Introduction

For many, it may be difficult to recall a time in which the placenta was believed to protect the fetus from potentially harmful substances ingested by pregnant women. Fetal harms resulting from the thalidomide and DES tragedies in the 1960s and 1970s put that fallacy to rest and led to protectionist policies aimed at preventing similar events in the future.¹ The FDA, for example, issued clinical trial guidelines in 1977 that prohibited the inclusion of pregnant women and women of childbearing potential in the vast majority of drug research. Although those restrictions were subsequently lifted, research with pregnant women remains subject to special federal regulations, commonly referred to as Subpart B,² and pregnant women and their health interests remain largely invisible in clinical studies and on the research agenda.

Since the late 2000s, bioethicists have been at the forefront of efforts to draw attention to harms of excluding pregnant women from research. Legal experts are participating in those efforts by examining the relevant issues from a legal perspective and developing practical legal interpretations that can support ethical considerations and arguments raised by bioethicists.

This paper first provides background information necessary to appreciate the ethical issues at stake. It then provides some reflections on how the law has played, and can play, a role in enriching, refining, and correcting misunderstandings in the conceptualization and resolution of the complex issues surrounding pregnant women’s participation in research. It concludes with preliminary bulleted thoughts that we hope will prompt discussion in considering how law can contribute to work in bioethics and how lawyers and bioethicists can work toward a common goal.

Background

Use of prescription and non-prescription medications during pregnancy is widespread. A recent study of women in their first pregnancy reported that nearly all (97%) took at least one medication and nearly one-third took five or more different medications.³ Despite those usage
statistics, pregnant women are routinely excluded from clinical trials, leaving women and their medical providers with a dearth of evidence to inform evidence-based care for obstetrical and non-obstetrical diseases and conditions. Reported data indicate, for example, that fewer than 3% of FDA-approved medications have sufficient safety and pharmacokinetic data to guide their use during pregnancy.4

Failure to include pregnant women in clinical trials leaves women without effective treatments during pregnancy, exposes fetuses to unknown risk when pregnant women take medications, and can lead to harms—to both the woman and her potential offspring—from non-treatment or undertreatment of diseases and conditions affecting pregnant women (such as asthma, depression, and diabetes). In addition, the lack of participation in trials that offer the prospect of direct benefit denies pregnant women and their potential offspring the opportunity to access those potential benefits,5 e.g., such as through participation in trials of potentially life-saving treatments for infectious diseases like HIV, Ebola, and Zika.

Bioethicists have expressed the need to develop a framework that reflects the ethical imperative to ensure that pregnant women and their potential offspring equitably share in research advancements. Scholars and advocates acknowledge that effort requires addressing numerous challenges, which include management of the ethical complexities of risk-benefit assessments involving pregnant women and their potential offspring, financial disincentives that deter funding for pregnancy-related research, as well as legal obstacles.

The Legal Perspective

Legal experts are contributing to the efforts to address the root causes of women’s virtual exclusion from research by reframing the legal context and identifying areas of flexibility in the law ripe for supporting pregnant women’s inclusion in research. Scholars in bioethics routinely classify two legal issues as hard (inflexible) obstacles: the constraints of Subpart B and the dissuading effects of potential tort liability for fetal injuries resulting from a pregnant woman’s participation in research. Our prior work has revealed a broader framing of perceived and real legal obstacles to research with pregnant women and their complexities, and work in submission and underway is demonstrating their permeability, and where merited, their mischaracterization as legal obstacles (versus cultural or financial obstacles, for example).

Incorporating a Legal Approach

In our experience, bioethicists not trained in law ask legal experts “what the law is,” suggesting an inflexible, hardness to the law. Legal academics and practitioners approach an issue asking whether the law on point can reasonably be interpreted to support a position, here the one so well-articulated earlier by bioethicists. Our work in this area attempts to bridge legal
theory and practice through legal research and by talking to legal decisionmakers and those who interact with laws and the legal system.

Using what we call an iterative pathway approach, we map and analyze potential legal decision points throughout the research pathway. Attention to stakeholders who exercise decisionmaking power, including research agenda setters, regulators, institutional administrators, general and outside legal counsel, IRBs, researchers, and research participants, allows us to bridge the bioethics, legal academic, and legal practitioner domains to identify and deeply analyze legal issues affecting pregnant women’s inclusion in research. In that work, we attempt to assess whether a legal issue is real or perceived, and examine flexibility in legal interpretation that would support women’s inclusion in research and perhaps shift an advocacy focus to adoption of that interpretation or the need to address a cultural or other barrier to its adoption.

Some Insights from the Pathway Approach

Simplistically stated using a traffic light analogy, the pathway approach has allowed us to identify and analyze “red lights” to pregnant women’s participation in research and then prompted us to consider what it would take to turn those factors “green.” We examined legal obstacles (aka red lights) through traditional legal research and by consulting with legal experts in private, public, and academic settings. That work fed into our research on factors facilitating pregnant women’s participation (aka green lights), which was amplified by interviews we conducted with stakeholders in an academic institution that successfully and regularly conducts research with pregnant women.

Most significantly, our work as a whole reveals the importance of iterative collaboration with bioethicists, both in initial framing and in developing approaches to address issues. Just a few examples of our findings follow.

- Lawyers participate in decisionmaking at every stage of product development, from conception through marketing. This fact suggests that addressing the issue of pregnant women’s participation must include perspectives of legal decisionmakers, each of whom may have a different perspective on risk and the opportunity to prevent research with pregnant women from moving forward. Our green-light interviews indicated that overcoming those red lights requires, at a minimum, a foundational and thoroughgoing ethical commitment to the importance of including pregnant women in research and consensus that it should be done ethically and legally.

- Bioethicists often critique the regulatory language of subpart B as inflexible and constraining and rightly have spent significant effort analyzing “risk” and “benefit” in that context. A legal perspective, in contrast, offers a permissive view of the language of subpart B: Without official guidance on interpretation, so-called soft law, legal decisionmakers who are risk-averse can use that regulatory language to justify exclusion, disguising underlying financial, political, or other reasons for exclusion. By contrast, our
green light interviewees used the “flexibility” of regulatory language to arrive at regulatory interpretations supporting pregnant women’s inclusion in research, and then incorporated those interpretations into widely disseminated written policies and procedures. Arriving at those shared understandings required integrated discussions among all stakeholders, including bioethicists and regulatory experts. Lawyers play an important role in evaluating flexibility in the law, and bioethicists similarly are important in guiding ethical approaches to that flexibility.

- The bioethics literature has articulated liability for fetal harm as a hard obstacle to pregnant women’s participation in research. A legal perspective frames tort liability as an issue of risk mitigation—if a client wants to pursue an action, liability risk is assessed and managed. Difficulties in obtaining clinical trials insurance, for example, can affect that risk calculation. Green light work suggests that an institutional compensation plan for research-related injuries—an issue that has long been advocated by bioethicists and lawyers— is a possible factor facilitating research with pregnant women. Further, our preliminary legal research suggests that legal risk calculations may need to begin to consider countervailing concerns for liability for exclusion of pregnant women: pregnant women and their offspring who are injured by products on the market have begun to claim that manufacturers should be held responsible for foreseeable harm because of their failure to include pregnant women in clinical trials.

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1 Ironically, the scope of both tragedies could have been mitigated if pregnant women had been included in early clinical research (thalidomide) or attention had been paid to prior research on effectiveness (DES).
2 The relevant regulations, collectively referred to as Subpart B, permit the imposition of fetal risk in research with pregnant women in two cases: (1) If the proposed research has “no prospect of direct benefit” for the pregnant woman or fetus, and “the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means,” then the research may proceed if the “risk to the fetus is not greater than minimal;” and (2) If the proposed research offers the “prospect of a direct benefit” to the pregnant women, the fetus, or both, then risk to the fetus may exceed minimal risk, provided the “risk is the least possible for achieving the objectives of the research.” 45 C.F.R. 46.204(b-e).