Research Involving Pregnant Women: An Ethical Imperative

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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 developing fetus.

This is ethically and medically unacceptable for two reasons: pregnant women get sick, and sick women get pregnant. Patients who happen to be pregnant are as entitled as anyone else to safe and effective treatments, yet they are denied this and will be for as long as pregnant 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. For example, some of the adjuvants in a recent H1N1 vaccine were tested extensively in clinical trials with different vaccines that excluded pregnant women.

There is an obvious alternative: small, well-designed trials for pregnant women, starting with phase I safety trials that would begin at 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.

- Pregnant women should have access to sound information and advice on the basis of which to make medical decisions for themselves and their fetuses.

Evidence-based medicine

- Medicine that successfully integrates "individual clinical expertise with the best available external clinical evidence from systematic research"

Sackett DL, et al. Evidence based medicine: What it is and what it isn't. *BMJ* 1996; 312(7023): 71-2.

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.

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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.

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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.

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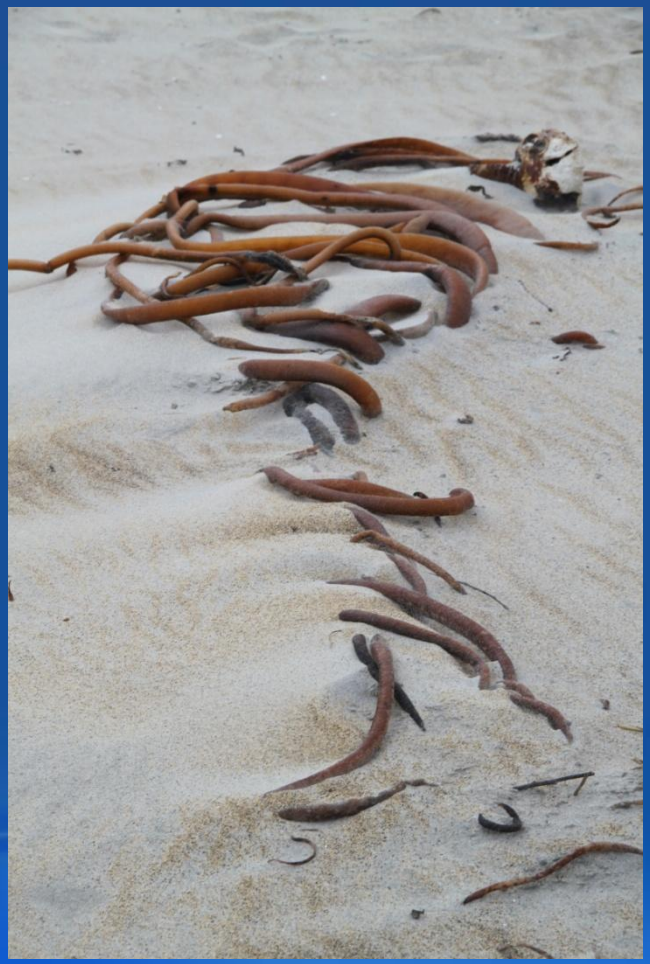
Reasons for inclusion

- 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)

Summary

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



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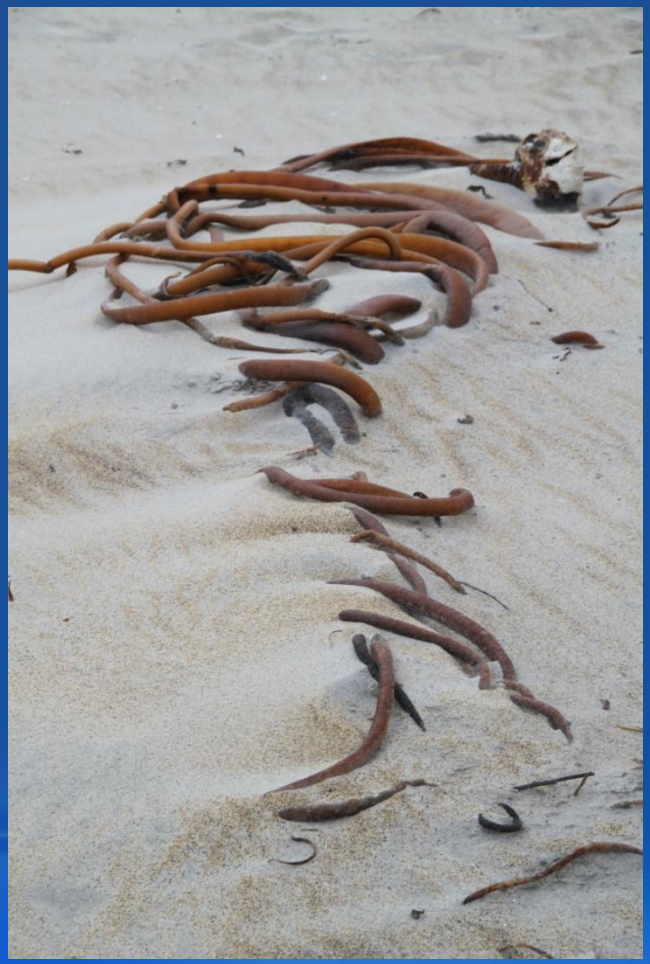


Some facts

- 64% of pregnant women take one or more prescribed medications for chronic medical conditions or acute problems (Goldkind 2010)
  - E.g., 4% affected by diabetes
  - E.g., 4% affected by hypertension

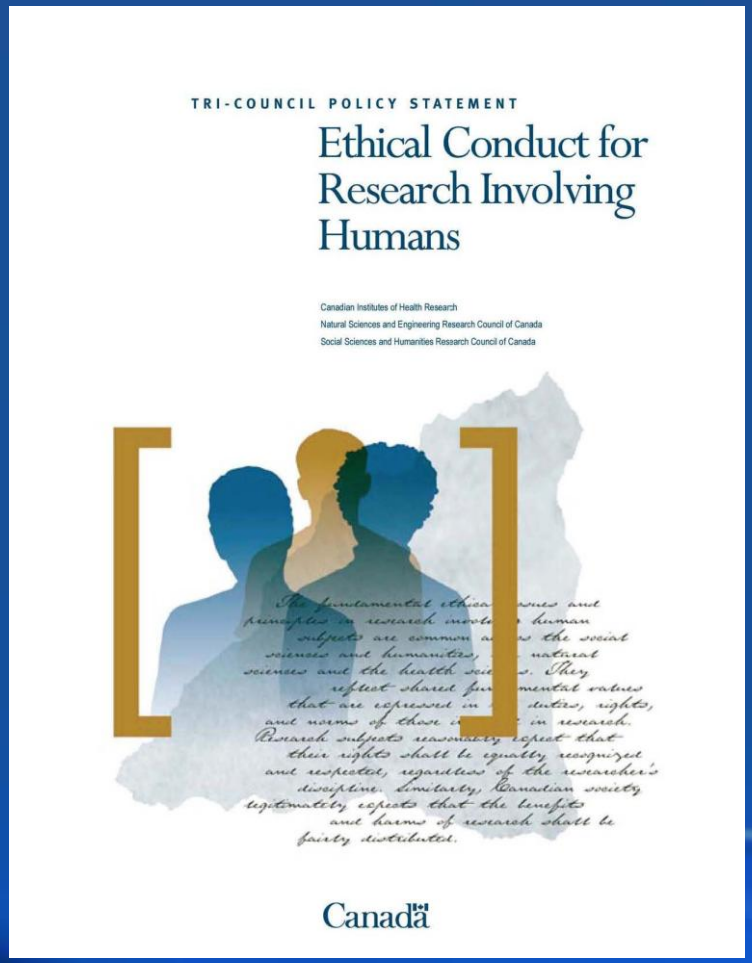
Some problems

- Most drugs are not labeled for use during pregnancy
- TCPS-2 is unhelpful
- REBs accept boiler-plate exclusions
- Research sponsors don't want to invest
- Widespread acceptance of status quo

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.”

TCPS-2 Article 4.3



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

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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

Exclusion from clinical trials

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

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 US and Canada in pregnant women since the 1960s

- 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 adjuvanted vaccine

- "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."

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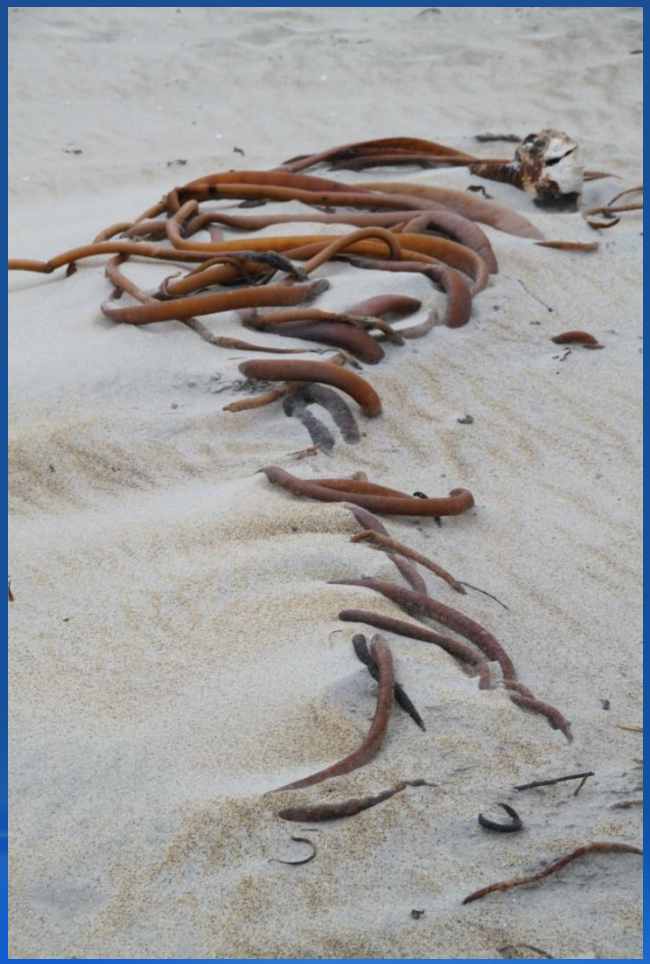

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Thalidomide

- 1954: Initially marketed in Germany as an anticonvulsant for epilepsy
- Found to be an effective sleeping pill; prescribed to pregnant women to treat morning sickness
- 1957-61: Sold over-the-counter

Thalidomide

- 1960-61: Found to cause birth defects
- 1962: US Congress enacted legislation that significantly broadened FDA authority.
  - Manufacturers required to show efficacy not just safety before marketing their products

What went wrong?

- Inadequate research standards
- Manufacturer ignored early evidence of side effects and reports that were critical of the drug
- Physicians' uncritical acceptance of promotional claims

Levine C. 1993. In: Blank and Bonnicksen eds. New York: Columbia University Press.

What went wrong?

- Thalidomide disaster did not result from women's participation in research

- Powerful aversion to involving pregnant women and women of childrearing age in drug research

Institute of Medicine. 1994. Women and Health Research. National Academy Press.

Responsible inclusion

- "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.

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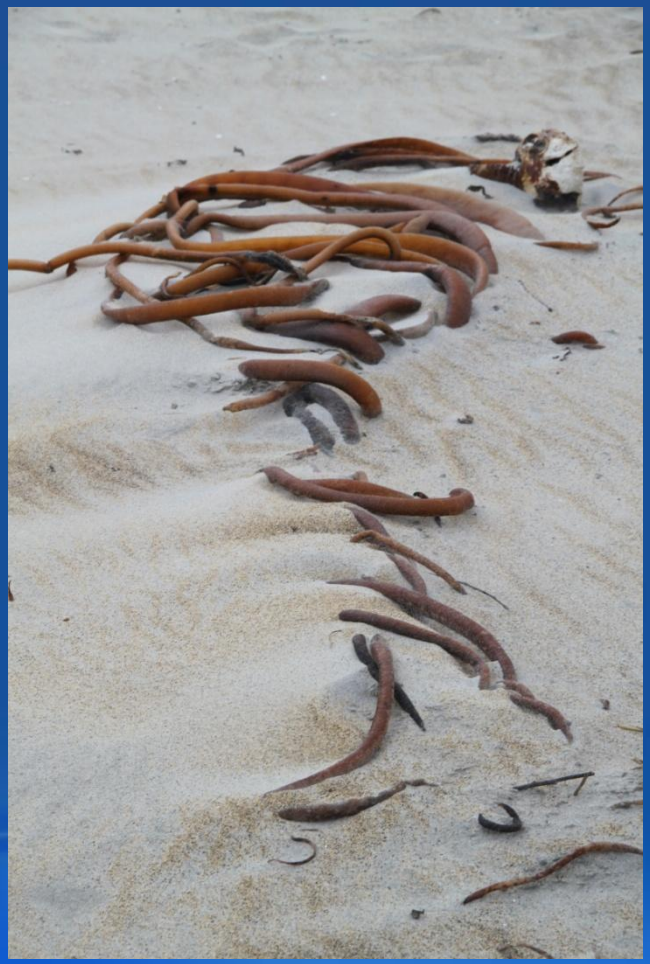

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Responsible inclusion

- 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

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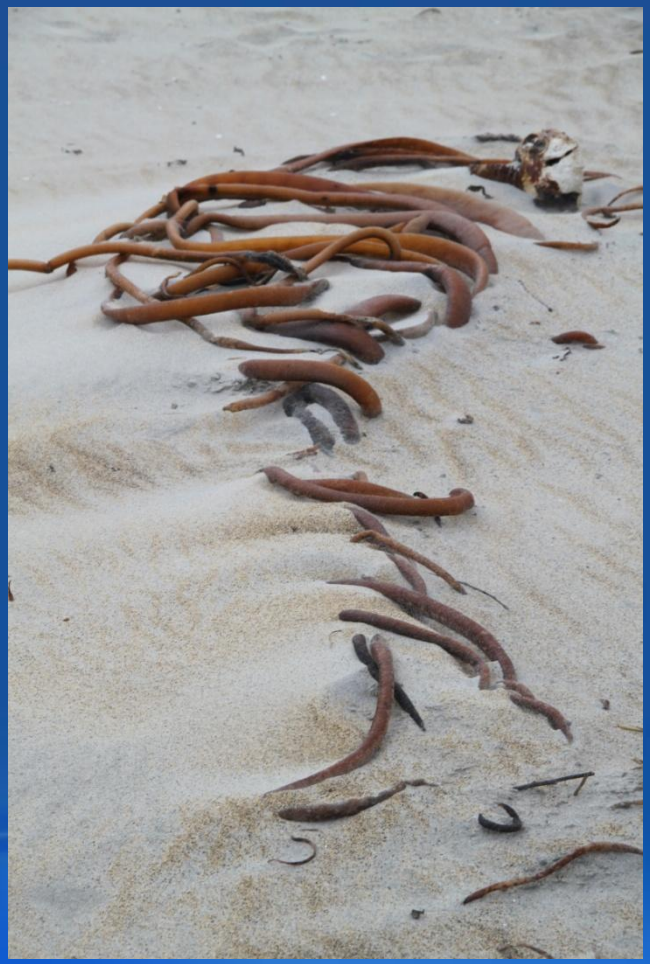

Barriers to inclusion

- Researchers
- REBs
- Oversight organizations (PRE; Health Canada)
- Research sponsors (CIHR)
- Manufacturers (Pharma)
- Research participants

Barriers to inclusion

- Research sponsors: Make research in pregnancy a priority
- Manufacturers: Incentivize
- Oversight organizations: Presumption of inclusion; clear criteria for exclusion
- REBs: Assess merits of proposed exclusion
- Researchers: Justify exclusion

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 I concurrent with Phase III

i. greater clarity in the design and increased ease in the review and monitoring of the clinical trial because only pregnant women are included in the trial;
ii. use of safety end points that are specific for pregnant women and that build on the knowledge gained from previous trials in nonpregnant adults;

Phase I concurrent with Phase III

iii. phased enrollment so that pregnant women in the later stages of pregnancy can be enrolled in research before women in the first trimester of their pregnancy are enrolled;

iv. increased probability that there will be planning for counselling regarding potential risks for the pregnancy;

Phase I concurrent with Phase III

v. increased probability that there will be planning for long-term follow-up of newborns;
vi. greater ease in recruiting qualified investigators and trial participants;
vii. possibility of reduced liability issues;
viii. timely analysis and reporting of data from pregnant participants.

Phase I embedded in late Phase II or in Phase III

i. full integration of pregnant women into the clinical research and regulatory approval processes (clearly signals the importance of normalizing the inclusion of pregnant women in research);
ii. involvement of investigators who are familiar with the protocol as they will have participated in earlier research phases with nonpregnant adults;

Phase I embedded in late Phase II or in Phase III

iii. reduced start-up costs and monitoring requirements;

iv. enhanced recruitment of pregnant women;

v. ability to generalize research data to the entire population, as pregnant and nonpregnant participants would be drawn from the same population;

Phase I embedded in late Phase II or in Phase III

vi. ability to provide pregnancy-specific data sooner than would be possible with stand-alone trials because the subgroup analysis could be given priority;

vii. enhanced reporting of gender-specific analyses among nonpregnant research participants

viii. potentially increased statistical power.

Well-designed trials are:

- Essential to avoiding the nontreatment, under-treatment or mistreatment or pregnant women and their fetuses.
- A way to promote pregnant women's health as well as fetal safety by reducing the number of pregnant women treated or vaccinated off-label.

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