The Inclusion of Pregnant Women and Lactating Women in Clinical Research: Ethical Issues

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Task Force on Research Specific to Pregnant Women and Lactating Women
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Disclaimer

- I have no conflicts of interest to declare.

- The views presented are my own.

Objectives – Ethical Issues

- **Background**
  - Historical perspective, paradigm shift
- **Current metrics of inclusion/exclusion**
  - How are we doing?
- **The cost of exclusion without justification**
  - Ethical considerations
- **Balancing risk/benefit tradeoffs**
  - Fetal vs. maternal

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Background

- ~4,000,000 births/year in US
- > 60% of US women
  - Reported taking a prescribed medication during pregnancy
- > 20% of women
  - 4+ prescription medications in the 1st trimester

National Vital Statistics Reports, Vol. 64, No. 1, January 15, 2015
Andrade et al., AJOG 2004
Mitchell et al., AJOG 2011

Background

- How many drugs are FDA approved for use in pregnancy?

- **<20**
  - Primarily for labor induction
  - Obstetrical indications

Kinch et al. 2014;
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Background

All other drugs are prescribed “off-label”			
Chronic disease	Psychiatric illness	Infections	Pregnancy-related conditions

Background

- **Extremely limited data on the dosing and safety of medications while breastfeeding**

- **NICHD pregnancy and lactation literature analysis (2006-2017)**
  - **Very limited basic research**
  - **Almost no PK/PD studies**
  - **Few RCTs**

https://www.nichd.nih.gov/about/meetings/2017/Documents/Task_Force_Zajicekresearchmeds.pdf

Background

- **Extremely limited data on the dosing and safety of medications while breastfeeding**
  - **Extrapolations based on:**
    - Degree of drug transfer to milk
    - Oral bioavailability
    - Amount of drug received → likely effect on infant
    - LactMed – peer reviewed database of National Library of Medicine

Sachs et al. *Pediatrics* 2013

Background

Clin Pharmacol Ther. 2009 Jan;85(1):31-5. doi: 10.1038/clpt.2008.157. Epub 2008 Aug 20.

Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study.

Madadi P[1], Ross CJ, Hayden MR, Carleton BC, Gaedigk A, Leeder JS, Koren G.

Author information

Abstract

A large number of women receive codeine for obstetric pain while breastfeeding. Following a case of fatal opioid poisoning in a breastfed neonate whose codeine prescribed mother was a CYP2D6 ultrarapid metabolizer (UM), we examined characteristics of mothers and infants with or without signs of central nervous system (CNS) depression following codeine exposure while breastfeeding in a case-control study. Mothers of symptomatic infants (n = 17) consumed a mean 59% higher codeine dose than mothers of asymptomatic infants (n = 55) (1.62 (0.79) mg/kg/day vs. 1.02 (0.54) mg/kg/day; P = 0.004). There was 71% concordance between maternal and neonatal CNS depression. Two mothers whose infants exhibited severe neonatal toxicity were CYP2D6 UMs and of the UGT2B7*2/*2 genotype. There may be a dose-response relationship between maternal codeine use and neonatal toxicity, and strong concordance between maternal-infant CNS depressive symptoms. Breastfed infants of mothers who are CYP2D6 UMs combined with the UGT2B7*2/*2 are at increased risk of potentially life-threatening CNS depression.

Background

- Majority of medications **NEVER** systematically studied during research & development for use in pregnancy and lactation
  - For basic pharmacokinetic/pharmacodynamic data
  - Proper dosing
  - Effectiveness
  - Safety (fetal and maternal)

Historical Reasons for Exclusion

1974 National Commission

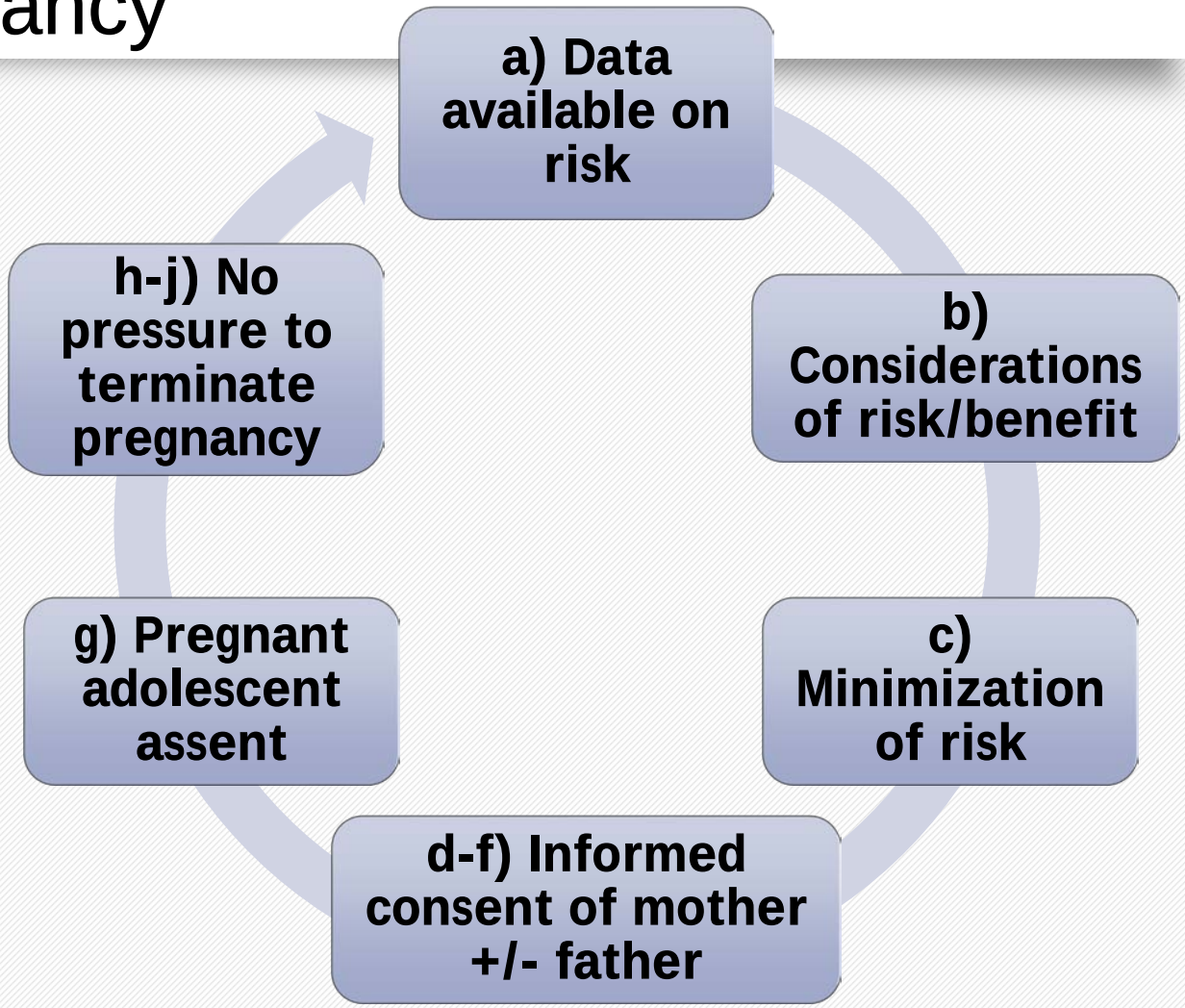
- Thalidomide and diethylstilbestrol tragedies
- Roe v. Wade
- Very conservative recommendations → Code of Federal Regulations

2001 Updated Code of Federal Regulations:

- Pregnant women or fetuses ***may be involved*** in research if 10 conditions are met

Blehar et al. *Women's Health Issues* 2013

U.S. Federal Regulations – 10 Conditions for Research in Pregnancy



Similar Pediatric Drug Tragedies

- **1936**
  - Strep throat ‘elixir’ of sulfanilamide dissolved in diethylene glycol (antifreeze)
  - >100 die, many of them children
  - Chemist commits suicide

http://www.fda.gov/aboutfda/whatwedo/history/productregulation/sulfanilamidedisaster/default.htm

Paradigm Shift for Pediatric Research

With pediatricians, scientific community, activism, legislation:

Children deserve research tailored to their physiology and clinical needs

It's unethical to do pediatric drug research

It's unethical not to

Shift to Presumption of Inclusion

Required inclusion of women, ethnic minorities

1993 NIH Revitalization Act

- >50 % of 17 million NIH-funded trial participants were women (2011-2012)
- **Presumption of inclusion**

Progress in pediatric research

1998 NIH policy +

2003 Pediatric Research Equity Act (PREA)

- **Presumption of inclusion**

NIH Comprehensive Inclusion Report 2013; Blehar et al. *Women's Health Issues* 2013

Presumption of Exclusion in Obstetrics

Required inclusion of women, ethnic minorities, and children in research

Pregnant women =

Only population with

presumption of exclusion

Blehar et al. *Women's Health Issues* 2013

Need for Paradigm Shift

Pregnant women deserve research tailored to their physiology and clinical needs

It's unethical to conduct drug research

It's unethical not to

Shift has already begun

ACOG COMMITTEE OPINION

Number 377, September 2007

Committee on Ethics

PDF Format

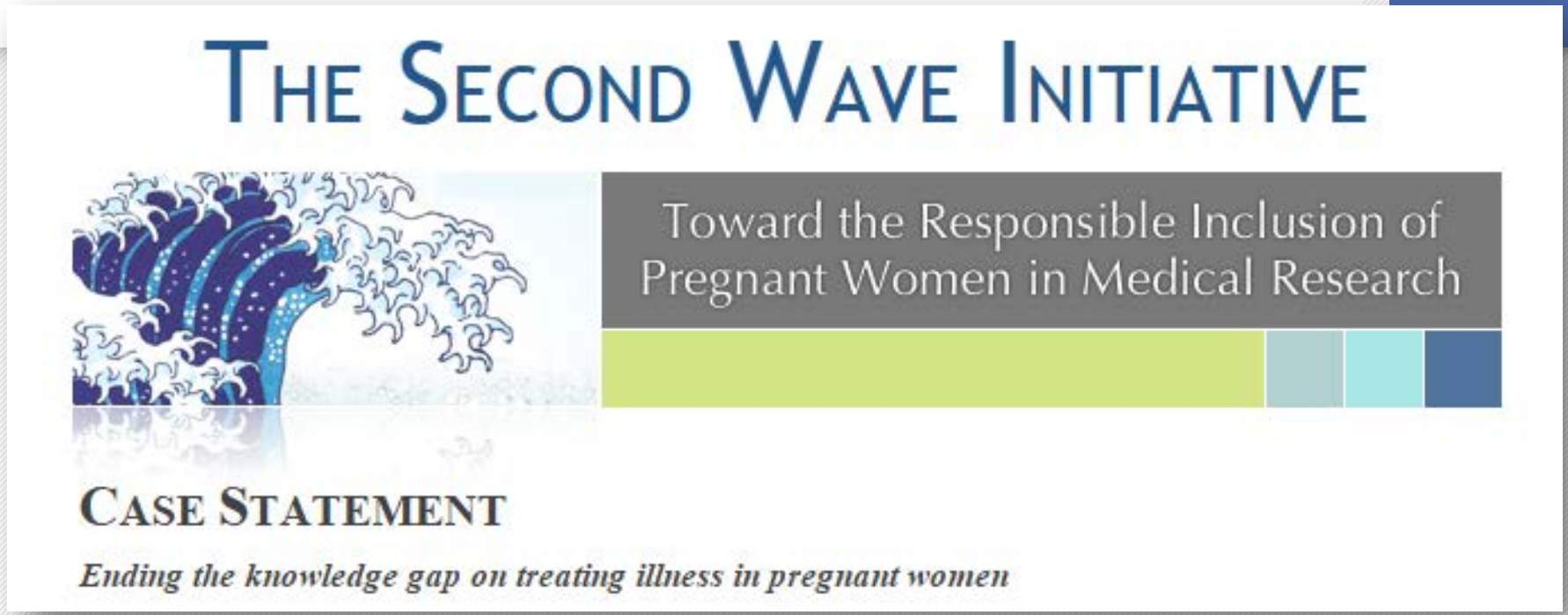
Research Involving Women

ABSTRACT: All women should be presumed to be eligible for participation in clinical studies. The potential for pregnancy should not automatically exclude a woman from participating in a clinical study, although the use of contraception may be required for participation. Research objectives should not interfere with appropriate clinical management. If a conflict arises between medically appropriate patient care and research objectives, patient care should prevail. Consent of the pregnant woman alone is sufficient for most research. Pregnant women considering participation in a research study should determine the extent to which the father is to be involved in the process of informed consent and the decision.

* Update of "Research Involving Women," in *Ethics in Obstetrics and Gynecology*, Second Edition, 2004.

ACOG Committee Opinion No. 377, 2007; ACOG Committee Opinion No. 646, 2015

Shift has already begun



- **Launched in 2009**
- **Consortium of physicians, scientists, and bioethicists**

Lyerly et al. *International Journal of Feminist Approaches to Bioethics* 2008
http://secondwaveinitiative.org

Shift has already begun

- U.S. Code of Federal Regulations:
  - "children, prisoners, ~~**pregnant women**~~, mentally disabled persons, economically or educationally disadvantaged persons"
  - Removed from Common Rule, effective January 19, 2018
  - **No longer an example of a "vulnerable" population**
    - (Although Subpart B restrictions still apply)

http://www.cogr.edu/sites/default/files/Summary%20of%20Changes%20to%20the%20Common%20Rule_COGR.pdf

Shift has already begun

- Advances in maternal immunization research
- Increasing attention from professional societies
  - Society for Maternal Fetal Medicine
  - American Congress of Obstetricians and Gynecologists

- Work of NICHD, this task force

➢ **Towards the presumed inclusion of pregnant women in clinical trials**

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Current Metrics

Search of clinicaltrials.gov

- 43,583 studies currently recruiting women/girls
- 4408 studies in the US recruiting women/girls since January 1, 2017

https://clinicaltrials.gov/ct2/home

Current Metrics

- Out of 4408 studies in the US recruiting women/girls from 1/1/17 – 10/25/17

➢How many include (or allow enrollment) pregnant women?

➢How many exclude pregnant women?

https://clinicaltrials.gov/ct2/home

Current Metrics

- Out of 4408 studies in the US recruiting women/girls (1/1/17-10/25/17)
- Search "pregnancy" or "pregnant" = 59 studies

- **51 pregnancy-related studies**
- **8 not pregnancy-related**
  - **6 exclude pregnant women**
    - **Only 1 provides justification** (infant/fetal toxicity with chemotherapy)

https://clinicaltrials.gov/ct2/home

Current Metrics

- Out of 4408 studies in the US recruiting women/girls (1/1/17- 10/25/17)
  - **51 studies clearly include pregnant women**
  - **6 studies clearly exclude pregnant women**
  - **Most – no mention**

➢ **Pregnancy rarely mentioned in inclusion/exclusion unless study is about pregnancy**

https://clinicaltrials.gov/ct2/home

Current Metrics

- Out of 4408 studies in the US recruiting women/girls (1/1/17 – 10/25/17)

➢How many include (or allow enrollment) breastfeeding women?

➢How many exclude breastfeeding women?

https://clinicaltrials.gov/ct2/home

Current Metrics

- Out of 4408 studies in the US recruiting women/girls (1/1/17 – 10/25/17)
- Search "breastfeeding" or "lactation" = 26 studies

- **22 infant/breastfeeding-related studies**
- **4 not infant/breastfeeding related**
  - **3 exclude breastfeeding women**
    - **Justification unclear**

https://clinicaltrials.gov/ct2/home

Current Metrics

- Out of 4408 studies in the US recruiting women/girls (1/1/17 – 10/25/17)
  - 22 clearly include breastfeeding women
  - 3 clearly exclude breastfeeding women
  - Most - no mention

➢ **Breastfeeding/lactation essentially not mentioned in inclusion/exclusion criteria unless study is about lactation**

https://clinicaltrials.gov/ct2/home

Current Metrics

- Take away:
  - **Challenging search on clinicaltrials.gov**
  - **Statistics about actual rates of inclusion/exclusion and justification would require review of individual protocols**
  - **Few studies clearly exclude pregnant women**
  - **But <u>much room for improvement</u>**

https://clinicaltrials.gov/ct2/home

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Research Gaps – Why Problematic?

- 3 main reasons for concern:

1. Pregnant women need safe, effective therapies
2. Untested therapies jeopardize fetal safety
3. Justice

Research Gaps – Effective Treatment

- **Ex) Amoxicillin for Anthrax**
  - 2001 bioterrorist attack, US postal service
  - **Amoxicillin** recommended for pregnant women exposed to spores
- 2007 PK study revealed
  - Due to increased renal clearance, concentration of Amoxicillin was **insufficient to treat Anthrax**

Andrew *et al. Clin. Pharmacol. Ther.* 2007

Research Gaps – Effective Treatment

Pregnant women deserve effective therapies with data on outcomes (e.g. Opioid dependence)

Exposing women and fetuses to medication risks with no benefit is ethically problematic

Research Gaps – Fetal Safety

- Less than 10% of medications approved by the FDA since 1980 have enough information to determine their risk for birth defects

Adam et al. 2011;
https://www.cdc.gov/pregnancy/meds/index.html#ref

Research Gaps – Fetal Safety

- **Selective Serotonin Reuptake Inhibitors (SSRI's)**
  - Slightly increased risk of fetal anomalies
  - Recognized after series of small, underpowered studies x past 20 years

Chambers et al. 2008, Reefhuis et al. 2015

Research Gaps – Fetal Safety

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Chambers et al. 2008, Reefhuis et al. 2015

Research Gaps – Fetal Safety

Uncertainty about fetal safety → reluctance to treat maternal disease

Use of untested therapies or no therapy may paradoxically increase fetal risks

The Case for Clinical Research in Pregnancy: Research Gaps

Profound research gaps

Safe dosing	Efficacy	Lack of evidence to guide clinical practice

- **Clinical practice w/o evidence base**

➢ **Ineffective or dangerous**

The Case for Clinical Research in Pregnancy: Justice

Access to participation in research has benefitted various populations

Pregnant women have largely been excluded →

Individual participants	Pregnant population

Have not benefitted fairly

Lyerly et al. *American Journal of Bioethics*. 2011.

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Balancing Tradeoffs: Risks and Benefits

No Longer a Vulnerable Population

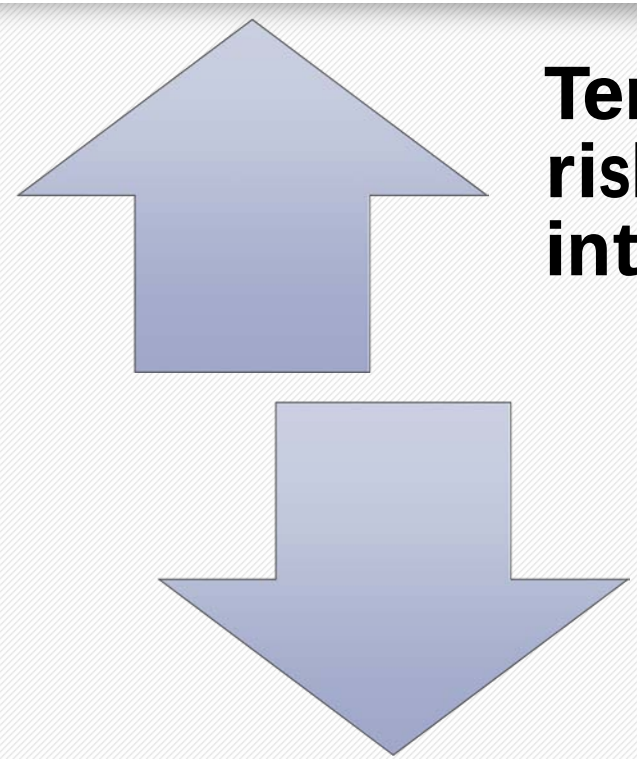
- **Why were pregnant women considered vulnerable in the Federal Regulations?**
  - Concern for fetal wellbeing
  - Fetal exposure to harm; cannot consent
- **But woman is able to protect her own interests**
  - She must consider interests of self *and* fetus
  - Interests often align
    - If her health deteriorates → so does fetal health

Not vulnerable but complex

- **Rather than "vulnerable"…**
  - **"Complex" population** is more appropriate description

- **Need for accurate information about maternal and fetal risks and benefits**
  - ➢ to make informed choice about research

Risk assessment – challenging in pregnancy…



Tendency to overestimate risk of medical interventions

But underestimate risk of failing to intervene

Lack of research data about safe interventions → risk distortions by women, clinicians, and researchers

Lyerly, et al. *Hastings Center Report*. 2009.

So what is an acceptable level of fetal risk?

Fetal risk

Intense focus on risk →

Benefits of study participation (compared to alternatives) sometimes overlooked:

Factor in:

- Current use of untested drugs
- Consequences of sub-therapeutic treatment
- Closely monitored trial may be *safer* than usual practice

Favorable Risk/Benefit Profile

- **Important to assess risks in relation to benefits**
  - **Should be at least as favorable as alternatives to study participation**

Favorable risk/benefit ratio		
Do the anticipated benefits justify the risks?	**Are risks as low as possible?**	**Would informed clinician recommend study participation?**

Reasonable Risk/Benefit Trade-offs

Beneficial Research

- Maternal benefit → marginal increase in fetal risk may be acceptable
- Fetal benefit → some maternal risk reasonable/altruistic
- Neonatal/infant benefit → some perinatal risk may be acceptable

Little et al. 2017

Reasonable Risk/Benefit Trade-offs

Non-beneficial Research

- No direct maternal or fetal benefit → no more than minimal fetal risk
- Pregnant women may altruistically volunteer just as other participants

Little et al. 2017

Risk/Benefit Tradeoffs - Women

Rodger et al. 2003, 50 women surveyed

- Willingness to join RCT with injections throughout pregnancy

37/50 (74%) of women WOULD participate in research when

- Benefits fetus (68%)
- Benefits them (27%)
- Benefits general population of pregnant women (5%)

Rodger et al. *Am. J. Perinatol*. 2003.

In summary

- **Reluctance to include pregnant women in clinical trials due to fetal concerns paradoxically increases fetal and maternal risks**

- **Current metrics show a need for more research on patterns of inclusion and exclusion in clinical research**

In summary

- **A paradigm shift is needed to change the presumption of exclusion to one of responsible, fair inclusion for pregnant women**

- **It is important to assess risks in relation to benefits, and focus on the favorability of the risk/benefit profile**

Thank you

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