TERATOLOGY RESEARCH IN THE SHADOW OF THE *DOBBS* DECISION

Robert L. Brent Lecture

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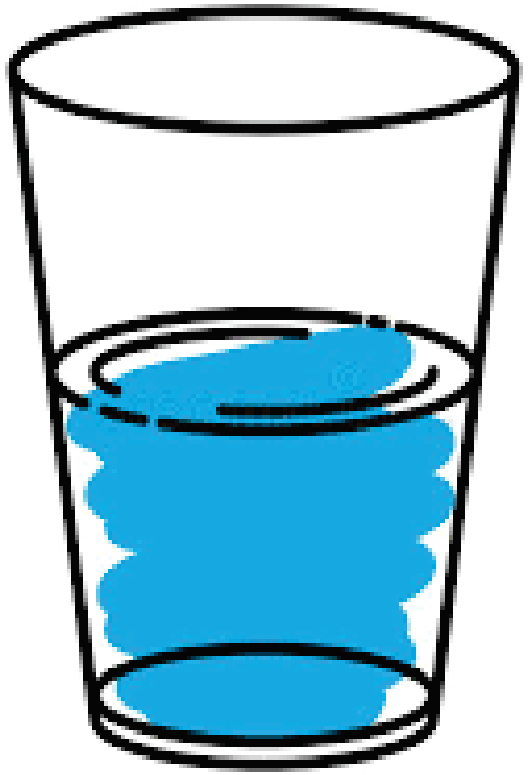
Robert L. Brent, MD, PhD

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

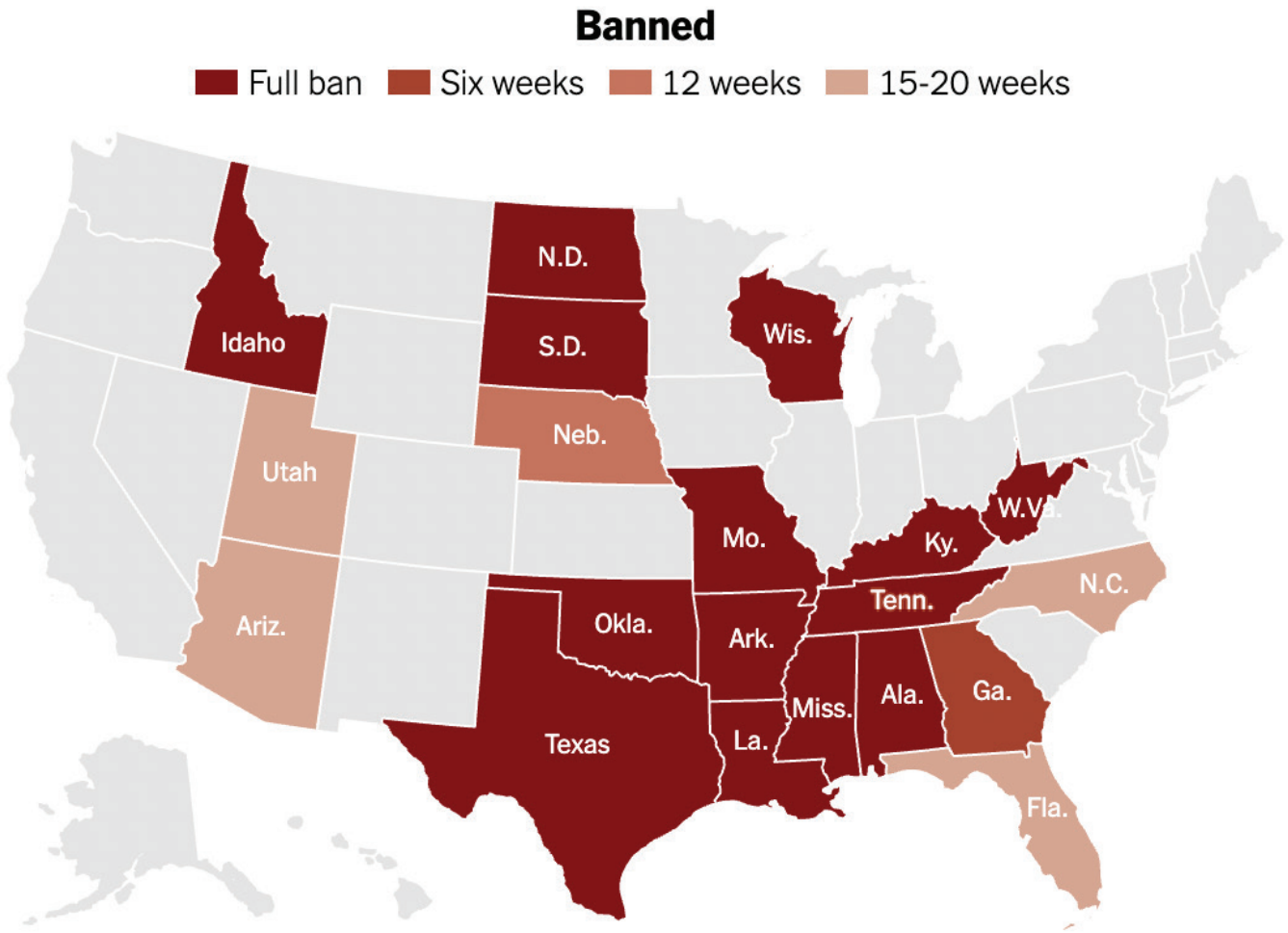
- Second Wave Initiative (2009) – research is a ***moral imperative***
- PHASES (NIH) and PREVENT (Wellcome) – ***ethics guidance*** for inclusion
- FDA – Draft Guidance for Industry “critical public health need”
- PRGLAC (NICHD) – Task Force Specific to Pregnant and Lactating Women
- NASEM – Inclusion 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

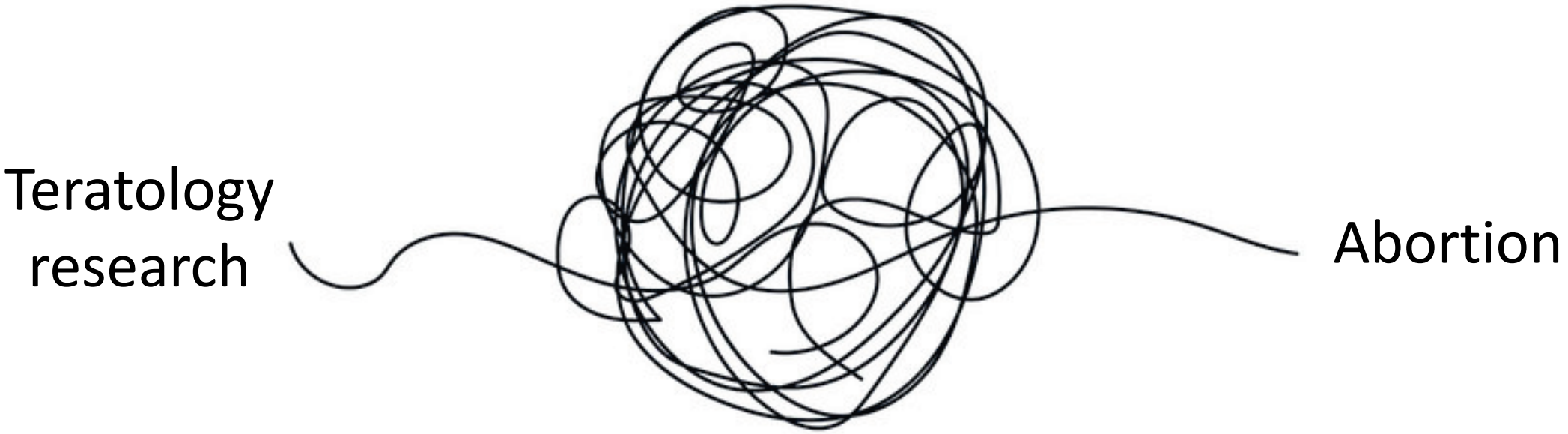
Why *Dobbs* matters

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

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

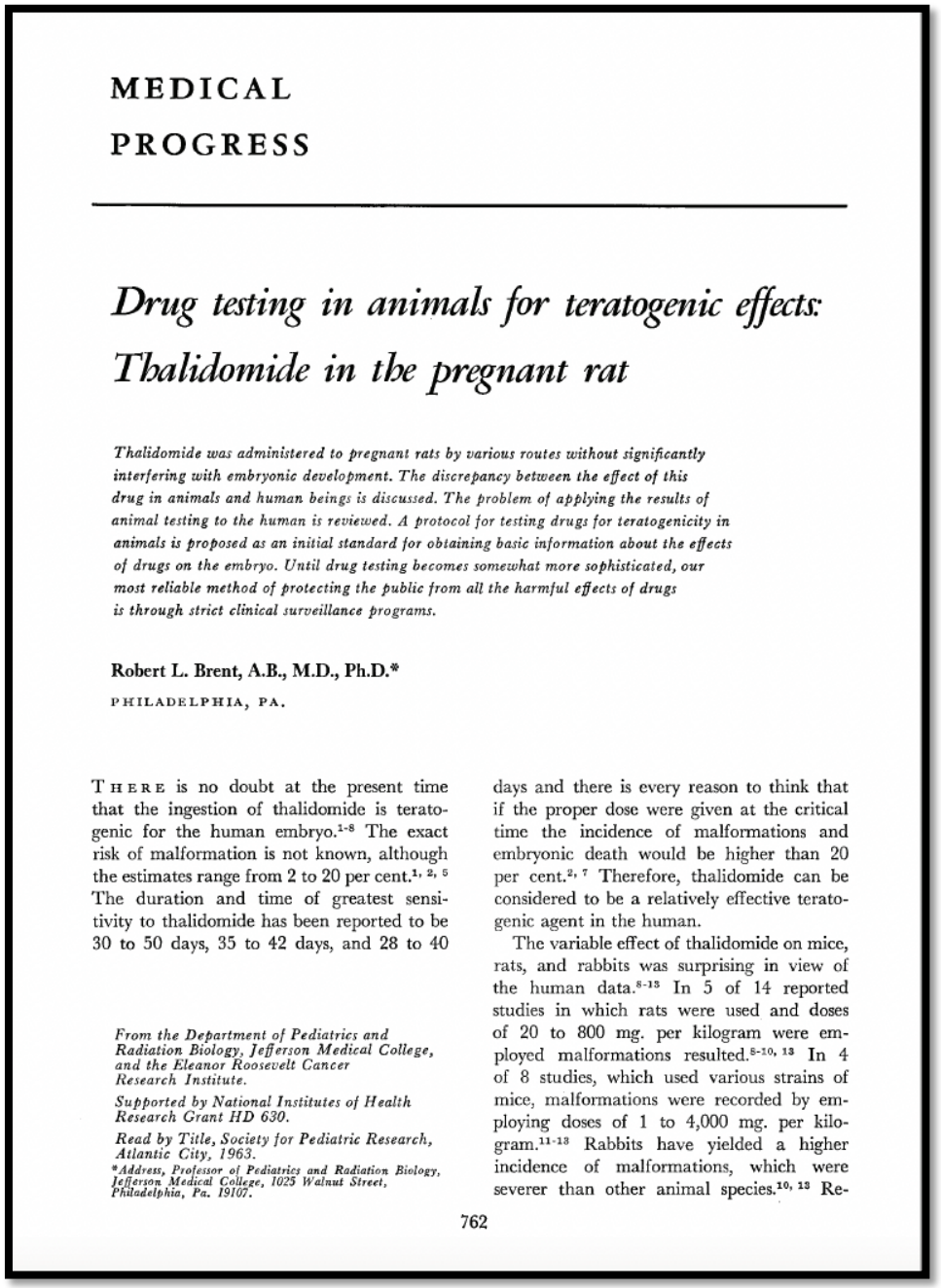
III. Restrictions on abortion will make teratology research *more important*

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



MEDICAL
PROGRESS

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 clinical surveillance programs.

Robert L. Brent, A.B., M.D., Ph.D.*
PHILADELPHIA, PA.

THERE is no doubt at the present time that the ingestion of thalidomide is teratogenic for the human embryo.[1-8] The exact risk of malformation is not known, although the estimates range from 2 to 20 per cent.[1, 2, 5] The duration and time of greatest sensitivity to thalidomide has been reported to be 30 to 50 days, 35 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.[2, 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.[8-13] In 5 of 14 reported studies in which rats were used and doses of 20 to 800 mg. per kilogram were employed malformations resulted.[8-10, 13] 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.[10, 13] Re-

From the Department of Pediatrics and Radiation Biology, Jefferson Medical College, and the Eleanor Roosevelt Cancer Research Institute.

Supported by National Institutes of Health Research Grant HD 630.

Read by Title, Society for Pediatric Research, Atlantic City, 1963.

**Address, Professor of Pediatrics and Radiation Biology, Jefferson Medical College, 1025 Walnut Street, Philadelphia, Pa. 19107.*

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

Frances Kelsey

Contemporary Clinical Trials 119 (2022) 106806

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Clinical trials in pregnancy and the "shadows of thalidomide": Revisiting the legacy of Frances Kelsey

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ABSTRACT

Despite great need for improved understanding of the use of drugs and biological products in pregnancy, clinical trials in pregnancy are rare, therapeutics in pregnancy are woefully understudied, and pregnant individuals are routinely excluded as trial participants. Recently, however, the U.S. Food and Drug Administration (FDA) has signaled strong support for advancing scientific research with pregnant populations, marking a significant shift from the past. Over the last sixty years, precaution and fear have largely characterized clinical research in pregnancy, deriving in large part from a protectionist ethic that materialized after the thalidomide drug disaster. FDA reviewer Frances Kelsey courageously prevented thalidomide from being marketed in the United States, and her work guided and solidified the FDA's image as protector of the general population from unsafe and ineffective drugs. Yet, when it comes to protection, pregnant persons have been left behind, and experts refer to the "shadows of thalidomide" that hamper clinical trials in pregnancy. Drawing on analysis of Frances Kelsey's archived papers in addition to focused media coverage of Kelsey and thalidomide, we discuss the durable cultural narrative surrounding Kelsey's important work. We argue that revisiting Kelsey's legacy with attention to themes that have characterized her achievement—staying vigilant, prioritizing safety, and mitigating pharmaceutical-based harm—in fact facilitates progress toward the ethical obligation to protect pregnant people through research, toward the generation of pregnancy-specific data for evidence-based care, and toward realizing Kelsey's legacy of safeguarding pregnant people and their offspring from the harms of untested drugs.

1. Introduction

In April 2018, the United States Food and Drug Administration (FDA) issued draft guidance for industry addressing scientific and ethical considerations for inclusion of pregnant women in clinical trials [1]. And in early 2021, the FDA, in conjunction with Duke University's Margolis Center for Health Policy, held a public meeting to discuss scientific and ethical issues related to including pregnant people in clinical trials [2]. Both indicated strong, bold endorsement of the need to advance scientific research with pregnant populations, and have been cited as key elements among growing efforts to advance evidence-based use of medications and vaccines in pregnancy [3,4].

Despite great need for improved understanding of the use of drugs and biological products in pregnancy, clinical trials in pregnancy are rare, therapeutics in pregnancy are woefully understudied, and pregnant individuals are routinely excluded as trial participants. For instance, a recent review found that, in a sample of clinical trials for novel drugs submitted to the FDA, 95% excluded pregnant individuals ([5]; see also [6]). Moreover, research participants who become pregnant during a trial are typically removed from the study. Habitual exclusion introduces significant harm to both pregnant people and fetuses [7].

While recent public communication from the FDA indicates support for responsibly including pregnant individuals in clinical trials, this stance is a marked shift from the past. Over the last sixty years, precaution and fear have characterized clinical research in pregnancy, deriving in large part from a protectionist ethic that materialized after the thalidomide drug disaster [7,8]. FDA reviewer Frances Kelsey is famous for courageously preventing thalidomide from being marketed in the United States, and, as a result of her work, protecting the public from the harms of medications became a hallmark of the FDA's reputation.

In many ways, Frances Kelsey's achievement came to represent the FDA's commitment to ensuring the safety of drugs used by the public, in part through enhanced and expanded clinical trial studies. At the same

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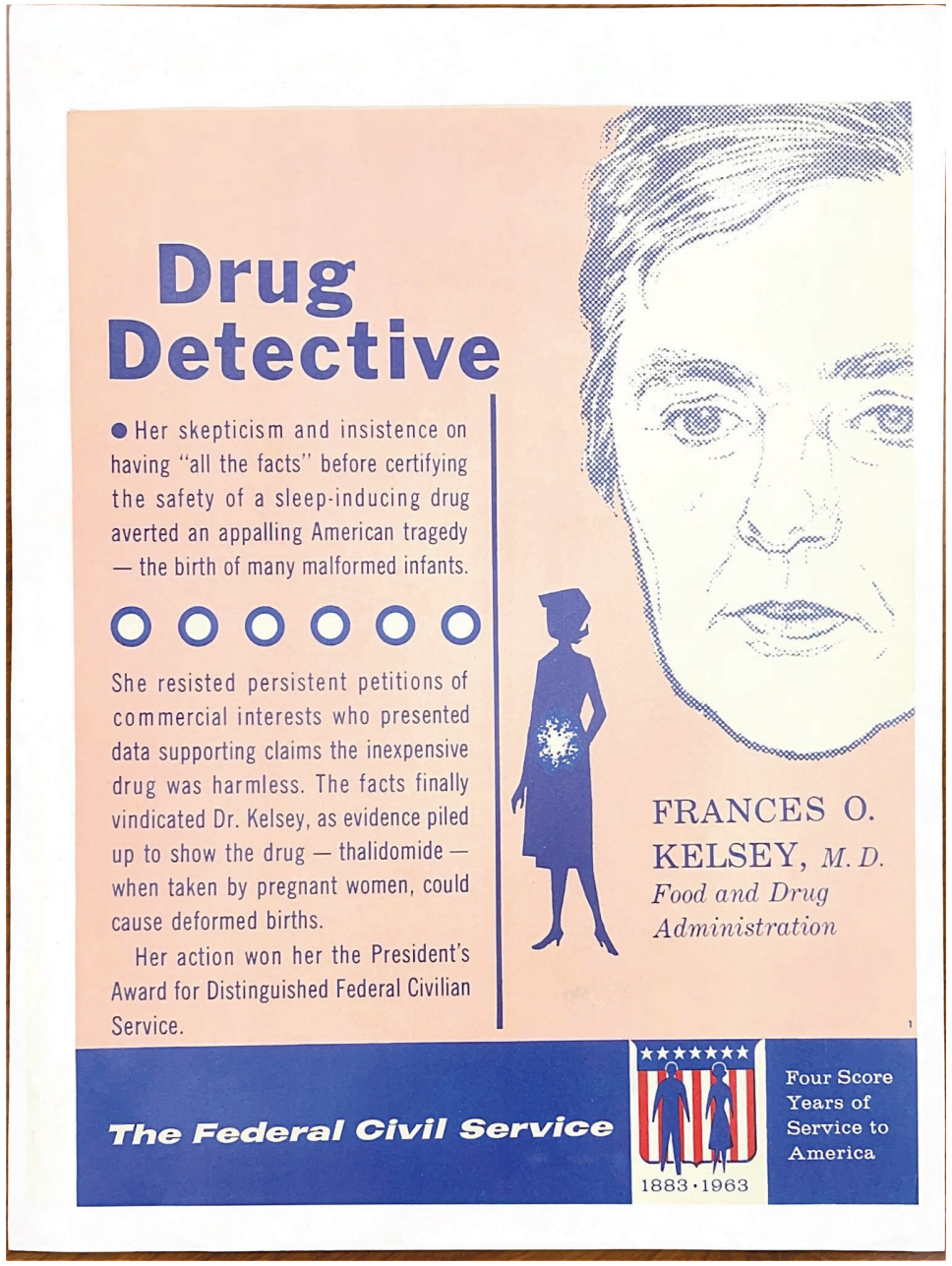
Frances Kelsey

- 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

FDA Broadside, circa 1963
Frances O. Kelsey Papers Collection, Library of Congress
Manuscript Division, Washington, DC

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*

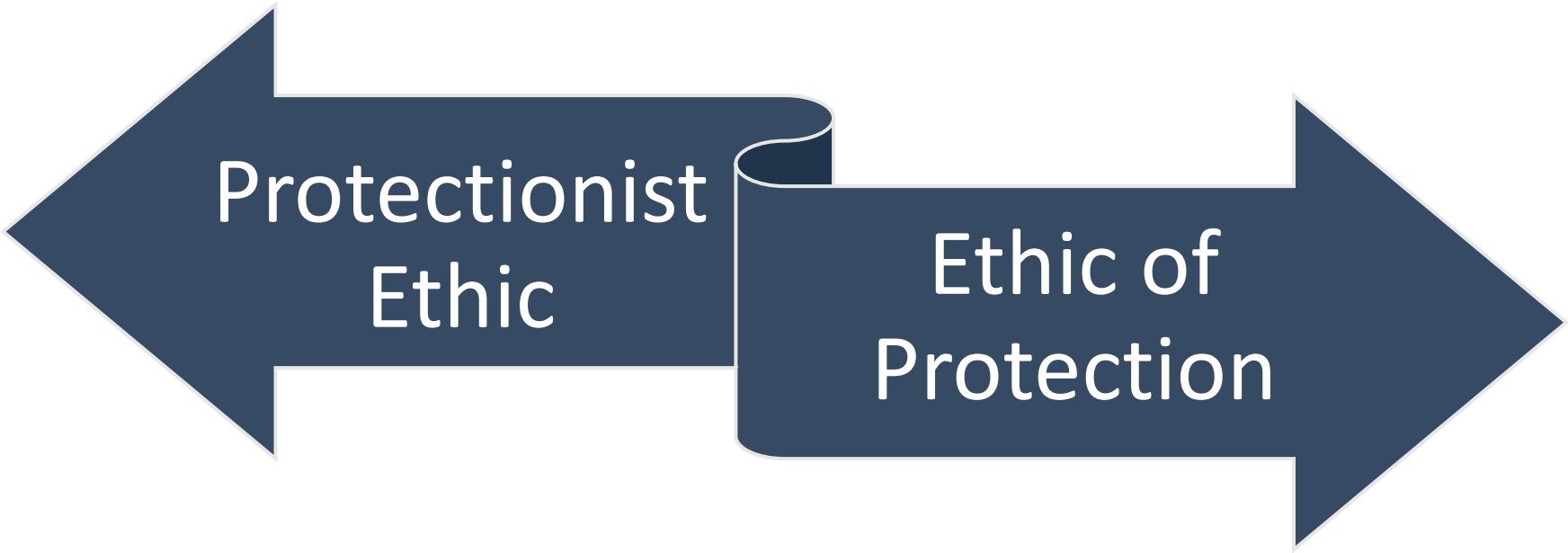
- **Pregnant population**
  - Subpart B (CFR) "No pregnant woman may be involved unless .." (1975)
  - Pregnant persons are "vulnerable"
  - FDA exclusion of women who are pregnant or "of childbearing potential" from early phase studies (1977)

  ➢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*



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

- 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"

Waggoner and Lyerly, 2022

*Reagan L, *Dangerous Pregnancies,* 2012

The harms of the *protectionist ethic*

Without adequate evidence, pregnant persons:

→May be given drugs at the ***wrong dose***

→May be given drugs with ***unacceptable risk***

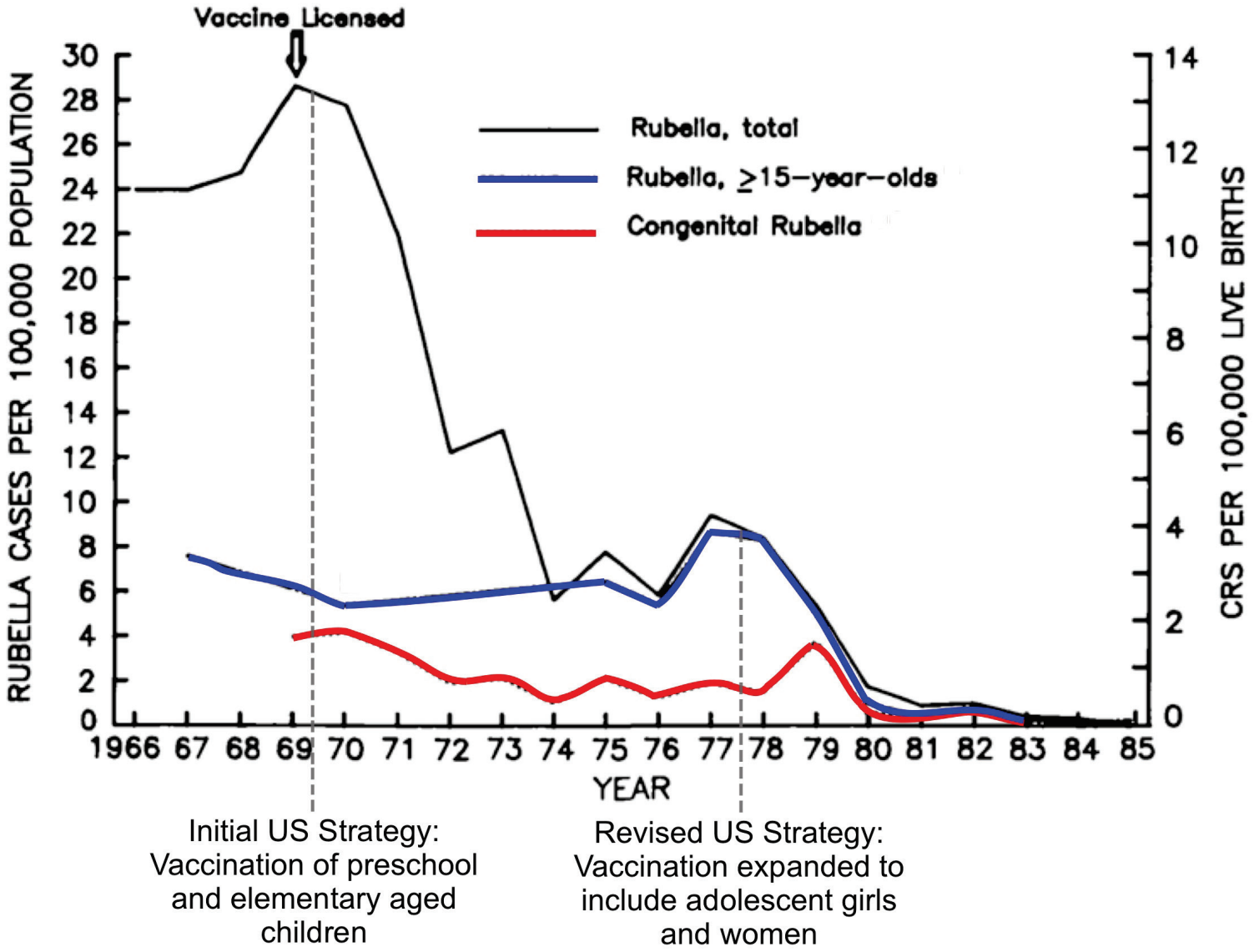
→May be ***denied access*** to beneficial drugs

→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”:



"paradoxical effect"

Vaccinating children can lead to an increase in the average age of infection

fear

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

Lyerly, Robin, Jaffe *JAMA Peds* 2017

Teratology research prevents abortion

OBSTETRICS

Saving lives and changing family histories: appropriate counseling of pregnant women and men and women of reproductive age, concerning the risk of diagnostic radiation exposures during and before pregnancy

Robert L. Brent, MD, PhD, DSc (Hon)

Over the past 50 years, our laboratory has provided consultations dealing with the risks of various environmental toxicant exposures during pregnancy. These contacts were primarily by telephone or written communications. Since the year 2000, the primary source of consultations has been via the internet. In 2007, the pregnancy website of the Health Physics Society received 1,299,672 visits. The contacts who downloaded information totaled 620,035. After reading the website information, 1442 individuals who were still concerned contacted me directly. Unfortunately, we have learned that many physicians and other counselors are not prepared to counsel patients concerning radiation risks. Approximately, 8% of the website contacts, who had consulted a professional, were provided inaccurate information that could have resulted in an unnecessary interruption of a wanted pregnancy.

Research from our and other investigators' laboratories has provided radiation risk data that are the basis for properly counseling contacts with radiation exposures. Mammalian animal research has been an important source of information that improves the quality and accuracy of estimating the reproductive and developmental risks of ionizing radiation in humans.

What are the reproductive and developmental risks of in utero ionizing radiation exposure?

1. Birth defects, mental retardation, and other neurobehavioral effects, growth retardation, and embryonic death are deterministic effects (threshold effects). This indicates that these effects have a no adverse effect level (NOAEL). Almost all diagnostic radiological procedures provide exposures that are below the NOAEL for these developmental effects.

2. For the embryo to be deleteriously affected by ionizing radiation when the mother is exposed to a diagnostic study, the embryo has to be exposed above the NOAEL to increase the risk of deterministic effects. This rarely happens when the pregnant women have x-ray studies of the head, neck, chest or extremities.

3. During the preimplantation and preorganogenesis stages of embryonic development, the embryo is least likely to be malformed by the effects of ionizing radiation because the cells of the very young embryo are omnipotential and can replace adjacent cells that have been deleteriously affected. This early period of development has been designated as "the all-or-none period."

4. Protraction and fractionation of exposures of ionizing radiation to the embryo decrease the magnitude of the deleterious effects of deterministic effects.

5. The increased risk of cancer following high exposures to ionizing radiation exposure to adult populations has been demonstrated in the atomic bomb survivor population. Radiation-induced carcinogenesis is assumed to be a stochastic effect (nonthreshold effect) so that there is theoretically a risk at low exposures. Whereas there is no question that high exposures of ionizing radiation can increase the risk of cancer, the magnitude of the risk of cancer from embryonic exposures following diagnostic radiological procedures is very controversial. Recent publications and analyses indicate that the risk is lower for the irradiated embryo than the irradiated child, which surprised many scientists interested in this subject, and that there may be no increased carcinogenic risk from diagnostic radiological studies.

Examples of appropriate and inappropriate counseling will be presented to demonstrate how counseling can save lives and change family histories. The reader is referred to the Health Physics Society website to obtain many examples of the answers to questions posed by women and men who have been exposed to radiation (www.hps.org). Then click on ATE (ask the expert).

Key words: cancer, congenital malformations, ionizing radiation risk, pregnancy risks

There have been many publications concerning the effects of radiation on the developing embryo. The subject includes the effects of ionizing radiation (x-rays, gamma rays, internal and external radionuclides, neutrons) and nonionizing radiation (ie, electromagnetic fields of various frequencies, microwave radiation, communication band radiation, diathermy, lasers, and ultrasound). Exposures to ionizing radiation will be emphasized in this publication. For further details the reader is referred to comprehensive reviews concerning the effects of various forms of radiation on the developing embryo and fetus.[1-17]

When attempting to evaluate the nature and magnitude of the effects of an environmental toxicant like radiation, it is important to utilize all the available approaches and methodologies. The process that our laboratory utilizes in evaluating reproductive and developmental risks is as follows.

Method of evaluating allegations of environmental developmental toxicity[11]

Epidemiologic studies

At what exposures do controlled epidemiologic studies consistently demon-

From the Thomas Jefferson University, Alfred I. duPont Hospital for Children, Wilmington, DE.

Received March 7, 2008; revised June 3, 2008; accepted June 11, 2008.

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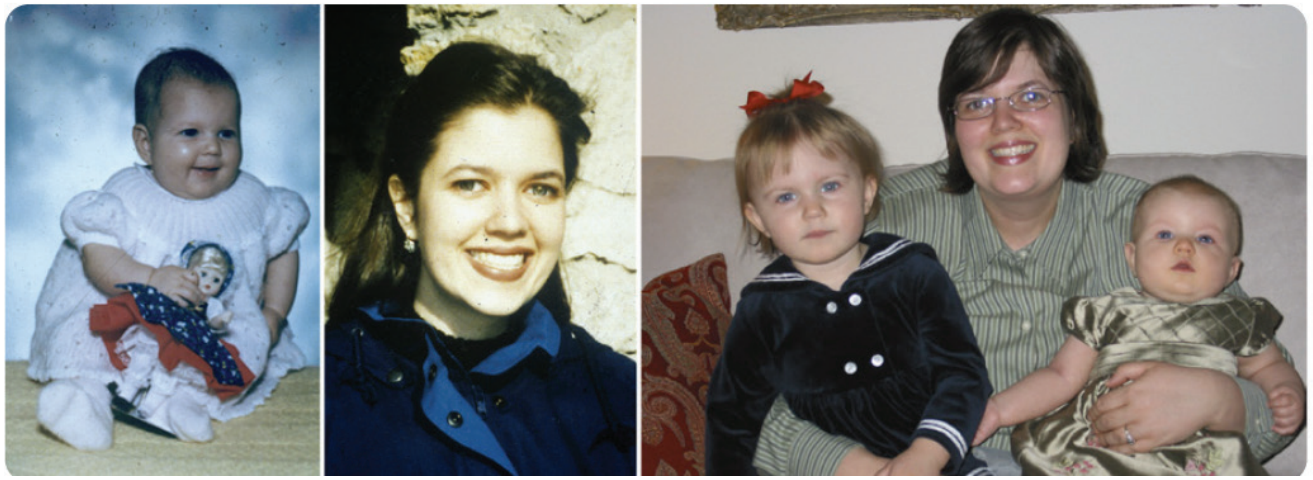
0002-9378/$36.00

doi: 10.1016/j.ajog.2008.06.032

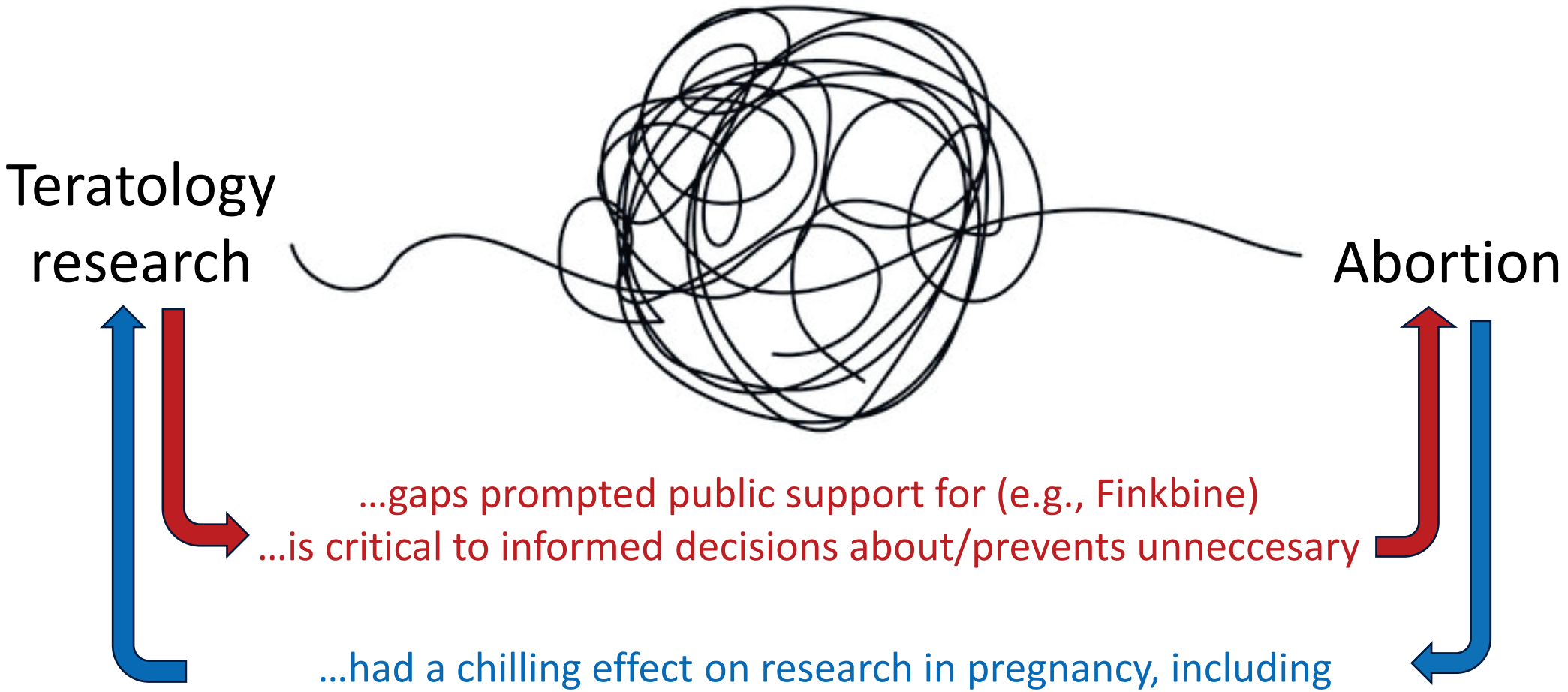
FIGURE 7
Three photographs of the Joergs family



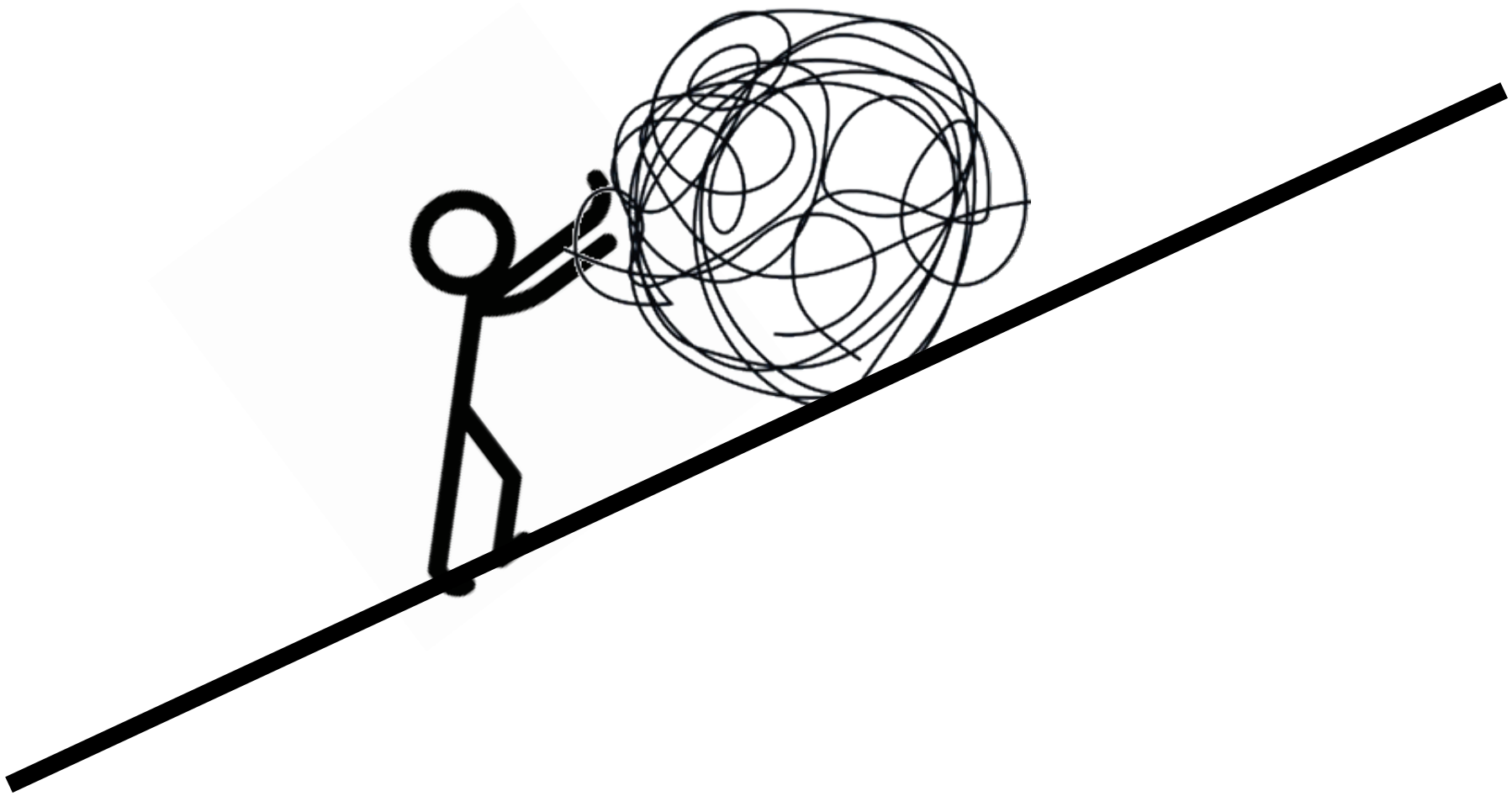
"There are probably 1,200 babies in this country alive today because I stopped their mothers from having an abortion once I knew the timing or dose of their exposure."

Robert Brent interview, *New York Times*, 2004

Teratology research and abortion are *intertwined*

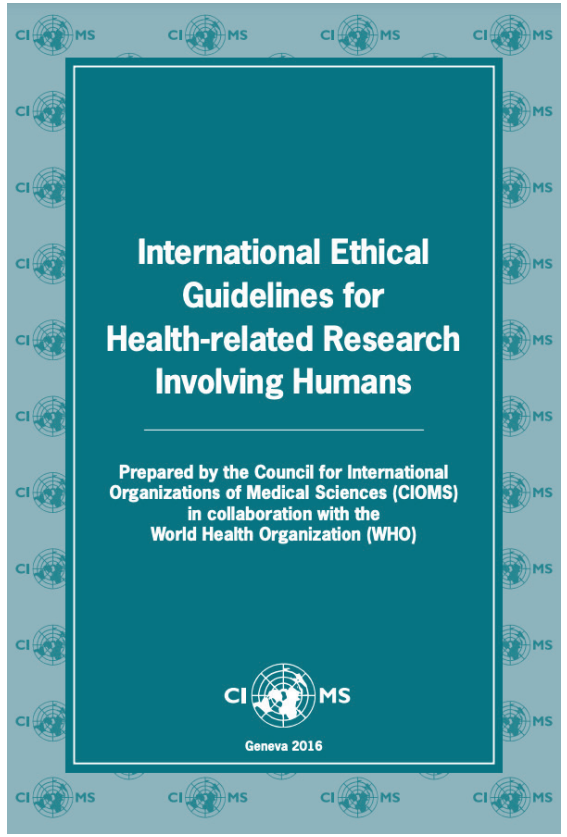


II. Abortion restrictions will make research in pregnancy *more difficult*



Abortion and Research in Pregnancy

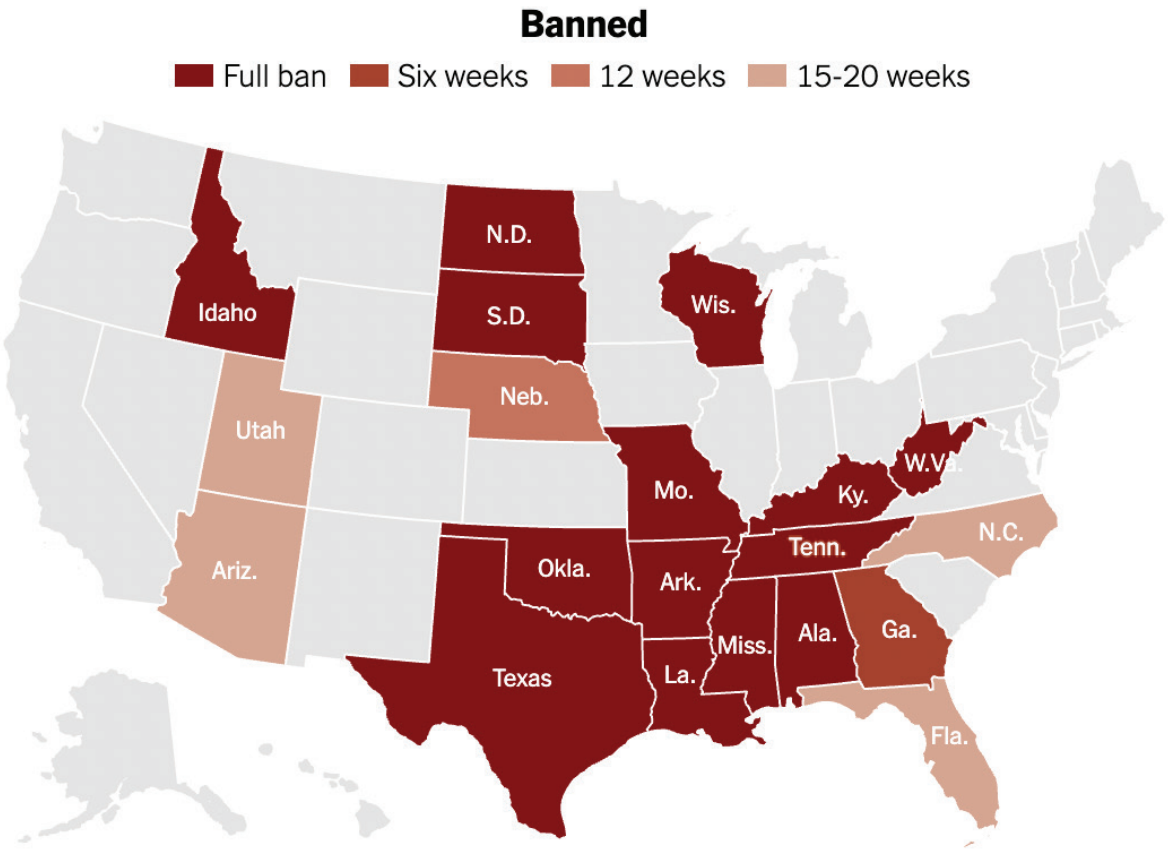
- "As a general rule, health-related research involving pregnant women that has the potential for harm to the fetus should be conducted only in settings where women can be guaranteed access to a safe, timely and legal abortion in the event that participation in the research makes the pregnancy unwanted."*



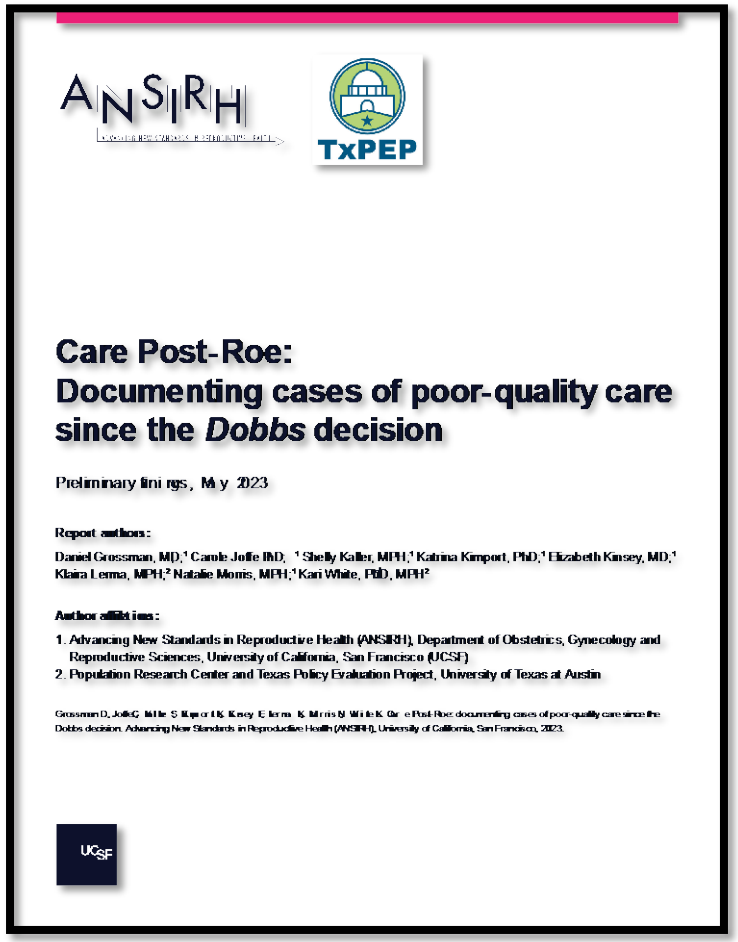
*may be conducted if a local research ethics committee determines that the research has compelling social value for pregnant women and the women are informed about existing restrictions on abortion and possible options for obtaining an abortion in another country.

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



ANSIRH

TxPEP

Care Post-Roe:
Documenting cases of poor-quality care since the *Dobbs* decision

Preliminary findings, May 2023

Report authors:

Daniel Grossman, MD,[1] Carole Joffe PhD,[1] Shelly Kaller, MPH,[1] Katrina Kimport, PhD,[1] Elizabeth Kinsey, MD,[1] Klaira Lerma, MPH,[2] Natalie Morris, MPH,[1] Kari White, PhD, MPH[2]

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1. Advancing New Standards in Reproductive Health (ANSIRH), Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF)
2. Population Research Center and Texas Policy Evaluation Project, University of Texas at Austin

Grossman D, Joffe C, Miller S, Kimport K, Kinsey E, Lerma K, Morris N, White K. Care Post-Roe: documenting cases of poor-quality care since the Dobbs decision. Advancing New Standards in Reproductive Health (ANSIRH), University of California, San Francisco, 2023.

UCSF

- 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

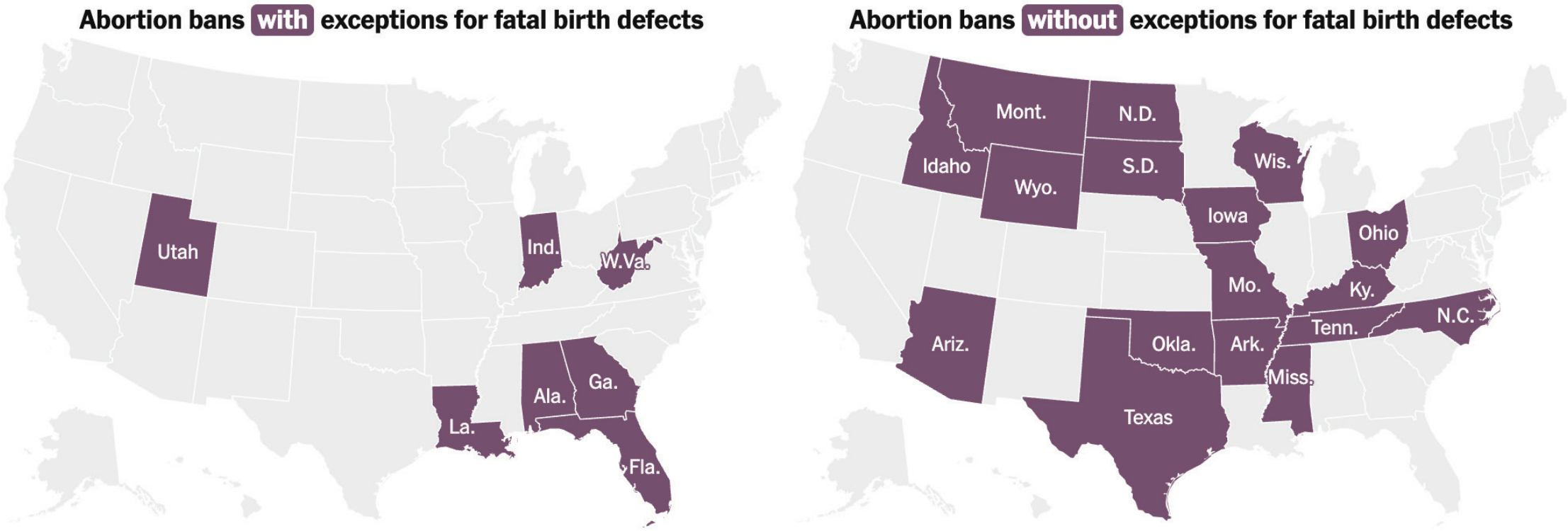
Scientific validity and feasibility

- 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?

III. Abortion restrictions make teratology research *more important*

Exceptions for fetal anomalies



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 really 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.”

“To me it’s just pure torture … the law has created torture.”

Sellars,” The Short Life of Baby Milo,” *Washington Post*, May 19, 2023

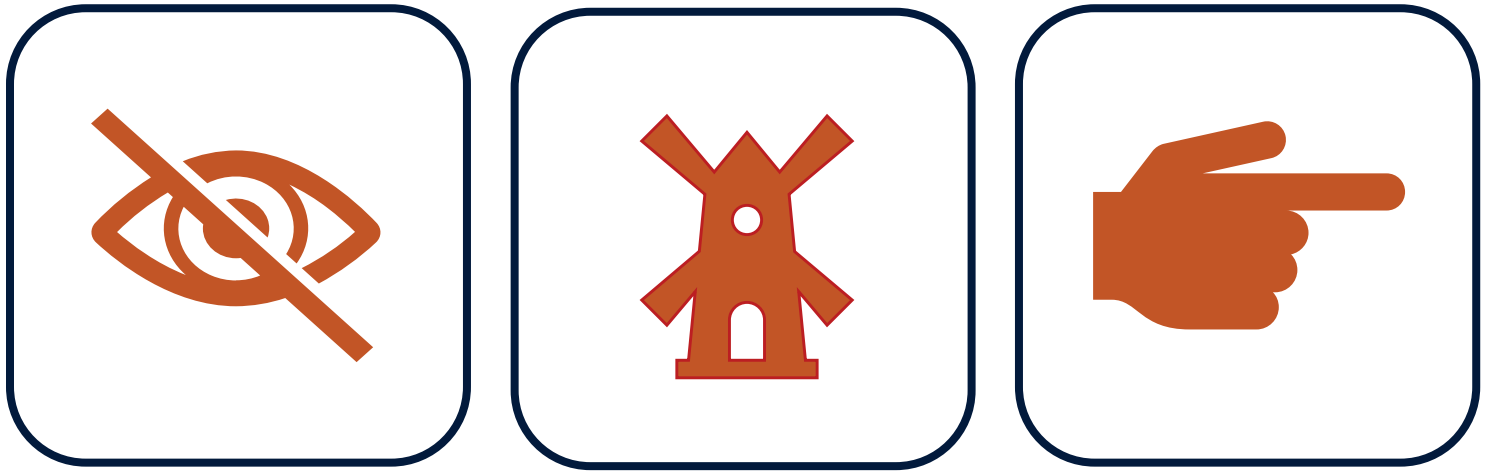
A double injustice

→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
Richardson et al, *Nature*, 2014

"**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**."

Brent and Fawcett, In: *Obstetrics: The Fetus and the Mother*, Reece and Hobbins (eds.), 2007

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

F.O. Kelsey, "Drugs and the Fetus." Presentation for The Children's Hospital Medical Center, Boston, November 26, 1968.
Frances Oldham Kelsey Papers, Manuscript Division, Library of Congress, Washington, D.C.
Box I:5, Folder 3.