inform you of important new safety information regarding the use of paroxetine during the first trimester of pregnancy.

- The preliminary report of a retrospective epidemiological study of 3,581 pregnant women exposed to paroxetine or other anti-depressants during the first trimester indicates an increased risk for paroxetine compared to other antidepressants, of:
  - Overall major congenital malformations (2 fold increase), and
  - Cardiovascular malformations (2 fold increase) with ventricular septal defects being the most frequent type of cardiovascular defect reported in the paroxetine-exposed group.
  - The prevalence of major congenital defects, and of cardiovascular defects, in paroxetine-exposed pregnancies were 4% and 2% respectively in the study, as compared to 3% and 1% respectively in one estimate of the overall prevalence in the US general population (i.e. inclusive of all births, regardless of drug treatment) (Honein, 1999[1]).
- Other independent studies of pregnancy outcome following first trimester exposure to antidepressants, including paroxetine, provide conflicting evidence regarding rate of birth defects.
- As currently stated in the Product Monographs, paroxetine should be used during pregnancy only if the potential benefit justifies the potential risks to the fetus. Prescribers should carefully evaluate this new information when considering the use of paroxetine in women who are pregnant or planning pregnancy. This information should be discussed with the patient.
- Due to the potential for discontinuation symptoms, if the decision is made to discontinue paroxetine in a patient, please refer to the Discontinuation of Treatment with PAXIL®/PAXIL CR™ subsection of the WARNINGS & PRECAUTIONS section in the Product Monograph for further information.
- GSK, has posted the results of this study to its Clinical Trial Website where it can be read by anyone with Internet access. The website is http://ctr.gsk.co.uk/welcome.asp.

BACKGROUND

GSK initiated a retrospective epidemiologic study of major congenital malformations in infants born to women taking antidepressants during the first trimester of pregnancy from January 1995 to June 2003. The study was conducted in 3,581 pregnant women. A preliminary analysis has recently been conducted which has shown a 2.2 fold increase [adjusted odds ratios of 2.20 (95% CI: 1.34-3.63)] for congenital malformations as a whole, and a 2.08 fold increase [2.08 OR (95% CI: 1.03-4.23)] for cardiovascular malformations alone, for paroxetine as compared to the other antidepressants in the database. The prevalences of congenital malformations as a whole and cardiovascular malformation alone were approximately 4% and 2%, respectively. Preliminary counts of the types of cardiovascular malformations suggest that of the 14 paroxetine-exposed infants with cardiovascular malformations, 10 included ventricular septal defects (i.e. 71%) in comparison to 17/ 37 (46%) for the other antidepressants combined. Exposure to paroxetine in the mothers of these 14 infants may or may not have been accompanied by co-exposure to other antidepressants in the database.



GlaxoSmithKline

GlaxoSmithKline Inc.
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Health Canada Endorsed
Important Safety Information on Paroxetine

December 16, 2005

Subject: New Safety Information Regarding Paroxetine: Second Large Study Shows an Increased Risk of Cardiac Defects, Over Other Antidepressants, Following First Trimester Exposure to Paroxetine

Dear Health Care Professional:

On September 29, 2005, GlaxoSmithKline (GSK), in discussions with Health Canada, wrote to you with important new safety information regarding the potential for an increased risk of cardiovascular malformations with maternal exposure to paroxetine, in response to preliminary data from a GSK-sponsored epidemiologic study. GSK is now providing an update on the use of paroxetine during pregnancy, on the basis of findings from a new analysis of data from the Swedish national registry data.

SUMMARY OF FINDINGS

- An independent epidemiological study of delivery outcome following maternal use of SSRI antidepressants in early pregnancy has been conducted utilizing the Swedish national registry data (n=5,123 women). The findings show an approximate 2-fold increased risk of cardiac malformations in infants exposed to paroxetine, compared with the total registry population (approximately 2% incidence vs. 1%, respectively).
- The above Swedish findings are similar to those from a GSK-sponsored, U.S. epidemiologic study (n=5,791 women): an approximate 1.5-fold increased risk of cardiovascular malformations in infants exposed to paroxetine, as compared to exposure to other antidepressants (approximately 1.5% incidence vs. 1%, respectively).
- The majority of paroxetine-associated cardiac malformations were ventricular septal defects (VSD) and atrial septal defects (ASD) in the Swedish study, and VSD in the US study. To date, the combined data from these epidemiological studies, which use different methodologies, suggest that the individual risk of a mother having an infant with a cardiac defect following maternal paroxetine exposure is approximately 1/50, compared with an expected rate for such defects of approximately 1/100 infants in the general population. In general, septal defects range from those that are symptomatic and may require surgery, to those that are asymptomatic, and may resolve spontaneously. Information about the severity of the septal defects reported in the above database is not currently available.

RECOMMENDATIONS

- If a patient becomes pregnant while taking paroxetine, she should be informed of the current estimate of increased risk to the fetus with paroxetine over other antidepressants. Examinations of additional databases, as well as updated analyses, may result in changes to the current risk estimates. Consideration should be given to switching to other treatment options, including another antidepressant or non-pharmaceutical treatment such as cognitive behavioral therapy. Paroxetine treatment should only be continued for an individual patient, if the potential benefits outweigh the potential risks.
- Due to the potential for discontinuation symptoms, doctors should inform patients that the drug should not be stopped without first discussing it with their doctor. If the decision is made to discontinue paroxetine in a patient, please refer to the Discontinuation of Treatment with PAXIL®/PAXIL CR™ subsection of the WARNINGS & PRECAUTIONS section in the Product Monograph for further information.
- For women who intend to become pregnant, or are in their first trimester of pregnancy, initiation of paroxetine should be considered only after other treatment options have been evaluated.

Some facts

- Most of the time, drugs are not studied in pregnant women.
- Most drugs are not labeled for use during pregnancy
- Most pregnant women (64%) take one or more prescribed medications for chronic medical conditions or acute problems
- Animal studies dating to the early 80s link SSRIs with increased risk of birth defects
- Pregnant women not allowed to participate in RCTs
- Epidemiological, or population, studies show risk of harm
- SSRIs not approved for use in pregnancy
- SSRIs top-prescribed drugs in pregnancy

Motherisk vs its critics

- Depression during pregnancy is a greater risk to pregnant woman and fetus than SSRIs
- Health Canada's 2005 Paxil advisory "based on small non-peer reviewed, unpublished studies"
- 2010 Motherisk report found no increased risk of neonatal heart defects
- "the benefits of [SSRI] therapy far outweigh the potential minimal risks"

- There is no good data suggesting that untreated depression is more dangerous to pregnant woman and fetus than SSRIs
- Clinical depression during pregnancy is a serious concern, but there are less risky effective treatment options

Impact on pregnant women: H1N1 vaccine

- Public health authorities in Canada initially recommend adjuvanted H1N1 vaccine for everyone (including pregnant women)

- Change in plan – prior to 20 weeks should take unadjuvanted vaccine

Seasonal influenza unadjuvanted vaccine

- Unadjuvanted seasonal flu vaccine has been used in the US and Canada in pregnant women since the 1950s.
- Recommended for use by all women who are or will be pregnant during the influenza season (based on observational data, not clinical trials)

TABLE

Summary of data on safety outcomes of studies of influenza immunization during pregnancy

Study	Design	Study group	Control group	Follow-up period	Maternal outcomes	Infant outcomes
Zaman et al,[30] 2008	Prospective, randomized, double-blind controlled trial	172 pregnant women in third trimester	168 pregnant women who received 23-valent pneumococcal polysaccharide vaccine	7 d postvaccination; mother-infant pairs followed up to 24 wk of life	No serious adverse events or differences in pregnancy outcomes	No differences in gestational age, proportion with cesarean delivery, birthweight, or APGAR score
France et al,[31] 2006	Retrospective, matched cohort	3160 infants born to vaccinated mothers	37,969 infants born to nonvaccinated mothers	End of influenza season	Not assessed	No difference with regard to birthweight, gestational age, or length of stay for birth hospitalization
Munoz et al,[32] 2005	Retrospective, matched cohort	225 pregnant women in second and third trimesters	826 nonimmunized pregnant women	42 d after immunization; birth to 6 mo of age	No serious adverse events or differences in pregnancy outcomes	No differences in outcomes of pregnancy (cesarean delivery and premature delivery) and infant medical conditions
Black et al,[33] 2004	Retrospective cohort	3719 pregnant women immunized	45,866 women	Until delivery	No difference in cesarean section	No difference in cesarean section or preterm delivery
Yeager et al,[34] 1999	Prospective cohort	319 pregnant women immunized in second and third trimesters	None	Next prenatal visit	No preterm labor or other serious events	Not assessed
Englund et al,[35] 1993	Randomized, controlled trial	13 pregnant women in third trimester	13 pregnant women who received tetanus toxoid vaccine	Not specified	No significant adverse reactions, including fever, moderate or severe pain, or need to visit a physician noted in either group	Similar gestational ages in both groups; no health concerns in infants examined between 1-3 mo of age
Deinard and Ogburn,[36] 1981	Prospective cohort	189 pregnant women (13 prior to conception; 41, 58, and 77 in first, second, and third trimesters, respectively)	517 nonvaccinated pregnant women	48 h after immunization; pregnancy outcome to 8 wk of life	No differences in maternal health, pregnancy outcome, or postpartum course	No significant differences in adverse pregnancy outcomes (congenital anomalies, neonatal mortality)
Sumaya and Gibbs,[37] 1979	Retrospective, matched cohort	56 women in second and third trimesters	40 nonvaccinated pregnant women	24 h after immunization	No significant immediate reactions or differences in pregnancy course	No increased fetal complications associated with vaccine
Murray et al,[38] 1979	Prospective, matched cohort	59 pregnant immunized women (5, 22, and 32 in first, second, and third trimesters, respectively)	27 nonpregnant vaccinated women	Not specified	No significant side effects after immunization in any women	Not assessed
Heinonen et al, 1973,[39] and 1977[40]	Prospective cohort	2291 pregnant immunized women; up to 650 in first trimester	None	Up to 7 y of age		No suggestive associations for congenital malformations, malignancies, or neurocognitive disabilities
Hulka,[41] 1964	Retrospective and prospective cohort	225 pregnant immunized women (19 in first trimester)	44 nonpregnant influenza immunized; 104 pregnant and 25 nonpregnant immunized with placebo	Up to 3 d after vaccination and at delivery	Local pain at injection site and some systemic symptoms greater in women immunized with influenza vaccine	No association with fetal anomalies or miscarriage

Tamma. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol 2009.

Seasonal influenza: adjuvanted vaccine

- No pregnant women enrolled
- “No adverse outcomes” in pregnant women inadvertently immunized
- Retrospective analysis (1991-2009) MF59 exposure during pregnancy not associated with increased proportion of abnormal outcomes compared with unadjuvanted vaccines

Vaccine 2010 28:1877-80

H5N1 influenza: adjuvanted vaccine

- Studies with several adjuvanted vaccines
  - Alum
  - MF59
  - AS03
- No pregnant women enrolled
- “No adverse outcomes” reported in pregnant women inadvertently immunized

At the time of H1N1 what did we 'know' about vaccines?

- Unadjuvanted seasonal vaccine
  - "safe and effective" (mostly observational data)

- Adjuvanted seasonal vaccine
  - (MF59) "no adverse outcomes" reported in pregnant women inadvertently immunized while pregnant
  - Retrospective analysis from 1991-2009

- Adjuvanted H5N1 vaccine
  - (Alum; MF59; AS03) "no adverse outcomes" reported in pregnant women inadvertently immunized while pregnant

- Adjuvanted H1N1 vaccine
  - (AS03) tested in 45,000 with no serious adverse events reported

H1N1 influenza

- “Unadjuvanted vaccine is recommended for use by pregnant women”
- “Although there is no evidence that adjuvanted vaccine is unsafe for pregnant women, this kind of vaccine hasn’t been tested in pregnant women, so unadjuvanted vaccine is the first choice for pregnant women.”

- Where are we?
- Where should we be?
- How can we get there?

Responsible inclusion

- If pregnant women are going to use drugs, then we need to study the drugs in this patient population.
- “Need to make reasoned decisions about risk in pregnancy”
- “Need to take responsible and calculated risks in order to garner evidence, lest we visit more risk on more people in the future.”

Responsible inclusion

- Wrong to tolerate the *status quo* where clinicians care for patients without evidence of safety and efficacy
- Need to include pregnant women in clinical trials, including Phase I trials
- Important to shift the burden of justification from inclusion to exclusion

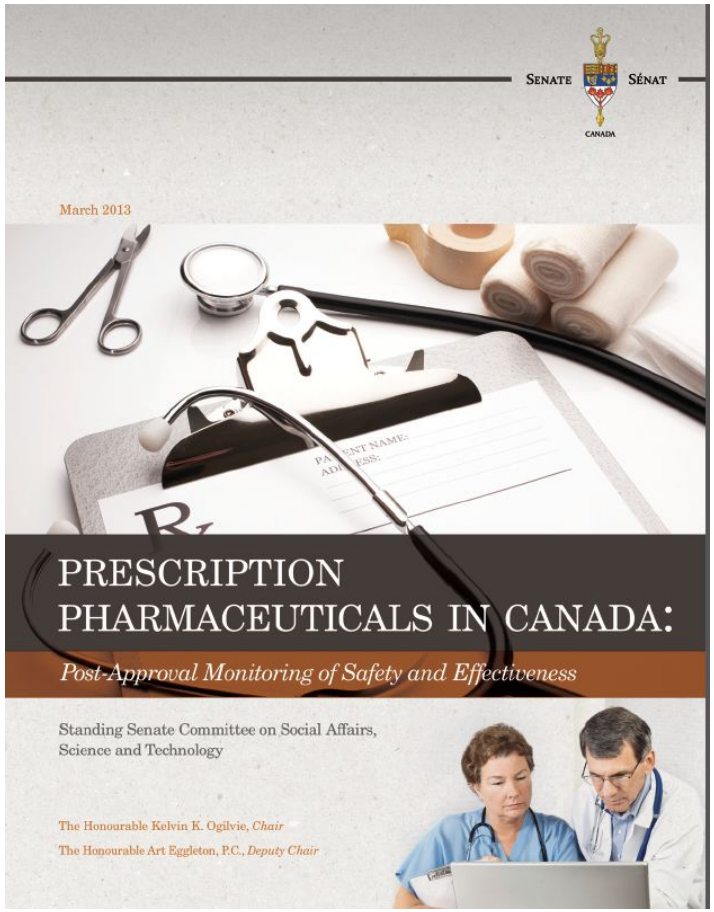
Senate Standing Committee on Social Affairs Science and Technology

It was suggested that the assumption should be one of inclusion, unless the sponsor of the drug has a compelling argument not to include them. Françoise Baylis, Professor at the Faculty of Medicine at Dalhousie University, made the observation that "[p]regnant women get sick and sick women get pregnant", and that they deserve the same level of evidence-based healthcare as any other Canadian.

Senate Standing Committee on Social Affairs Science and Technology

The committee feels it is necessary to require that drug developers test their drugs in a population that is reflective of who could reasonably be expected to consume that product, should it obtain market approval.

Senate Standing Committee on Social Affairs Science and Technology



… greater emphasis must be placed on testing a candidate drug's safety and efficacy in groups that reflect those who can reasonably be expected to consume the drug once it becomes marketed to the general population.

- Where are we?
- Where should we be?
- How can we get there?

Ending the knowledge gap

- Pursue innovative study designs
- Develop more nuanced research regulations
- Alter labelling to more effectively communicate evidence-based guidance to medication use in pregnancy
- Establish an Institute of Medicine working group to issue a report on the under-representation of pregnant women in research
- Create incentives for inclusion of pregnant women in biomedical research

http://secondwaveinitiative.org/Case_Statement.html

Ending the knowledge gap

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http://secondwaveinitiative.org/Case_Statement.html

Create incentives for inclusion of pregnant women in biomedical research

Barriers to inclusion

- Manufacturers (Pharma)
- Regulators (Health Canada, FDA)
- Research sponsors (CIHR, NIH, MRC)
- Oversight organizations (PRE, OHRP)
- Research ethics guidelines/legislation (TCPS-2; 45 CFR 46 Subpart A)
- Research ethics review committees (REBs)
- Researchers
- Clinicians
- Participants
- General public (beliefs, customs, practices)

Incentives for inclusion

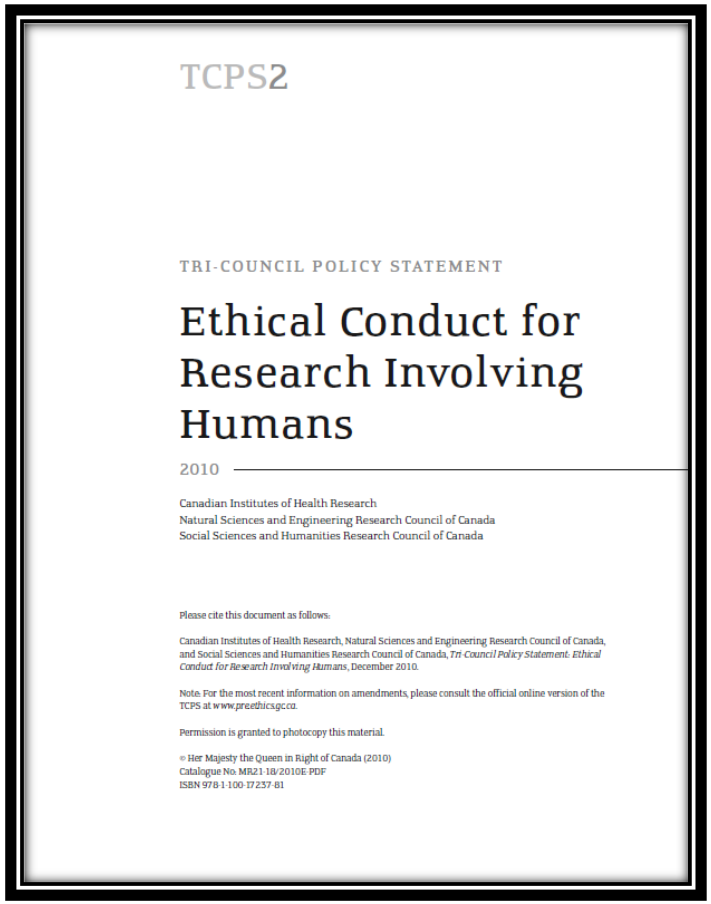
- Manufacturers: Protect from tort liability. Provide data exclusivity. Prohibit off-label prescribing
- Regulators: For research involving additional risks to the fetus, index levels of risk to the severity of need.
- Research sponsors: Make research in pregnancy a funding priority – expand funding for cohort registries, case-control surveillance studies.

Incentives for inclusion

- Oversight organizations: Presume inclusion and provide clear criteria for managing risk; clear criteria for exclusion
- REBs: No boiler-plates
- Researchers: Justify exclusion
- Clinicians: Educate about preventive medicine for themselves and their patients.
- Research participants: Increase public awareness.
- Public: Time ….

Develop more nuanced research regulations

TCPS-2 Article 4.3



TCPS2

TRI-COUNCIL POLICY STATEMENT

Ethical Conduct for Research Involving Humans

2010

Canadian Institutes of Health Research
Natural Sciences and Engineering Research Council of Canada
Social Sciences and Humanities Research Council of Canada

Please cite this document as follows:

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, December 2010.

Note: For the most recent information on amendments, please consult the official online version of the TCPS at www.pre.ethics.gc.ca.

Permission is granted to photocopy this material.

Catalogue No. MR21-18/2010E-PDF
ISBN 978-1-100-17237-81

Women shall not be inappropriately excluded from research solely on the basis of their reproductive capacity, or because they are pregnant or breastfeeding

TCPS-2 Application

Application:

Researchers should not exclude women from research on the basis of their reproductive capacity, or their pregnancy, or because they are breastfeeding, *unless there is a valid reason for doing so.*

… REBs shall take into account foreseeable risks and potential benefits for the woman and her embryo, fetus or infant, as well as the foreseeable risks and potential benefits of excluding pregnant … women from the research.

Risk/benefit assessment

- Nature and severity of the disease
- Availability and results of previous nonclinical data on pregnant and nonpregnant women
- Results from clinical data
- Availability of alternative therapies and knowledge of associated risks
- Stage of pregnancy in relation to overall development of fetus
- Potential for harm to woman, fetus, or child

Health Canada Guidance Document Jan 2012

CIOMS: *Guideline 17*

- "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 fetus and their subsequent offspring, and to their fertility."

UNAIDS/WHO Guidance document: *Guidance Point 9*

- 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 breast-feeding, should be recipients of future safe and effective biomedical HIV prevention interventions.

UNAIDS/WHO Guidance document: *Guidance Point 9*

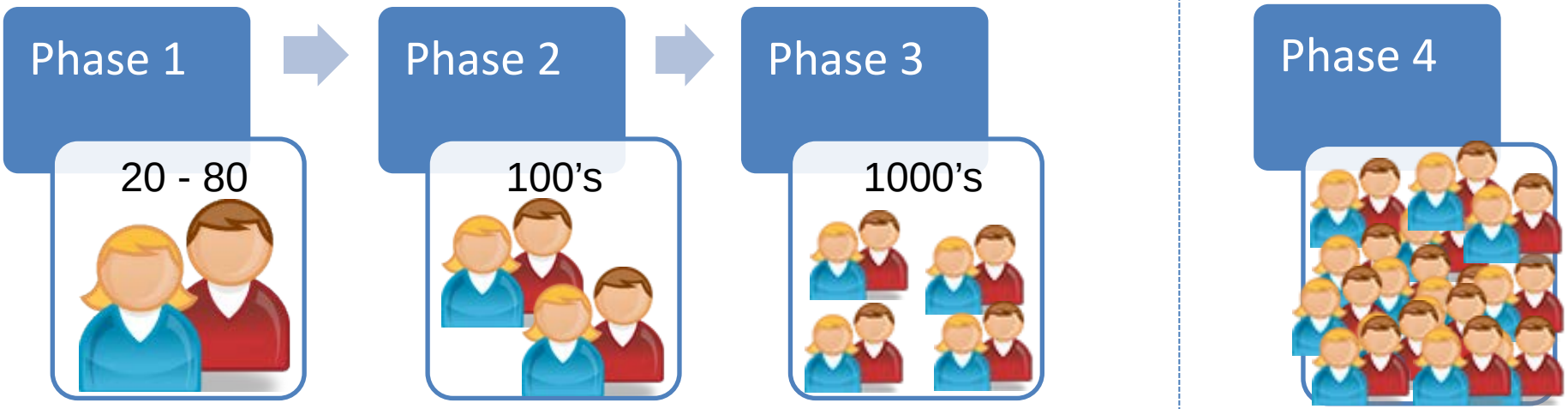
- During such research, women should receive adequate information to make informed choices about risks to themselves, as well as to their foetus or breastfed infant, where applicable.
- …women should be viewed as autonomous decision-makers, capable of making an informed choice for themselves and for their foetus or child.

Pursue innovative study designs

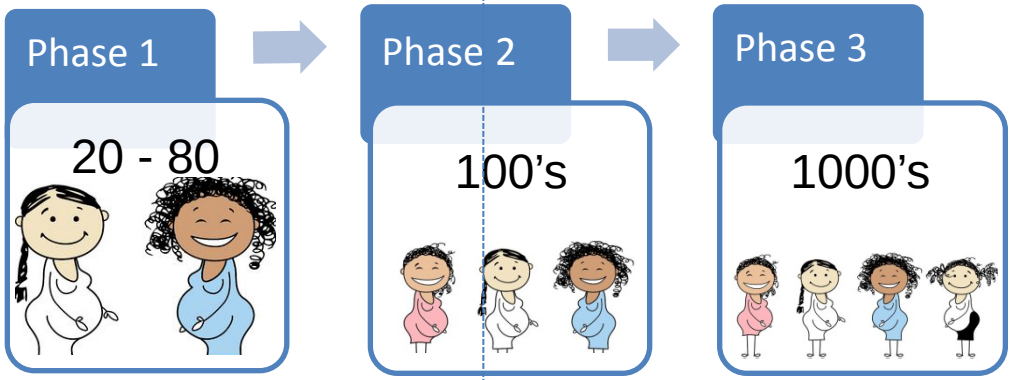
Two options

- Stand-alone Phase I trials concurrent with Phase III trials
- Phase I trials embedded into late Phase II or Phase III trials

Baylis, F. and Halperin S. *Clinical Investigation* 2012


Phase 1
20 - 80
Phase 2
100's
Phase 3
1000's
Phase 4

Option 1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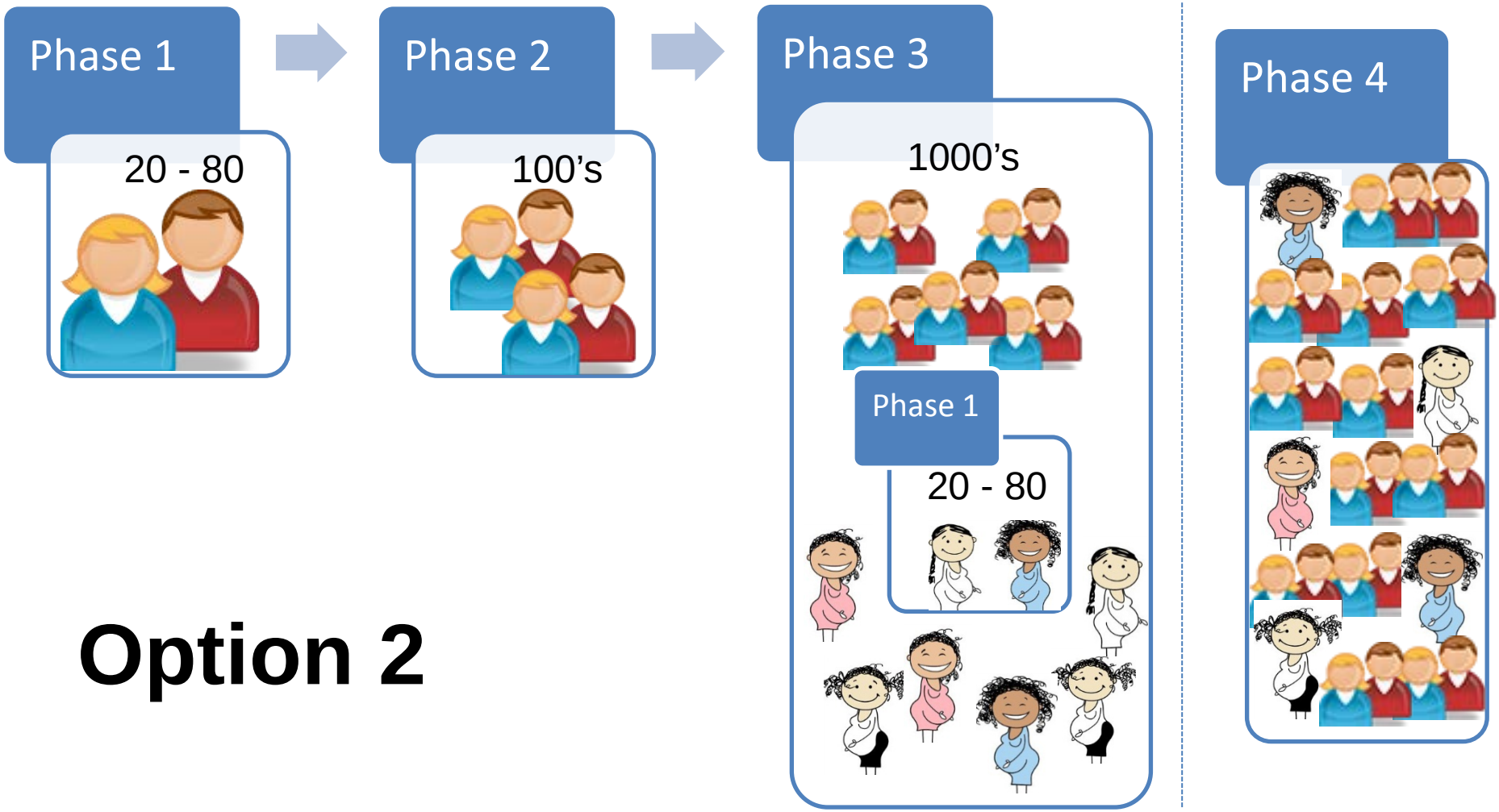

Option 2

Responsible inclusion of pregnant women in research

- Promote the inclusion of pregnant women in vaccine research among all relevant parties
  - Presumed eligible for research participation
  - Presumed autonomous (able to make informed decisions)
- Create incentives for inclusion
- Develop more nuanced research guidelines
- Pursue innovative study designs

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Impact Ethics.ca

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ABOUT SUBMISSION GUIDELINES

Making a Difference in Bioethics

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