TERATOLOGY RESEARCH
IN THE SHADOW OF THE *DOBBS* DECISION

Robert L. Brent Lecture

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Research and pregnancy

- There is great need for an improved understanding of the use of drugs and biological products in pregnancy.

- Yet, clinical research in pregnancy is insufficient and therapeutics in pregnancy are understudied, including and perhaps most impactfully in teratology.

- Both physicians and patients lack necessary information about the safety and efficacy of medicines and vaccines in pregnancy, putting childbearing women and their children in harm’s way.

- This predicament has been driven by a fear of fetal harm and a protectionist ethic that led to widespread exclusion of pregnant individuals from clinical studies.
Progress – toward responsible inclusion

- Second Wave Initiative (2009) – research is a *moral imperative*

- PHASES (NIH) and PREVENT (Wellcome) – *ethics guidance* for inclusion

- FDA – Draft Guidance for Industry “critical public health need”

- PRGLAC (NICHD) – Task Force Specific to Pregnant and Lactating Women

- NASEM – Inclusion of Pregnant and Lactating Women in Clinical Trials
“We are still living in the shadows of thalidomide—we haven’t moved from there.”

Dr. Christine Nguyen, FDA 2021
Post *Dobbs*: Legal Status of Abortion by State

- **14 states ban most abortions**
- **8 states** – bans are currently blocked
- **26 states** – legal (20 with additional protections)

New York Times, June 2023
The ‘shadow of Dobbs’

“Roe protect[ed] all pregnant women, not just those seeking abortion.”

Paltrow, Harris and Marshall AJOB 2022
Why *Dobbs* matters

I. Teratology research and abortion are (and have always been) *intertwined*

II. Restrictions on abortion will make teratology research *more difficult*

III. Restrictions on abortion will make teratology research *more important*
I. Teratology research and abortion are *intertwined*
The Thalidomide Disaster

- Drug developed for treatment of morning sickness 1950s
- Approved in more than 20 countries (Canada, Europe, Australia)
- By 1962, drug linked to severe birth defects (phocomelia)
- Affected > 10,000 pregnancies worldwide

Drug testing in animals for teratogenic effects

Thalidomide in the pregnant rat

Thalidomide was administered to pregnant rats by various routes without significantly interfering with embryonic development. The discrepancy between the effect of this drug in animals and human beings is discussed. The problem of applying the results of animal testing to the human is reviewed. A protocol for testing drugs for teratogenicity in animals is proposed as an initial standard for obtaining basic information about the effects of drugs on the embryo. Until drug testing becomes somewhat more sophisticated, our most reliable method of protecting the public from all the harmful effects of drugs is through strict ethical surveillance programs.

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There is no doubt at the present time that the ingestion of thalidomide is teratogenic for the human embryo.1-4 The exact risk of malformation is not known, although the estimates range from 2 to 20 per cent.5-7 The duration and time of greatest sensitivity to thalidomide has been reported to be 30 to 50 days, 33 to 42 days, and 28 to 40 days and there is every reason to think that if the proper dose were given at the critical time the incidence of malformations and embryonic death would be higher than 20 per cent.5-7 Therefore, thalidomide can be considered to be a relatively effective teratogenic agent in the human.

The variable effect of thalidomide on mice, rats, and rabbits was surprising in view of the human data.8-10 In 5 of 14 reported studies in which rats were used and doses of 20 to 300 mg. per kilogram were employed malformations resulted.8-10 In 4 of 8 studies, which used various strains of mice, malformations were recorded by employing doses of 1 to 4,000 mg. per kilogram.11-13 Rabbits have yielded a higher incidence of malformations, which were severer than other animal species.14, 15 Re-
Sherri (Finkbine) Chessen

- 1961 – “Miss Sherri” on Romper Room
- Mother of four, pregnant with 5th
- Took a sedative husband brought home from UK

“I wasn’t upset … that medicine from Europe couldn’t be sitting in my home, on my kitchen shelf, waiting for me.”

- Shared story with media
- Abortion scheduled (AZ), then cancelled by hospital
- Obtained abortion in Sweden
- “Pivotal” in shifting public support for abortion rights

*Life Magazine, August 10, 1962*
Clinical trials in pregnancy and the “shadows of thalidomide”: Revisiting the legacy of Frances Kelsey

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Abstract

Introduction

In April 1962, the United States Food and Drug Administration (FDA) issued draft guidelines for industry addressing obstetric and ethical considerations for inclusion of pregnant women in clinical trials [1]. And in early 1963, the FDA, in conjunction with Duke University’s M diverse Center for Health Policy, held a public meeting to discuss sci-entific and ethical issues related to including pregnant women in clinical trials [2]. Both joined national, broad awareness of the need to advance scientific research with pregnant populations, and have been cited in key elements among growing efforts to advance evidence-based use of medications and vaccines in pregnancy [3-6].

Despite great need for improved understanding of the use of drugs and biologic products in pregnancy, clinical trials in pregnancy are rare. (Thalidomide in pregnancy is mostly underestimated, and pregnant individuals are currently excluded as trial participants. For instance, a recent review found that, in a sample of clinical trials for novel drugs returned to the FDA’s 98% of excluded pregnant individuals [2], see also [1]. Moreover, research participants who become pregnant during a trial are typically removed from the study; therefore exclusion is widespread significant harm to both pregnant people and unborn [3].

While strong public communications from the FDA indicate support for responsible including pregnant individuals in clinical trials, this is a hard shift from the past. Over the last sixty years, pre-vention and care have been characterized clinical research in pregnancy, driving in large part from a perception either that maternal autonomy outweighs the thalidomide drug disaster. This review explores how this courageous statement from being excluded in the United States, and how much ignored and subsumed for its role in protecting the pregnant population from cancer and heart diseases. If not, it is not to prevent, preselected women have been left behind, and research built on the clinical trials to date is not generalizable to pregnant women.

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1. Introduction

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In many ways, Frances Kelsey’s contribution to reforming the FDA’s committment in ensuring the safety of drugs used by the public, in part through enhanced and expanded clinical trial studies. At the same
Frances Kelsey

- 1960 – FDA physician and pharmacologist
  Assigned to review Kevadon (thalidomide)

- Refused to authorize, despite immense pressure; requested further studies

- Averted disaster in the US
“Her exceptional judgment averted a major tragedy”

- John F. Kennedy
- Kelsey became an icon, not just for the public but also for the FDA

- She became the face of the FDA’s mission to protect the public from unsafe and ineffective medications

- No one is perhaps more famous for protecting pregnant people and their offspring

- Her work led to policy change regarding drug evaluation in the US
Divergent policy responses

• **General population**
  - Kefauver-Harris Drug Amendments (1962)
  - Improved FDA’s ability to determine safety and efficacy, require pre-market approval of new drugs, gave FDA authority over clinical trials
  - Established FDA reputation (and duty) to protect public from harms
  - Led to more and better evidence, improved drug safety *for non-pregnant people*

• **Pregnant population**
  - Subpart B (CFR) “No pregnant woman may be involved unless ..” (1975)
  - Pregnant persons are “vulnerable”
  - FDA exclusion of women who are pregnant or “of childbearing potential” from early phase studies (1977)
  - Led to a paucity of evidence, drug safety *uncertain for pregnant people*
Kelsey on pregnancy

- **Disaster was due to inadequate research in pregnancy**: the effects of thalidomide “should have been recognized in a well-controlled clinical study involving comparatively few patients in pregnancy.”

- **Protective effects of drugs**: “There has been considerable apprehension concerning the effect of drugs and environmental factors on the developing embryo [but consideration should "also be given to the role that drugs may play in protecting the offspring.”

- **Importance of research**: Conduct of clinical trials in pregnant women ... present special problems [but are] necessary to assure safe and effective drugs will be available for their use.”

  ➢ *The logical response would have been to pursue research, not forbid it*
Protectionist Ethic

- Thalidomide’s legacy
- Pregnant population
- Prioritizes elimination of reproductive risk in clinical studies
- Protection *from* research

Ethic of Protection

- Kelsey’s legacy
- Non-pregnant population
- Prioritizes vigilance, safety, protection from pharmaceutical-based harm
- Protection *through* research
The **roots** of the *protectionist ethic*

- **Thalidomide**
  - Intense media attention brought teratogen “to the American public’s consciousness”*
  - Ushered in an era in which drugs that should be seen as therapeutic were “instead seen as frightening or dangerous”

- **Roe v. Wade**
  - Prompted a “culture of fetal protection” and had chilling effect on research with childbearing women
  - Contributed to framing issues in reproductive medicine as “maternal-fetal conflict”
  - Research in pregnancy focused on areas where maternal condition was a threat to fetal health (e.g., HIV) and women studied primarily as “vessels and vectors”

*Reagan L, Dangerous Pregnancies, 2012*
The *harm* of the *protectionist ethic*

Without adequate evidence, pregnant persons:

→ May be given drugs at the *wrong dose*

→ May be given drugs with *unacceptable risk*

→ May be *denied access* to beneficial drugs

→ May be *denied access* to beneficial clinical trials
Rubella – a cautionary tale about caution

• Acute, contagious virus that causes mild illness in adults
• Infection in pregnancy – congenital rubella syndrome
• 1960s – epidemic
• Live attenuated vaccine developed in 1969 (children, adults)
• US Strategy: vaccinate “around” women of childbearing potential (and pregnant women) – preschool + elementary school age children

➢ TWO UNINTENDED CONSEQUENCES OF “CAUTION”:
Vaccinating children can lead to an increase in the average age of infection.

Many exposed pregnancies were terminated, though no cases of vaccine-related rubella ever documented.

“paradoxical effect”
Teratology research prevents abortion

“There are probably 1,200 babies in this country alive today because I stopped their mothers from having an abortion once I knew the timing or dose of their exposure.”

Robert Brent interview, New York Times, 2004
Teratology research and abortion are intertwined.

...gaps prompted public support for (e.g., Finkbine)
...is critical to informed decisions about/prevents unnecessary
...had a chilling effect on research in pregnancy, including
II. Abortion restrictions will make research in pregnancy *more difficult*
Abortion and Research in Pregnancy

• “As a general rule, health-related research involving pregnant women that has the potential for harm to the fetus should be conducted only in settings where women can be guaranteed access to a safe, timely and legal abortion in the event that participation in the research makes the pregnancy unwanted.”*

*may be conducted if a local research ethics committee determines that the research has compelling social value for pregnant women and the women are informed about existing restrictions on abortion and possible options for obtaining an abortion in another country.
Risks to pregnant persons

- **Limited access** to abortion in cases of research-related harm
- **Legal consequences** of abortion or pregnancy loss
- **Violations of confidentiality**
Deviations from standard of care

- Pre-viability complications: PPROM, hemorrhage, hypertension
- Ectopic pregnancy
- Underlying conditions that make pregnancy dangerous
- Severe fetal anomalies
- Early miscarriage
- Extreme delays in abortion care
- Delays in medical care unrelated to abortion
Risks to researchers/staff

• Clinicians face risks of **civil and criminal penalties** for performing or helping patients to access abortion in some contexts

• Clinicians also risk **loss of licensure**, board status, jobs

• Ambiguity in the law leads to **uncertainty** about when it is being broken, and aversion to **even discussing** the option of termination

• Also leading reproductive health professionals to leave restrictive states, retire; 10.5% decrease in applications to ob-gyn residency programs in restrictive states (AAMC, 2022)

_Zurawski vs. State of Texas, March 2023_
_AAMC, April 2023_
Scientific validity and feasibility

- **Limited recruitment**, especially in areas of high risk may lead to biased sample

- **Under-reporting** of abortions (e.g., as miscarriage) may lead to inaccurate attribution

- **Reluctance of researchers/staff** to risk criminal/civil penalties (or work in reproductive health contexts) may limit research in states with restrictive laws

- **Limited availability of reproductive tissue** may limit feasibility of human embryo/fetal tissue research
Abortion restrictions: fuel for the protectionist ethic?
Abortion restrictions make teratology research more important.
Exceptions for fetal anomalies

Abortion bans with exceptions for fatal birth defects

Abortion bans without exceptions for fatal birth defects

Note: Courts have blocked the bans used in this analysis for Indiana, Iowa, Montana, North Dakota, Ohio, Utah and Wyoming.

New York Times, 2023
Deborah Dorbert

- Fetus diagnosed with Potters syndrome
- State law in FL had exception for “lethal fetal anomalies”
- Doctors refused abortion due to presence of fetal heartbeat
- Induced at 37 weeks gestation

“...When he came out you could hear him gasping for air. He was just trying to breathe. ... He didn’t cry when he was born and he didn’t open his eyes at all. But I mean, he struggled.”

A double injustice

→ Lack of access to reproductive care

→ Lack of evidence to prevent harm, inform care
Evidence gaps compound suffering

- In the absence of data regarding risk to the fetus, several harmful risk distortions associated with pregnancy take hold:

  - Better safe than sorry
  - Purity
  - Mother-blame

Lyerly et al., Risk and the Pregnant Body, *HCR* 2009
“Concerns about environmental chemicals and physical agents are clearly justified because, in most cases, not enough information is available on the potentially differential effects on the fetus and child. Such information, for example, the population exposure and the NOAEL, can only be obtained from high-quality human and animal toxicology and epidemiological studies which include toxicokinetic and toxicodynamic data and, therefore, it is essential that we expand our research programs in these areas.”

Conclusions

- Teratology research and abortion are *intertwined*.

- Thalidomide cast a long shadow, but it is starting to recede, marked by recognition that conducting *pregnancy-specific research is a moral imperative*.

- The *Dobbs* decision threatens to impede progress toward evidence-based care, raising concerns about the ethics and feasibility of research, but also potentially contributing to the harmful *protectionist ethic*.

- *Pregnant women need and deserve evidence* to inform their care, provide information about the impact of exposures, prevent unnecessary harm, and promote efforts to prevent birth defects, *especially as access to abortion is restricted*.

- We need to *address*—rather than *avoid*—the ethical challenges of pregnancy-related research in the post-*Dobbs* landscape.
“It would indeed be unfortunate if fear of adverse effects to the offspring deprived the mother of drugs that might be essential to her well-being and indeed, possibly also to the successful outcome of the pregnancy itself.”

- Frances Kelsey, 1968