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.

Keywords: pregnancy, thalidomide, Frances Kelsey, culture, FDA, ethics

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In April 2018, the United States Food and Drug Administration (FDA) issued draft guidance for industry addressing scientific and ethical considerations for inclusion of pregnant women in clinical trials [1].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 time, numerous barriers to inclusion of pregnant people in biomedical research emerged as a means to protect them—and more pointedly their offspring—from research-related risk. Paradoxically, this cultural response to thalidomide limited the evidence needed to ensure the safety of drugs used in pregnant populations. During the FDA/Duke meeting in 2021, Dr. Christine Nguyen, Director of the Division of Urology, Obstetrics, and Gynecology at the FDA, articulated the need to reframe the message that has

predominated since thalidomide: “We are still living in the shadows of thalidomide—we haven’t moved from there. That’s why we are having this workshop.”

In this paper, we draw on our analysis of Frances Kelsey’s archived papers in addition to focused media coverage of Kelsey to characterize and reassess the “shadows of thalidomide”. We discuss the durable narrative surrounding the ethic of protection established at the FDA after Kelsey prevailed in blocking thalidomide, then highlight the ways that ethic was misinterpreted in the context of pregnancy. Finally, we revisit Kelsey’s cultural legacy and argue that it in fact aligns with and supports an imperative for advancing research in pregnant populations. During the current historical moment—when the COVID-19 pandemic has exposed the high costs of excluding pregnant people from clinical trials [9] and the FDA is signaling change in this arena—a unique opportunity exists for reflecting on where the FDA has been and where it is heading in this area of immense importance to reproductive health.

2. Kelsey, the FDA, and the Ethic of Protection

No one is perhaps more associated with protecting pregnant people and their offspring from the harmful effects of drugs than Frances Kelsey. As a physician reviewing drug applications at the FDA in the early 1960s, Kelsey courageously prevented thalidomide—a drug that would soon be linked to terrible birth defects, most prominently phocomelia—from being approved in the United States. While the harms of thalidomide were largely averted in the U.S., the scope of the tragedy was large in other countries where the drug was approved and affected more than 10,000 pregnancies worldwide, reflecting the key role that regulators can play in ensuring medication safety [10].

For the public and for the FDA, Kelsey became an icon. In his authoritative book on the agency, Daniel Carpenter notes that the standard history of the FDA is often divided into two eras: “Before Thalidomide” and “After Kelsey” [11]. Kelsey’s work on thalidomide led to the passage of the Kefauver-Harris Drug Amendments of 1962, which, among other things, improved the FDA’s ability to determine the safety and efficacy of drugs, required pre-market FDA approval of new drugs, and gave the FDA authority over clinical trials [11, 12]. In 2010, the FDA named an award after Kelsey and honored her with it, bolstering her pivotal place within the agency’s history [13].

After her death in 2015, the *New York Times* referred to Kelsey’s “double legacy”, as her work both prevented a medical tragedy and improved drug protections [14]. More contemporary pieces solidify the narrative of how Kelsey’s work improved protection for everyone. In a recent critique of the FDA’s role regarding the opioid epidemic and “confused” response to the COVID-19 pandemic, journalist Farhad Manjoo openly wondered: “What might Frances Kelsey think of today’s F.D.A.?” [15]. Medical experts cite Kelsey’s work as crucial to the ability of clinicians and the public to “assume that the medications we take or prescribe have been found to be sufficiently safe and effective by the F.D.A.” [16].

3. The Paradox of Pregnancy: Thalidomide’s Shadows

Clearly, Kelsey’s legacy extended beyond the special case of pregnancy to represent the FDA as protector of the general population from unsafe and ineffective drugs. Yet, when it comes to protection, pregnant persons have been left behind.

Indeed, contemporary presumptions regarding the safety and efficacy of drugs do not in fact pertain to pregnancy. Drugs approved for use in adults are approved in all adult populations—including women of reproductive age and pregnant people, unless otherwise specified [17]. Yet less than 10% of drugs approved since 1980 have sufficient data to determine whether they cause birth defects; at the time of approval, most drugs have no human pregnancy data [18, 19]. Nor do they have pharmacokinetic data to ensure appropriate dosing and efficacy in the physiologically distinctive context of pregnancy [20].

The dismal situation is particularly shocking when juxtaposed against the concerns of Kelsey in the aftermath of the thalidomide episode. Kelsey continued to work at the FDA and was a prolific public speaker in the ensuing decades. Here, we draw on a set of 132 speeches that Kelsey gave to professional societies, governmental organizations, and university audiences, among others, between the early 1960s and the early 1990s [21]. These texts suggest a clear contrast between the move toward exclusion of pregnant persons from research and the priorities Kelsey highlighted in public comments following the averted tragedy.

About thalidomide, Kelsey bemoaned the lack of responsible clinical studies, noting that the effects of thalidomide "should have been recognized in a well-controlled clinical study involving comparatively few patients during early pregnancy", but that "apparently no such studies preceded its introduction on the market" [22]. "Had such studies been undertaken," she explained, "they would surely have revealed the nature of the drug" [23].

While Kelsey spoke at length about possible and actual teratogenic effects of drugs—urging physicians and women to consider whether the benefits of a drug outweigh the potential

risks—she also emphasized the potential *protective* effect of drugs for both the fetus and the mother. She said, “Unquestionably during the past few years there has been considerable apprehension concerning the effect of drugs and other environmental factors on the developing embryo”, but that consideration should “also be given to the role that drugs may play in protecting the offspring and the newborn” [24]. She offered the example of untreated diabetic patients, in whom “congenital abnormalities are believed to be higher…than in those under control with anti-diabetic agents, even though there is evidence from animal experiments and limited clinical reports that some of these agents may in themselves have an adverse effect on the developing young.” She elaborated:

> “However, there are times in pregnancy when the withholding of a drug would have a much more serious consequence than the possible risk of adverse effects to either mother or child. 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” [24].

Kelsey also highlighted the importance of research—for example, she stated that “there is great need for continued research in the area of drugs in pregnancy” [24, 25]. And while she explained that thalidomide “prompted a more cautious approach to the use of drugs during pregnancy” among patients and physicians, it also “stimulated a search for newer and better

ways to evaluate the safety of drugs during pregnancy" [26]. Kelsey's speeches magnified the need to learn more about teratogenic effects, improve basic research, and expand surveillance of drugs in pregnancy. She detailed the steps the agency outlined after thalidomide (1966) that must be taken before a new drug is administered to women of childbearing age (i.e., animal reproduction studies), recognizing that clinical trials of investigational new drugs may be appropriately undertaken in pregnancy. In such cases, she emphasized the importance of documenting information about dosing, stage of pregnancy, treatment duration, and pregnancy outcome. Throughout her speeches, as she discussed "wide gaps in our present knowledge in this area" [24], her words did not suggest blanket exclusion of pregnant people from clinical research but rather expressed the need to know and learn more about the role of drugs in pregnancy.

Into the 1980s, Kelsey noted that "the Food and Drug Administration recognizes that the conduct of clinical trials in pregnant women and in infants and children present certain special problems", but that "such trials are necessary to assure that safe and effective drugs will be available for their use" [27]. In her public remarks over the years, Kelsey consistently kept pregnant people in mind as end users of drugs, and repeatedly underscored the FDA's role in evaluating the safety of drugs in pregnancy.

Protecting the safety of pregnant women and their offspring—an ethic of protection—was a key motivator for Kelsey, and yet pregnant people are a notable exception to the expectation of safety that has been linked to the FDA and Kelsey's work. Why?

3.1. The rise of pregnancy's protectionist ethic

A key contributor to this paradox was a particular form that the ethic of protection took with regard to pregnancy—a "protectionist ethic" that led to broad exclusion of pregnant persons from research. For one, the thalidomide tragedy prompted a policy response that emphasized prevention of risk exposure in clinical studies. Thalidomide "created an aversion" to involving pregnant women or women of reproductive age in research on drugs [28]. In addition, the effect of diethylstibesterol (DES) "would bolster this aversion" [29], as it was becoming known in the 1970s that young women whose mothers, while pregnant, had been given DES twenty years earlier developed a rare form of vaginal cancer. It appeared to researchers and the public that the fetus was both immediately (as with thalidomide) and enduringly (as with DES) vulnerable to the effects of drugs.

The aversion was soon codified. In 1975, Subpart B—"additional protections" for research activities related to fetuses, pregnant women, and in vitro fertilization—was added to DHEW regulations on the protection of human subjects in research, and it struck a markedly precautionary tone, indicating that "no pregnant woman may be involved" in research unless certain criteria are met [30]. Pregnant women were subsequently listed as part of the "vulnerable populations" category in the regulations. This designation of pregnant persons as "vulnerable" (a category that concerns whether a person can adequately consent to research) was denounced by many as disregarding women's autonomy [29]. (Pregnant women were at last removed from the "vunerable populations" category in the 2018 revision to the Common Rule.) In 1977, the FDA issued guidelines that explicitly excluded pregnant women—and all women "of childbearing potential"—from early-phase clinical trials [31]. Although thalidomide and DES were problems of inadequate research, rather than cases of harm caused by

participation in research, both sourced a protectionist policy stance [28, 32] as well as a dominant ethical focus on fetal risk avoidance in research [33].

This protectionist stance was challenged by scholars and commentators in the 1980s and 1990s, who argued that it both impeded research with women and facilitated a "special neglect of pregnant women" [34]. HIV/AIDS activists concurrently and crucially shifted the broader conversation in research ethics from protectionism to access, especially access to potentially life-saving investigational therapeutics, with significant implications for gender equity in research [28, 35, 36]. By 1993, FDA policy had changed, along with that of the NIH, to foster inclusion of women in clinical trials [37, 38]. Some still raised concerns about this change in FDA policy, citing worry about "another thalidomide" [39]. And routine exclusion of *pregnant* women continued despite an IOM report recommending they be presumed eligible for clinical studies [29]. While the FDA made efforts to address exclusion of pregnant individuals from research [40, 41], government reports continued to gesture to earlier episodes, especially thalidomide, that undergirded protectionist guidelines [38].

A cultural shift in thinking about the harms of pregnancy exclusions in clinical trials did not take hold until years later, as the Second Wave Initiative convened leaders across the research community to address the problem of ongoing evidence gaps specific to pregnancy [7]. FDA officials joined these discussions; following a 2009 Second Wave Workshop at Georgetown, they asserted that "it is not only permissible but also imperative that pregnant women be judiciously included in research" [42]. Nevertheless, thalidomide had cast—and would continue to cast—a "long shadow" over conversations about pregnancy and clinical research [7].

Indeed, thalidomide offered its own legacy beyond Kelsey's work, for the tragedy tapped into and expanded deep fears about the permeability of the pregnant body—made manifest by the alarming fact that something ingested by a pregnant woman could harm the fetus, and terribly. As such, the tragedy shifted not just policy but *culture*. As historian Leslie Reagan notes, intense media attention to thalidomide—including photos of babies with severe limb abnormalities—brought thalidomide to "the American public's consciousness" [43]. Such images ushered in an era in which women were strongly advised to avoid any medications whatsoever in pregnancy, as medicines that "should be seen as therapeutic or lifesaving are instead seen as frightening or poisonous" [44].

Additionally, the thalidomide tragedy intersected with other events that furthered the notion that the fetus needs protection—from drugs, but also from research. For instance, a culture of fetal protection became pronounced post-Roe v. Wade [36], producing a "chilling effect" on research involving women of childbearing age [45]. Moreover, the legality of abortion was a potent backdrop for reasoning about risk and pregnancy, contributing to a tendency to frame issues in reproductive ethics as "maternal-fetal conflict," foregrounding trade-offs between the pregnant woman and fetus, and characterizing the intersection of research and pregnancy as something to be avoided. Where research in pregnancy did go forward, it primarily did so in contexts where a woman's medical condition posed an urgent threat to fetal health—e.g., research aimed at preventing vertical transmission of HIV. Such studies often tended to focus on the health needs of the fetus, with pregnant individuals studied as either "vessels or vectors", but not as ends in themselves [46].

Ultimately, pregnancy has been marked by a particular *protectionist ethic*, in which protection has largely manifested as exclusion of pregnant people from research, rather than protection of the public from harms of exposure to unsafe medications in pregnancy.

3.2. The harms of pregnancy's protectionist ethic

The protectionist ethic surrounding pregnancy has resulted, paradoxically, in harms to pregnant persons and fetuses. First, the protectionist ethic contributed to a failure to responsibly address research-related risk in pregnancy. News reports and FDA publications—then and now—rarely mention that thalidomide was a tragedy that stemmed from the *absence* of robust research in pregnancy and responsible oversight [7, 47–49]. As mentioned above, this point was not lost on Kelsey, who detailed this fact in multiple speeches. Yet, the dominant cultural and regulatory interpretation of this episode was to exclude pregnant people—and, for a time, potentially pregnant people—from research.

Second, the protectionist ethic failed to make drugs safer. It prompted regulators, IRBs, clinical investigators, and sponsors to focus on their ethical duty to protect research subjects and their (sometimes potential) fetuses from research-related risks. This form of protection took hold without consideration of the perspectives of pregnant people on their potential participation in research that might benefit them or inform care of others (something that researchers have more recently begun to study [50, 51]). In pursuing protection through exclusion, the protectionist ethic obscured the responsibility to gather data to inform safe and effective clinical use. Rather than eliminate risk, this approach simply shifted risks to clinical

settings where, unchecked by evidence, they expanded. As a result, clinicians must make recommendations and offer care to pregnant patients without adequate data to inform them.

Third, the protectionist ethic failed to make pregnant people or their offspring safer. Pregnancy and illness often co-occur [52], and require treatment or prevention. The protectionist ethic led to harmful evidence gaps: without data, pregnant people may be prescribed drugs that turn out to have unacceptable risks for them or their offspring or are ineffective or toxic at doses determined in non-pregnant adults; they may lack access to newer drugs that lack a track-record of safety; or, because of questions about safety, may lack access to needed drugs or vaccines, thus bearing the risks of untreated disease. Even in Phase IV clinical studies, where enrolling pregnant people is "potentially the most appropriate and least controversial", they are routinely excluded [53]. And even in instances of trials for life-saving therapeutics, such as drug and vaccine trials for Ebola, pregnant people have been excluded, prompting the observation that pregnant people are "protected to death" [54].

To be sure, some regulatory changes after thalidomide did facilitate evidence regarding pregnancy, especially preclinical studies now required for drugs. Yet, such studies are far from sufficient to establish safety or indicate harm, as Kelsey noted repeatedly in her public remarks. "Negative results in animal reproduction tests do not ensure the safety of drugs in human subjects during pregnancy any more than positive results in animals mean that such will necessarily occur in human subjects", she said in one speech [26]. Moreover, preclinical requirements have often been cited as the key reason for exclusion of pregnant people from studies, including, most recently, studies leading to authorization of COVID vaccines.

4. Revisiting Kelsey's Legacy: Toward an Ethics of Research and Pregnancy

It was thalidomide, not Kelsey's work to protect the public from thalidomide, that prompted a protectionist ethic. The cultural and regulatory response that unfolded after the thalidomide episode went beyond Kelsey—beyond her words and her influence. Rather than serving as an example of inadequate research in pregnancy that put people in harm's way, or as a reason for advancing responsible clinical trials in pregnancy, it instead furnished a backdrop of fear that is still referenced today as a stifling force on research in pregnancy ("the shadows of thalidomide"). Since Kelsey's work is in many ways inextricable from the thalidomide episode and from the very notion of protection that the FDA strives to uphold, the legacy of thalidomide (protectionist ethic) and the legacy of Kelsey (the ethic of protection) have become entangled over time.

We can do better by Kelsey. Refocusing on Kelsey's work enhances understanding of the cultural legacy of her achievement, as potentially distinguishable from the cultural response to thalidomide. Here, we aim to characterize the broad cultural response to Kelsey's work. Using grounded theory [55], we undertook a thematic analysis of articles published in the *New York Times* from 1962 to early 2022, using the search terms thalidomide and Kelsey (n=90). While this focused sample of articles is obviously not exhaustive of news coverage, as a paper of record, the *Times* reflects one key cultural lens on the work of Frances Kelsey. In addition to Kelsey's well recognized courage and persistence, we report on emergent and overlapping themes that, together, can be understood as the *ethic of protection* that Kelsey exemplified: an ethic that reveals how her legacy might relate to—and indeed support—new efforts to advance research in pregnancy.

4.1. Staying vigilant

First, much coverage of the thalidomide episode—from the 1960s to today—mentions the importance of Kelsey *staying vigilant*, emphasizing her approach of asking questions, being skeptical, suspicious, aware, and watchful, of examining closely what data are or are not available [56–58]. Kelsey illuminated these themes in her speeches, as she was attuned to pregnancy effects throughout her work. “Despite the failure in recent years to identify additional teratogenic drugs in humans, continued vigilance in this regard is necessary,” she said in 1971, as she also noted that “on the average between three and four drugs are prescribed during pregnancy” [59].

Such vigilance is key to the Second Wave agenda, which has emphasized the importance of gathering data specific to pregnancy—of asking questions about the safety and efficacy of drugs in development, designing studies that can answer such questions, gathering and reporting data about pregnancy exposures in trials, enhancing pharmacovigilance efforts in post-approval settings (which recommendations from the FDA in 2019 reaffirm [60]), and attending to evidence gaps by conducting research on drugs widely used in pregnancy. Pregnancy in the context of research is not an “adverse event”, but an opportunity to gather data critical to safe use of drugs. Vigilance pertains not to the detection or prevention of pregnancy in studies, but to data that might be gathered in medication-exposed pregnancy.

This conception of vigilance reflects Kelsey’s legacy. Vigilance can be deployed in this way—by asking good questions and being thoughtful about the end users of drugs. Vigilance may also lead to reasoned recommendations to exclude pregnant people from a trial—where a

safety signal or known mechanism points toward unacceptable toxicity or where the disease being studied does not affect pregnant populations. But vigilance—following Kelsey—should prompt investigators (and also IRB and DSMB members) to ask questions about pregnancy: whether pregnancy is relevant to the clinical trial and its impact, and what the implications—ethical and otherwise—of excluding pregnant people from a trial or failing to collect pregnancy-specific data might be.

4.2. Prioritizing safety

A second theme, closely related to vigilance, is *prioritizing safety*. Over the years, news coverage has consistently referenced how Kelsey demonstrated for the FDA and for the public what prioritizing safety looks like; she emphasized safety as a counterpoint to intense pressure she was under from pharmaceutical companies at the time [15, 61, 62]. Popular reporting of her work solidified her place as the standard-bearer of drug safety for Americans as a whole, and Kelsey often highlighted the FDA's role in ensuring drug safety for the public—including for pregnancy.

As is true for other populations, prioritizing safety for pregnant people requires gathering evidence. Failures to gather such evidence suggest other priorities: delays in conducting DART studies have been linked to expense; exclusion of pregnant people from studies—including those of life-saving interventions—have been linked to barriers such as trial insurance and liability concerns; researchers often cite lack of expertise, experience, and guidance as barriers to conducting needed studies. These are serious challenges indeed, and the notion of "prioritizing safety" is often used as a reason to limit research with pregnant

people. But we argue that prioritizing safety requires a commitment to addressing these ongoing challenges—and to endorsing research in pregnancy as ethically imperative.

4.3. Mitigating pharmaceutical-based harm

Third, Kelsey is often lauded for *mitigating pharmaceutical-based harm*. As she kept thalidomide off the market, she spared the nation a tragedy, as so many news stories about her work note [63–65]. Kelsey's legacy is typically framed as one of keeping hazardous drugs out of the homes of Americans—a benefit to all. The thalidomide story and Kelsey's achievement have been invoked for decades as an exemplar of broad-based protection from the dangers of pharmaceutical-based harm.

But exclusion of pregnant people from biomedical research has left them and their offspring *exposed* to pharmaceutical-based harm, shifting risk from research to clinical settings. Without data to inform decisions, pregnant people may use drugs that pose unacceptable risks to the fetus, may receive ineffective or toxic doses of drugs, or be denied access to drugs for lack of data, leaving them consigned to regimens less optimal to their health. Conducting responsible research in pregnancy is critical to mitigating pharmaceutical-based harm—and, we would argue, more authentic to Kelsey's important legacy.

5. Conclusions

Sixty years after Kelsey's foundational work, the FDA is signaling a new era— a "paradigm shift" toward inclusion of pregnant and breastfeeding people in clinical research [66]. Recent FDA activities such as the 2018 draft guidance reflect the expanding recognition of

the ethical obligation to consider pregnancy not as an exclusion criterion but as an opportunity to collect data critical to ensuring the safety of drugs and biological products for the population who will use them. The guidance calls attention to pregnancy-specific data as a "critical public health need" and the specific harms of the profound evidence gaps around drugs in pregnancy. It highlights the role of pre-market research, the problems of reliance on post-marketing studies, and the urgent need for dosing specific to pregnancy. It also offers important clarifications regarding technical issues in the service of facilitating inclusion and removing regulation-related barriers, suggesting concrete ways the guidance aligns with a paradigm that prioritizes protection through research, rather than from it. To be sure, there is still work to do in implementing a collective effort to advance clinical research in pregnancy. Vigilance is key—not just in terms of asking the right questions and gathering data, but in protecting against the powerful and distorting influence of thalidomide's shadows.

Ultimately, the shift toward responsible inclusion can and should be understood not as a shift away from Kelsey's legacy but toward a more expansive ethic of protection that she illustrated through her work—as a way to more robustly align with the ideals she upheld, including vigilance, safety, and prevention of pharmaceutical-based harm. The assumption that drugs used by the public are both safe and effective should apply to the context of pregnancy. In recognizing that pregnant individuals and their offspring can be protected *through* ethical research, the FDA's recent activities indicate not just a substantial evolution and turning point in its orientation to the ethics of clinical trials and pregnancy, but an opportunity to live up to the public reputation as protector that Frances Kelsey helped instill.

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References

[1] FDA (U.S. Food and Drug Administration). 2018. Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry – Draft Guidance.

[2] "Scientific and Ethical Considerations for the Inclusion of Pregnant Women in Clinical Trials". 2021. Public Meeting, Robert J. Margolis Center for Health Policy at Duke University, in cooperation with the U.S. Food and Drug Administration (FDA).

[3] PRGLAC (Task Force on Research Specific to Pregnant Women and Lactating Women). 2018. Report to the Health and Human Services Secretary and Congress. https://www.nichd.nih.gov/about/advisory/PRGLAC

[4] PHASES (The PHASES Working Group). 2020. *Ending the evidence gap for pregnant women around HIV & co-infections: A call to action*. Chapel Hill, NC. http://www.hivpregnancyethics.org

[5] Duggal, M., Sacks, L., and Vasisht, K.P. 2021. Eligibility criteria and clinical trials: An FDA perspective. *Contemporary Clinical Trials* 109: 106515. https://doi.org/10.1016/j.cct.2021.106515

[6] Spong, C.Y. and Bianchi, D.W. 2018. Improving Public Health Requires Inclusion of Underrepresented Populations in Research. *JAMA* 319(4): 337–338. doi: 10.1001/jama.2017.19138

[7] Lyerly, A.D., Little, M.O., and Faden, R. 2008. The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research. *International Journal of Feminist Approaches to Bioethics* 1(2): 5–22. https://doi.org/10.3138/ijfab.1.2.5

[8] Langston, L. 2016. Better Safe Than Sorry: Risk, Stigma, and Research During Pregnancy. Pp. 33–50 in *Clinical Research Involving Pregnant Women*, Baylis, F. and Ballantyne, A. (Eds.) Springer International Publishing.

[9] Minkoff, H. and Ecker, J. 2021. Balancing risks: making decisions for maternal treatment without data on fetal safety. *American Journal of Obstetrics & Gynecology* 224(5): 479–483. https://doi.org/10.1016/j.ajog.2021.01.025

[10] Brynner, R. and Stephens, T. 2001. *Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine*. New York: Perseus Books.

[11] Carpenter, D. 2010. *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton University Press.

[12] Greene, J.A. and Podolsky, S.H. 2012. Reform, Regulation, and Pharmaceuticals—The Kefauver-Harris Aamendments at 50. *New England Journal of Medicine* 367(16): 1481–1483. DOI: 10.1056/NEJMp1210007

[13] Kuehn, B.M. 2010. Frances Kelsey Honored for FDA Legacy: Award Notes Her Work on Thalidomide, Clinical Trials. *JAMA* 304(19): 2109–2112.

[14] McDonald, W. 2015 (December 29). In 2015 Obituaries, Distant Eras Were Evoked. *The New York Times*.

[15] Manjoo, F. 2021 (September 2). America Desperately Needs a Much Better F.D.A. *The New York Times.*

[16] Kesselheim, A.S. and Avorn, J. 2021 (June 15). The F.D.A. Has Reached a New Low. *The New York Times*.

[17] Wesley, B.D., Sewell, C.A. Sewell, Chang, C.Y., Hatfield, K.P., and Nguyen, C.P. 2021. Prescription medications for use in pregnancy—perspective from the US Food and Drug Administration. *American Journal of Obstetrics & Gynecology* 225(1): 21–32. https://doi.org/10.1016/j.ajog.2021.02.032

[18] Adam, M.P., Polifka, J.E., and Friedman, J.M. 2011. Evolving Knowledge of the Teratogenicity of Medication in Human Pregnancy. *American Journal of Medical Genetics Part C (Seminars in Medical Genetics)* 157: 175–82. https://doi.org/10.1002/ajmg.c.30313

[19] Byrne, J.J., Saucedo, A.M., and Spong, C.Y. 2020. Evaluation of Drug Labels Following the Pregnancy and Lactation Labeling Rule. *JAMA Netw Open* 3(8):e2015094. doi:10.1001/jamanetworkopen.2020.15094

[20] Pariente, G., Leibson, T., Carls, A., Adams-Webber, T., Ito, S., and Koren, G. 2016. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. *PLoS Med* 13(11): e1002160. https://doi.org/10.1371/journal.pmed.1002160

[21] Frances Oldham Kelsey Papers, Manuscript Division, Library of Congress, Washington, D.C. Box I:4, Folder 10.

[22] Kelsey, F.O. Chemical Teratogens. Presentation for the Annual Health Conference, New York City, June 11, 1963. Frances Oldham Kelsey Papers, Manuscript Division, Library of Congress, Washington, D.C. Box I:4, Folder 12.

[23] Kelsey, F.O. The Role of the Investigational Drug Branch of the Food & Drug Administration. Presentation for the Science Writers Seminar, La Jolla, April 5–10, 1963. Frances Oldham Kelsey Papers, Manuscript Division, Library of Congress, Washington, D.C. Box I:4, Folder 11.

[24] Kelsey, F.O. 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.

[25] Kelsey, F.O. Drugs and Pregnancy. Presentation for the American Association on Mental Deficiency, Boston, May 1, 1968. Frances Oldham Kelsey Papers, Manuscript Division, Library of Congress, Washington, D.C. Box I:5, Folder 3.

[26] Kelsey, F.O. The Effect of Drugs on the Fetus. Presentation for Symposium on Congenital Malformations, 93rd Annual Meeting, American Public Health Association, Chicago, October 21, 1965. Frances Oldham Kelsey Papers, Manuscript Division, Library of Congress, Washington, D.C. Box I:4, Folder 14.

[27] Kelsey, F.O. Clinical Trials in the Perinatal Period—FDA Requirements. Presentation for International Symposium for Pediatric Pharmacology, Ahmedabad (India), January 21–22, 1985. Frances Oldham Kelsey Papers, Manuscript Division, Library of Congress, Washington, D.C. Box I:6, Folder 2.

[28] Levine, C. 1990. Women and HIV/AIDS Research: The Barriers to Equity. *Evaluation Review* 14(5): 447–463.

[29] Mastroianni, A.C., Faden, R., and Federman, D. (Eds.). 1994 *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies, Volume 1*. National Academy Press.

[30] DHEW (Department of Health, Education, and Welfare). 1975. Protection of Human Subjects: Fetuses, Pregnant Women, and In Vitro Fertilization. Federal Register 40(154): 33526–33551.

[31] FDA (U.S. Food and Drug Administration). 1977. General Considerations for the Clinical Evaluation of Drugs. HEW Publication No. (FDA) 77-3040.

[32] Merkatz, R.B. and Junod, S.W. 1994. Historical Background of Changes in FDA Policy on the Study and Evaluation of Drugs in Women. *Academic Medicine* 69(9): 703–707.

[33] Lyerly, A.D. forthcoming. 'Experimental Pregnancy' revisited. *Theoretical Medicine and Bioethics*.

[34] Merton, V. 1996. Ethical Obstacles to the Participation of Women in Biomedical Research. Pp. 216 – 251 in *Feminism & Bioethics: Beyond Reproduction*, S.M. Wolf (Ed.) Oxford University Press.

[35] Epstein, S. 1996. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press.

[36] Johnson, T. and Fee, E. 1994. Women's Participation in Clinical Research: From Protectionism to Access. Pp. 1–10 in *Women and Health Research: Ethical and Legal Issues of*

Including Women in Clinical Studies, Volume 2. Mastroianni, A.C., Faden, R., and Federman, D. (Eds.). National Academy Press.

[37] FDA (U.S. Food and Drug Administration). 1993. Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs; notice. *Federal Register* 58(139): 39406–39416.

[38] GAO (U.S. General Accounting Office). 2001. Women's Health: Women Sufficiently Represented in New Drug Testing, but FDA Oversight Needs Improvement. GAO-01-754.

[39] Epstein, S. 2007. *Inclusion: The Politics of Difference in Medical Research*. The University of Chicago Press.

[40] Merkatz, R.B., Temple, R., Sobel, S., Feiden, K., Kessler, D.A., et al. 1993. Women In Clinical Trials of New Drugs: A Change in Food and Drug Administration Policy. *New England Journal of Medicine* 329(4): 292–296. DOI: 10.1056/NEJM199307223290429

[41] Merkatz, R.B. 1998. Inclusion of Women in Clinical Trials: A Historical Overview of Scientific, Ethical, and Legal Issues. *JOGNN* 27: 78–84. https://doi.org/10.1111/j.1552-6909.1998.tb02594.x

[42] Goldkind, S.F., Sahin, L., and Gallauresi, B. 2010. Enrolling Pregnant Women in Research — Lessons from the H1N1 Influenza Pandemic. *N Engl J Med* 362(24):2241–2243. doi: 10.1056/NEJMp1003462

[43] Reagan, L.J. 2010. *Dangerous Pregnancies: Mothers, Disabilities, and Abortion in Modern America*. University of California Press.

[44] Lyerly, A.D., Mitchell, L.M., Armstrong, E.M., Harris, L.H., Kukla, R., Kuppermann, M., and Little, M.O. 2009. Risk and the Pregnant Body. *Hastings Center Report* 39(6): 34–42. https://doi.org/10.1353/hcr.0.0211

[45] McCarthy, C.R. 1994. Historical Background of Clinical Trials Involving Women and Minorities. *Academic Medicine* 69(9): 695–698.

[46] Faden R., Kass, N., and McGraw, D. 1996. Women as vessels and vectors: Lessons from the HIV epidemic. Pp. 252–281 in *Feminism and Bioethics: Beyond Reproduction*, S.M. Wolf (Ed.) Oxford University Press.

[47] Levine, C. 1993. Women as research subjects: new priorities, new questions. In *Emerging issues in Biomedical Policy*. Volume 2, R.H. Blank and A.L. Bonnicksen (Eds). New York: Columbia University Press.

[48] Ballantyne, A. 2019. Pregnant Women Can Finally Expect Better. *Hastings Center Report* (January–February): 10–11. https://doi.org/10.1002/hast.971

[49] Little, M.O. and Wickremsinhe, M.N. 2017. Research with pregnant women: a call to action. *Reproductive Health* 14(Suppl 3):156. DOI 10.1186/s12978-017-0419-x

[50] Jaffe, E., Lyerly, A.D., Goldfarb, I.T. 2020. Pregnant women's perceptions of risks and benefits when considering participation in vaccine trials. *Vaccine* 38(44): 6922–6929. doi: 10.1016/j.vaccine.2020.08.059

[51] Lyerly, A.D., Namey, E.E., Cray, B., Swamy, G., and Faden, R.R. 2012. Women's Views about Participating in Research While Pregnant. *IRB: Ethics & Human Research* 34(4): 1–8.

[52] Wisner K.L., Jeong, H, and Chambers, C. 2016. Use of Antipsychotics During Pregnancy: Pregnant Women Get Sick—Sick Women Get Pregnant *JAMA Psychiatry* 73(9): 901–3. doi:10.1001/jamapsychiatry.2016.1538

[53] Shields, K.E. and Lyerly, A.D. 2013. Exclusion of Pregnant Women from Industry-Sponsored Clinical Trials. *Obstetrics & Gynecology* 122(5): 1077–1081.

[54] Gomes, M.F. de la Fuente-Núñez, V., Saxena, A., and Kuesel, A.C. 2017. Protected to death: systematic exclusion of pregnant women from Ebola virus disease trials. *Reproductive Health* 14(Suppl 3): 172.

[55] Charmaz, K. 2014. *Constructing Grounded Theory, 2nd ed.* Thousand Oaks, CA: Sage Publications.

[56] Special to The New York Times. 1962 (December 28). Thalidomide Opponent Named to Head New U.S. Drugs Unit. *The New York Times*.

[57] Geng, V. 1973 (April 29). Thalidomide: the American experience. *The New York Times*.

[58] McFadden, R.D. 2015 (August 7). Frances Oldham Kelsey, Who Saved U.S. Babies From Thalidomide, Dies at 101. *The New York Times*.

[59] Kelsey, F.O. Drugs in Pregnancy and Their Effects on Pre- and Postnatal Development. Presentation for Annual Meeting of the Association for Research in Nervous and Mental Disease, New York, December 4, 1971. Frances Oldham Kelsey Papers, Manuscript Division, Library of Congress, Washington, D.C. Box I:5, Folder 4.

[60] FDA (U.S. Food and Drug Administration). 2019. Postapproval Pregnancy Safety Studies Guidance for Industry – Draft Guidance.

[61] Harris, G. 2010 (September 13). The Public's Quiet Savior From Harmful Medicines. *The New York Times*.

[62] Thomas, K. 2020 (March 23). The Unseen Survivors of Thalidomide Want to Be Heard. *The New York Times*.

[63] Burkholz, H. 1991 (June 30). A Shot in the Arm for the F.D.A. *The New York Times*.

[64] Stolberg, S.G. 1997 (September 23). 37 Years Later, A Second Chance For Thalidomide. *The New York Times*.

[65] Kristof, N. 2015 (November 5). Drugs, Greed and a Dead Boy. *The New York Times*.

[66] Kweder, S. Thor, S., Vasisht, K., Yao, L., and Everett, D. 2021. Global Regulators Envision Paradigm Shift Toward Inclusion of Pregnant and Breastfeeding Women in Clinical Research for Medicines and Vaccines. *FDA Voices*. Retrieved from https://www.fda.gov/news-events/fda-voices/global-regulators-envision-paradigm-shift-toward-inclusion-pregnant-and-breastfeeding-women-clinical