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The perils of protection: vulnerability and women in clinical research

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Abstract Subpart B of 45 Code of Federal Regulations Part 46 (CFR) identifies the criteria according to which research involving pregnant women, human fetuses, and neonates can be conducted ethically in the United States. As such, pregnant women and fetuses fall into a category requiring "additional protections," often referred to as "vulnerable populations." The CFR does not define vulnerability, but merely gives examples of vulnerable groups by pointing to different categories of potential research subjects needing additional protections. In this paper, I assess critically the role of this categorization of pregnant women involved in research as "vulnerable," both as separate entities and in combination with the fetuses they carry. In particular, I do three things: (1) demonstrate that pregnant women qua pregnancy are either not "vulnerable" according to any meaningful definition of that term *or* that such vulnerability is irrelevant to her status as a research participant; (2) argue that while a fetus may be vulnerable in terms of dependency, this categorization does not equate to the vulnerability of the pregnant woman; and (3) suggest that any vulnerability that appends to women is precisely the result of federal regulations and dubious public perceptions about pregnant women. I conclude by demonstrating how this erroneous characterization of pregnant women as "vulnerable" and its associated protections have not only impeded vital research for pregnant women and their fetuses, but have also negatively affected the inclusion of *all* women in clinical research.

Keywords Pregnant women · Clinical research · Vulnerability · Research subjects

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Introduction

Part 46 of title 45 of the Code of Federal Regulations (CFR) identifies the criteria according to which research involving human subjects can be conducted ethically in the United States. In addition to listing the basic requirements for conducting research, including what is required for the Institutional Review Board (IRB) assessment of the ethics of the research, the regulations also include guidance for conducting research with groups identified as requiring "additional protections." Notably, Subpart A refers to such groups repeatedly as "vulnerable populations": "When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects" [1, §46.111b]. Only a few of the groups listed above have special sections dedicated to their "protections," notably, pregnant women, human fetuses, and neonates involved in research [1].

One clue to the potential rationale for including pregnant women as vulnerable is in the framing of the regulations. Subpart B of 45 CFR 46 "applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Department of Health and Human Services" [1, §46.201]. Subsection 204 details the conditions according to which pregnant women and their fetuses can be included in research. The considerations focus exclusively on the origin and magnitude of the risk to the fetus as compared with the potential benefits to the fetus or to the pregnant woman herself; no mention is made of risk directly to the pregnant woman [1, §46.204]. One might infer from this that it is the existence of the fetus alone that suffices to categorize the pregnant woman as "vulnerable." Yet it seems to me that this analysis misses important nuances of this classification.

In this paper, I will assess critically the role of this categorization of pregnant women involved in research as "vulnerable," both as separate entities and in combination with the fetuses they carry. In particular, I will do three things: (1) demonstrate that pregnant women qua pregnancy are either not "vulnerable" according to any meaningful definition of that term, *or* that such vulnerability is irrelevant to her status as a research participant; (2) argue that while a fetus may be vulnerable in terms of dependency, this categorization does not equate to the vulnerability of the pregnant woman; and (3) that any vulnerability that appends to women is precisely the *result* of the Federal Regulations and dubious public perceptions about pregnant women. I will conclude by demonstrating how this erroneous characterization of pregnant women as "vulnerable" and its associated protections have not only impeded vital research for pregnant women and their fetuses, but have also negatively affected the inclusion of *all* women in clinical research.

Before proceeding, however, it is useful to describe a few exemplar studies that may be helpful to keep in the back of one's mind when assessing the forthcoming analysis. Essentially, why should we care? Consider an experimental dental rinse that is not thought to be systemically absorbed. Some IRBs may judge, based on the

regulations, that pregnant women ought to be excluded from this research, despite its clear lack of probability of harm and potential for benefit. Or consider a more compelling case: research involving vaginal microbicides aimed at reducing the transmission of HIV. This is a product that will very likely be used by pregnant women in countries where other forms of HIV prevention may be less accessible or appropriate, and yet, pregnant women are often barred from participating in research on such products. This means that there will be few data available for those pregnant women who choose to use the product when it comes onto the market. And if I am right in my argument that the label of "vulnerability" has a negative impact on the inclusion of all women in research, the examples of inappropriate protections may go on and on (e.g., lesbians who refuse to take oral contraceptives to participate in a study of a new endocrine drug despite a zero rate of reproductive risk, etc.). Regardless, thinking about specific trials (and their subsequent exclusions) may enhance the salience of the analysis in this essay.

Concepts of vulnerability in clinical research

The CFR does not define vulnerability, but merely gives examples of vulnerable groups by pointing to different categories of potential research subjects needing additional protections [2]. For example, the CFR requires IRBs to have individuals "knowledgeable about and experienced working with" members of vulnerable groups [1, §46.107a], and to be "particularly cognizant of the special problems of research involving vulnerable populations" [1, §46.111a3]. The closest the CFR comes to outlining essential characteristics of these groups is in the section detailing criteria for IRB approval of research. In this section, the regulations include language that says "when some or all of the subjects are *likely to be vulnerable to coercion or undue influence*… additional safeguards have been included in the study to protect the rights and welfare of these subjects" [1, §46.111b, emphasis added]. We will return to these criteria shortly.

In fact, the concept of vulnerability in clinical research remains enigmatic. Attempts to define vulnerability in this context include: susceptibility to exploitation [3], those at an increased likelihood to incur "additional or greater wrong" [4], and facing "a significant probability of incurring an identifiable harm while substantially lacking ability and/or means to protect oneself" [5]. Linking the concept of vulnerability to specific protections is another strategy; the Consortium to Examine Clinical Research Ethics suggests that the concept of vulnerability be replaced with the notion of "special scrutiny," and identifies three criteria that should trigger careful attention to a protocol and certain relevant features [6]. Others link vulnerability to the precise notions of that to which human subjects are especially vulnerable: issues with informed consent, the risk/benefit ratio in research, and the distribution of benefits and burdens are commonly cited [2].

The most productive attempt at discriminating carefully the concept of vulnerability in research has been done by Kipnis [7, 8]. Kipnis expressly challenges what he terms the "subpopulation view" of the concept of vulnerability

in research and, instead, replaces it with analytical categories. He identifies seven[1] exhaustive categories that are meant to identify the morally relevant features of vulnerability. He argues that this analysis serves three purposes: (1) to provide a "checklist of circumstances that, along with other conditions, can invalidate the permissibility of research"; (2) to identify the necessary features of vulnerability and determine the "supplementary measures" required to address these vulnerabilities; and (3) to serve as grounds for adjudicating an investigator's culpability in taking unfair advantage of a particular population [7, p. G6]. A group is considered "vulnerable" if there is a positive response to any of the questions that obtain to a particular analytic category. The categories and corresponding questions can be found in Table 1.

In the following section, I apply Kipnis's definitions of vulnerability in clinical research to pregnant women as a group as a mechanism for analyzing the suitability of the "additional protections" required by the CFR. Given the comprehensive nature of Kipnis's categorization of vulnerability, what I will show is that if pregnant women cannot be considered vulnerable by one of these sets of criteria in a way that is relevant to their participation in research, then there is no justification for the kinds of regulatory restrictions levied by the Common Rule to protect them as "vulnerable" research participants. Ostensibly, the additional protections exist to safeguard the rights and welfare of pregnant women as research subjects. What this analysis will demonstrate, however, is that not only do these protections *not* achieve this stated goal but, in fact, may themselves contribute to the harm of individual pregnant research participants or to pregnant women more generally as a class of subjects.

Pregnant women as "vulnerable" subjects

So on what basis do pregnant women deserve additional protections when they are research participants? Applying Kipnis's criteria enables us to answer that question.

Cognitive vulnerability

Cognitive vulnerability obtains when potential participants have some intellectual barrier to participating fully in an informed consent process. Kipnis refers to this form of vulnerability in later works as "incapacitational" vulnerability to point to its key feature: the inability of a potential subject "to deliberate about and decide whether to participate in the study" [8, p. 111]. Some of these vulnerabilities may be

[1] In his earlier, more general, work on vulnerabilities in research [7], Kipnis identifies six exhaustive categories. However, in a later work on pediatric vulnerability [8], Kipnis identifies seven varieties of vulnerability. All but one of those varieties are either included or subsumed in the work presented to the National Bioethics Advisory Commission [7]. However, since the one type of vulnerability not expressly included—social vulnerability—is crucial to my analysis of the inclusion of women in research, I have included it in both the table and the narrative account of analytic vulnerabilities. Since I take Kipnis to be concerned with the same fundamental project in both works, this strikes me as a legitimate move.

Table 1 Kipnis' categorizations of vulnerability in clinical research (assembled from [7, 8])

Cognitive: Does the C-S have the capacity to deliberate about and decide whether or not to participate in the study?
Juridic: Is the C-S liable to the authority of others who may have an independent interest in that participation?
Deferential: Is the C-S given to patterns of deferential behavior that may mask an underlying unwillingness to participate?
Medical: Has the C-S been selected, in part, because he or she has a serious health-related condition for which there are no satisfactory remedies?
Allocational: Is the C-S seriously lacking in important social goods that will be provided as a consequence of his or her participation in research?
Infrastructural: Does the political, organizational, economic, and social context of the research setting possess the integrity and resources needed to manage the study? [7, p. G6]
Social: Does the C-S belong to a group whose rights and interest have been socially disvalued? [8, p. 114]

C-S Candidate-subject

immediately remediable, to wit, the presentation of protocol information in clear language (free of jargon), additional educational measures, and, when appropriate, effective uses of surrogates, while others, such as mental retardation, dementia, and some forms of mental illness, may not be amenable to immediate resolution [7, p. G7].

Notwithstanding differences among individuals, there is no evidence to suggest that pregnant women qua pregnancy lack the intellectual or educational experience to enable them to make an informed choice about participation in research. There is some evidence that women in active labor have impaired recall of the informed consent process when assessed post-delivery, which, some have suggested, indicates diminished decisional capacity during labor and delivery [9, 10]; others dispute these findings [11, 12]. Yet even if we are persuaded that women may have diminished cognitive ability during active labor, this fact should not preclude the vast majority of research that would be conducted outside of this small window.[2] Indeed, it is standard practice to involve the woman in decision making throughout her pregnancy precisely because this is the way to respect the autonomy of an individual who is cognitively intact. Note that the inclusion of women's preferences does not mean automatically acceding to them, especially when a woman's preference may conflict with other ethical principles of the physician or of medicine in general [13–15]. But elucidating and respecting a woman's preferences are one important part of good clinical practice. And while the context of research differs markedly from that of clinical care, there is no reason to think that a pregnant woman's *cognitive functioning* is the vulnerability making feature of research.

Some here will argue that the cognitively vulnerable entity is not the woman, but the fetus itself. To the extent that the fetus lacks deliberative capacity, they would argue, it is up to others to ensure that the welfare of the fetus remains an important feature in the risk/benefit analysis of the proposed research. Even if we grant this

[2] It may also not preclude research conducted during this window, provided that adequate safeguards (consent discussions during prenatal care, etc.) are in place.

claim, it is unclear why the pregnant woman herself is not in the best position to incorporate these considerations into her deliberations about participation in research. Certainly, this is the standard in the analogous case of research involving children; given a child's cognitive vulnerability (i.e., underdeveloped cognitive processes that often result in children valuing short-term gain over considerations of long-term risk), the parent is considered to be the most appropriate decision maker. And in response to those who cite a potential conflict of interest between the health of the mother and the welfare of the fetus, which would impair deliberation, the same could be said for pediatric cases. Yet, we recognize that despite (or because of?) this potential conflict, parents are often best suited to make decisions that are in the best interests of their children.

Regardless of who remains the appropriate decision maker in this case, it should be clear that while the cognitive incapacity of the fetus does imply the need for a surrogate decision maker, the cognitive vulnerability of the fetus does not imply a similar cognitive vulnerability for the pregnant woman. In respect to cognitive capacity alone, fetal vulnerability does not equate to maternal vulnerability.

Juridic vulnerability

Juridic vulnerability obtains in situations in which others have legal authority over the decisional processes of someone. Common examples of these social situations are parents over children, wardens over prisoners, and military commanders over enlisted soldiers. But this category will also include those with special, albeit temporary, sorts of "control," like professors over students and attending physicians over their trainees [7, p. G7] and those whose social structure confers authority, like that of "third-world women who are legally subject to their husbands" [8, p. 112]. The vulnerability creating feature here is the extent to which consent or permission to participate in a study reflects the desires and values of the surrogate decision maker rather than of the potential participant herself, given that she may not be in a position to make a decision based on a true exercise of her preferences. Researchers can make provisions to discuss the protocol separately with the potential subject (this is, in fact, standard practice for adolescents in research), but the ultimate decisional authority will rest with the surrogate decision maker.

To the extent that the fetus is inseparable from the pregnant woman, I suppose one could claim that the fetus is juridically vulnerable. However, the concept of legal authority fails to capture much that is meaningful about the relationship between the pregnant woman and the fetus. Regardless, the federal regulations do confer juridic authority to *both* the biological mother and biological father in certain instances of research; namely, when the research holds out the prospect of direct benefit solely to the fetus (provided that the father is not unavailable, incompetent, or temporarily incapacitated, or that the pregnancy resulted from incest or rape) [1, §46.204e]. The parallel to this situation in the regulations is for research involving children that is greater than minimal risk to the child [1, §406–407]. In those cases, consent from both parents is required (with exceptions similar to those listed above).

So the "protections" offered for the juridically vulnerable fetus, then, are the same as for children being considered for research that is greater than minimal risk.

The justification for two parent consent in the latter case is that the increased level of risk requires an increased level of protection. Ostensibly, the child's welfare is better safeguarded with both parents providing permission for research participation than simply one parent doing so.[3] The implication with fetuses, therefore, is that all research involving the potential for direct benefit to the fetus alone must be considered to be of a sufficient risk to require what is known as "two parent consent." Yet recall that the fetus exists dependently with the woman, so that any risk to the fetus *is also a risk to the woman*. Rare instances of fetal surgery, for example, confer significant risk (but the possibility of benefit) on the fetus, but also involve surgical procedures on the woman herself. The implication of conferring juridic authority on the father, then, is that it gives him the power to consent for research that will happen to someone *who does not lack decisional authority*. This is odd, to say the least. The regulations remain silent on what happens if the mother and the father disagree about research participation in these instances, although presumably refusal by one would fail to meet the criteria that consent is obtained by both parties. Regardless, the purported juridic vulnerability of the fetus has the paradoxical effect of *making* the pregnant woman juridically vulnerable, which gives others authority over choices affecting her own body—a situation we would judge unethical in any other population retaining cognitive decisional capacity [16]. Therefore, as it stands, the regulations do *not* protect the rights and welfare of pregnant women who are research participants; rather, they serve to *create* additional vulnerability for the pregnant women.

Deferential vulnerability

Deferential vulnerability refers to patterns of behavior of the individual where she routinely or typically transfers decisional authority onto others, even if there is no legal reason to do so. Kipnis argues that this form of vulnerability may in fact mask an individual's true desires by the impetus to accede to the wishes of others [8, p. 113]. What is important to note here is that an individual's social situation may confer this kind of vulnerability, but so too may the health care environment itself. The key feature of this form of vulnerability is the external pressures a potential research participant can feel to cooperate with the wishes of others.

Importantly, deferential vulnerability in pregnant women may have the opposite effect of what Kipnis argues obtains for children. For minors, acceding to the expectation of others may mean assenting to participation in research even when they would rather not. For pregnant women, on the other hand, the expectations of others are most often that she *refrain* from doing something—namely, anything that might have the potential to harm her fetus. This is true no matter the magnitude of risk to the fetus; researchers and policymakers have judged that exposing a fetus "…to a small, even miniscule, risk in the context of research that may entail even a large direct benefit to the woman (and probably to both woman and fetus) has seemed an unreasonable risk" [17, p. 14]. Lyerly et al. argue that this situation

[3] Obviously, there are cases when this is explicitly not the case, as when one parent has motives other than the child's best interests at heart, or when the parent is abusive, neglectful, or absent.

results in a "worrisome double standard" [17, p. 14]. Parents routinely subject their children to small risks—driving a car, playing football, etc. Some risk is an inescapable part of life, yet we seem to want to protect fetuses from any risk at any cost. This creates a standard to which we do not hold fathers or mothers, but to which we do subject pregnant women. Hence, deferential vulnerability creates a situation of injustice.

This reticence to expose a fetus to risk can be attributed to a "cultural anxiety" about the very idea of placing the fetus at risk for the sake of the pregnant woman [18]. Studies have shown that women take independent steps to protect their fetuses, sometimes on account of a poor information delivery process [19]; women often overestimate the fetal risk associated with medications during pregnancy, which may lead to unnecessary termination of a wanted pregnancy or to the failure of a women to get treatment even when this is safer than leaving a disease untreated [20, 21]. Yet the failure to treat conditions in pregnancy may result in harms to both the woman and her fetus [22, 23]. As a result, the harms of undertreatment in pregnancy may outweigh the risks of medication use. Additionally, since the vast majority of drugs prescribed to pregnant women are off label, the perception that clinical trials are riskier than taking prescribed medications is false [24]. The upshot of this is that deferring to social pressures or the prevailing wisdom about pregnancy may result in increased harm for both the pregnant woman and the fetus.

Medical vulnerability

Serious, irremediable health conditions create contexts of medical vulnerability. This includes incurable conditions like HIV and metastatic cancer, but also includes circumstances where available therapies are inappropriate for particular individuals because of their expressed values or preferences (e.g., blood products for a Jehovah's Witness) [7, p. G8]. In the research context, medically vulnerable patients are often specifically recruited because of their disease, but the fact that they are left with few other options makes them liable to consent to a protocol regardless of the attendant risks; essentially, this is an instance of "forced choice" [7, p. G8]. However, as Kipnis notes, "forced choices alone do not annul consent" [8, p. 115]; rather, investigators should be encouraged to consider carefully the context of the research to ensure that there is a fair sharing of benefits and burdens precisely because of the "poor bargaining position" of the patient and/or the patient's proxy [8, pp. 115–116]. It may not be possible to do this in every case; "therapeutic misconception," where an individual agrees to participate in a trial because she erroneously believes she is likely to benefit from such participation, is a real and compelling concern. However, investigators can reduce the likelihood or the impact of this phenomenon by ensuring that the trial design itself maximizes benefit to the potential participants [8, p. 116]. In this way, research arrangements with medically vulnerable participants are less exploitative and better ensure a fairer distribution of benefits and burdens [8, p. 117].

While it is true that pregnant women may be selected for inclusion in research specifically because of their condition, it is not clear that such selection makes them medically vulnerable to the extent that they would be willing to take risks they

would otherwise deem unreasonable [8, p. 115]. There may be occasions, however, when the fact of pregnancy *coupled* with another medical problem confers medical vulnerability on the pregnant woman. The classic example would be a pregnant woman with a newly diagnosed cancer. Yet, one could plausibly argue that the cancer is responsible for the medical vulnerability here, not the pregnancy, even though treatment decisions about one will invariably affect decisions about the other. Once again, such decisions fall into the category of "forced choice," which Kipnis persuasively argues do not annul consent by themselves, but which confers special responsibilities on the part of the researchers to ensure fairness in the arrangement with research participants [8, pp. 115–116].

It seems to me that the most plausible account of the ways in which pregnant women are medically vulnerable is as a direct result of the *lack* of inclusion of pregnant women in research. One large retrospective study found that two thirds of pregnant women were prescribed a drug "other than a vitamin or mineral supplement" during their pregnancy, and nearly half of those prescriptions involved a drug of either unknown teratogenicity or drugs that had demonstrated teratogenic effects [25]. Other studies confirmed the rate of overall exposure to prescription medications, but differed on the rates of drugs of unknown or teratogenic harm: some reported the rate to be as low as 8 % of overall exposure, while other studies report a rate as high as 19 % [26, 27]. When analyzing maternal characteristics of women who were likely to be exposed to this risk during pregnancy, the single most important determinant of exposure was chronic illness: the rate of exposure in women with a chronic health problem was four times as likely as those without comorbid conditions [27, p. 272]. This is a particular concern since, as Françoise Baylis notes, "pregnant women get sick and sick women get pregnant" [24]. Additionally, since approximately half of all pregnancies in the United States are unplanned [28], fetuses are exposed to medications when their mothers unexpectedly become pregnant [17].

What this means is that any of the medications used to treat women during pregnancy are used "off label," that is, without specific guidance from the FDA or the manufacturer or data on their likely outcomes. We know that "pregnancy extends and alters the impact of sex differences on absorption, distribution, metabolism, and excretion of drugs—often times in ways that are both dramatic and difficult to predict" [17, p. 8]. The upshot is that clinicians have little solid evidence for prescribing practice in pregnant women, as even their previous clinical experience may be untrustworthy since pharmacokinetic parameters vary significantly with pregnancy [17, 24, 29, 30].

This does more than create a situation of uncertainty; rather, it is a failure to respect the principle of justice. Pregnant women deserve to have effective treatment during pregnancy, and this goal can only be fostered by responsibly including pregnant women in clinical research [24]. As Lyerly et al. argue, "a pregnant woman is not just a woman with a bigger belly … if we are to treat pregnant women's illnesses effectively—something crucial to the health of *both* pregnant women and that of the children they may bear—we must study medications in pregnant women" [17, p. 9].

Kipnis argues that with instances of medical vulnerability, justice demands that the trials be scientifically sound, and that individuals be not prohibited from

experiencing the potential benefits that may result from the trial. Standard practice in clinical research that involve pregnant women has routinely violated the first criterion. If a woman gets pregnant during the course of a clinical trial, she is removed from the trial and followed to obtain data about her pregnancy. But, as Ruth Macklin argues, this is "faulty science"; harm to a fetus can occur at any gestational stage, and therefore, the effect of investigational agents should be studied throughout pregnancy [31]. Doing "good" science coheres with what Lyerly and others have argued regarding the responsible inclusion of pregnant women in research: access to research, not just protection from its risks, must be an integral consideration in the ethics of clinical research [17, 32, 33].

With regard to Kipnis's second criterion of justice, consider clinical trials that have the prospect of direct benefit, such as the microbicides that aim to prevent maternal and fetal exposure to HIV infection. It is not the case that we should disregard fetal risk in these cases; rather we should consider them in the context in which they occur—in this case, a very real threat of a serious illness to both the woman and the fetus [17, 33]. "When a clinical trial is the only way pregnant women with a life-threatening condition could have access to the only possible beneficial treatment that is still under investigation, then it is essential to include them" [31, p. 632].

Critics may once again claim that we are missing the boat here—that it is the fetus that is medically vulnerable in pregnancy, not the pregnant woman. In fact, a study in 2002 found that teratogenic risk in human pregnancy was still undetermined in 91.2 % of therapeutic treatments approved by the FDA between 1980 and 2000 [34]. A more recent review found that teratogenic risk in human pregnancy was undetermined in 168 of 172 drugs approved by the FDA from 2000 to 2010 [35]. Additionally, once a medication is approved for use, there is no requirement that the drug manufacturer collect or investigate adverse pregnancy outcomes [30, 36].

Yet, if the concern is solely about fetal risk of exposure to agents during pregnancy, then there is a compelling argument that pregnant women *must* be included in clinical research. For one thing, relying on observations from clinical practice is simply impractical. Adam and colleagues estimate "the mean time necessary to assign a more precise risk to treatments initially judged to have an 'undetermined' risk to be twenty-seven years" [35, p. 179]. This is far too long to wait for the health of pregnant women and fetuses.

Secondly, consider the implications of drugs that are, after clinical observation, associated with fetal harm. Lyerly et al. ask us to consider the case of ACE inhibitors, which are widely prescribed to treat hypertension. Because no rigorous studies were done that included pregnant women, the only way the teratogenicity of the drugs was discovered was through three decades of poor outcomes. Had this class of drugs been studied earlier in pregnant women, these outcomes might have been avoided [17]. As a result, concerns about the medical vulnerability of the fetus—as well as the pregnant woman—argue for the greater inclusion of pregnant women in research, not for preventing them from enrolling in clinical trials.

Allocational vulnerability

Some pregnant women may be lacking in important social goods that may be provided to them as a condition of participating in research. Goods such as increased access to health care or even monetary compensation that will enable her to pursue other projects (such as feeding herself or her family) may encourage the woman to disregard risks she would normally consider unreasonable in favor of obtaining these goods. Kipnis compares this situation to one of a job seeker who agrees to a fair employment arrangement, even if he had no other options to consider [8, pp. 117–118]. In situations of allocational vulnerability, Kipnis directs our attention to the substance of the bargain: ensuring that the weaker party still makes out fairly, and that there is a just sharing of the benefits and burdens of the research [8, p. 118].

It is not clear that pregnant women disproportionately suffer from allocational vulnerability in comparison to the rest of the population. To the extent that they may be more inclined to agree to research participation by virtue of the receipt of additional goods and services, those discrepancies should be minimized. Fair compensation is a topic beyond the scope of this paper, but suffice it to say that to the extent that pregnant women lack social goods as a function of their pregnancy, investigators must address this vulnerability by ensuring the fairest distribution of benefits and burdens possible given the nature of the study.

Infrastructural vulnerability

The concern with infrastructional vulnerability rests on the political, organizational, economic, and social context of the research setting [7, p. G11]. These challenges most clearly arise in the context of international research, where a host country's infrastructure may make participation in research morally problematic. For example, there may be inadequate safeguards for the protection of participants, or there may be inadequate resources for the safe and ethical conduct of a clinical trial. Regardless, infrastructural vulnerabilities require attending to the particular context of the proposed trial and the likely implications for human participants.

Attending to the situations in which women find themselves reveals infrastructural vulnerabilities.[4] Women, whether pregnant or not, often are the primary caregivers for their children, and therefore, researchers must make provisions for childcare should they expect women to be able to attend the clinic for regular research appointments. Similarly, making transportation to the clinic available may also be necessary; the woman who has to change buses three times just to get to the clinic may be less likely to participate in research than the woman who can jump on a shuttle to get her to her research appointments.

Some individuals cite liability concerns for including pregnant women in clinical trials. To the extent that pregnant women are vulnerable to the legal system, this kind of vulnerability could be considered infrastructural. Yet, legal precedent does not support the concern about increased liability. Rather, sponsors and investigators

[4] See, e.g., [37], under the heading "Understanding cultural differences in clinical trials."

may be subject to suit whether or not pregnant women are included.[5] Some have argued that they can best reduce their exposure by providing adequate informed consent to pregnant women enrolled in their studies [33].

Social vulnerability

Social vulnerability[6] obtains when "entrenched prejudice and stereotypical thinking can compromise the care and consideration that would normally be present" [8, p. 114]. The concern here is that the overall social context of the potential participant may adversely affect the way protocols are designed, reviewed, and implemented; stigmas are likely to influence each of these stages of research [8, p. 114]. In his work on pediatric vulnerability, Kipnis expresses worry that acting in the "best interests of children" often results in those with authority disregarding or dismissing "opinions, judgments, and preferences advanced by the young."

Without question, the category of vulnerability to which pregnant women are subject most regularly is social vulnerability. We expect pregnant women to conform to a host of social expectations, whether or not those expectations have any evidence-base or connection to real benefits for the fetus [38]. Consider routine electronic fetal monitoring (EFM) in pregnancy: "randomized controlled trials of EMF have demonstrated statistically significant increases in instrumental and cesarean deliveries for women but provides no long-term benefits for children" [39, p. 1397]. Yet this practice has become standard of care. Grimes and Peipert argue that this public health measure has been erroneously used to predict (badly) rare conditions in the fetus, yet we continue to use the technology despite the demonstrated lack of clinical efficacy [39].

In the context of research, this gets worked out in terms of an attitude of protectionism towards the fetus. The regulations make it clear that risk to the fetus is the operative concern, and therefore, that all decisions—and decision makers—should focus on ways to minimize risk to the fetus, sometimes at great cost to the pregnant woman herself.[7] This concern stems from historical instances like that involving Thalidomide, where babies were born with severe birth defects as a result of the medication. The irony, of course, is that such disasters resulted from *excluding* women from clinical trials. In fact, had rigorous studies been done of this and similar drugs, the magnitude of the problem would likely have been attenuated [17, 36]. Instead, the response has been to exclude pregnant women—and most women of childbearing potential (see below)—from clinical trials. As Ruth Macklin

[5] It is impossible to know the magnitude of the risk on either side, especially because pregnant women are routinely excluded from clinical trials. Investigators worry about liability for fetal harm conferred during research, however, women can also sue drug manufacturers and physicians for drugs prescribed in clinical care that are not well studied [33]. In either case, disclosure of known information about teratogens—as well as gaps in knowledge—are essential.

[6] This variety of vulnerability is described in Kipnis's work on pediatric vulnerability but has clear implications for a much wider group of participants in clinical trials (see footnote 1).

[7] For instance, consider the physician who refuses to perform standard imaging on a pregnant woman with an indication of appendicitis for fear of harming the fetus, when evidence demonstrates that "delayed diagnosis and appendicle rupture carries a tenfold risk of miscarriage" [17, p. 5].

argues, "the most compelling reason [for including pregnant women in a greater number of clinical trials] is the need for scientific evidence gathered under rigorous scientific conditions, in which fewer women and their fetuses would be placed at risk than the much larger number who are exposed to medications once they come to market" [31, p. 632].

Importantly, it is not just women themselves who are subject to these social pressures; health care practitioners are also victims of these values. There is "the tendency in pregnancy (more accurately, the tendency until we get to labor and delivery) to notice the risks of intervening to the exclusion of noticing the risks to the woman and the fetus of *not* intervening" [17, p. 12]. Consider the resident who hesitates to resuscitate a pregnant woman who has experienced cardiac arrest because of the concern that one of the drugs might be teratogenic [17]; or consider the neurologist who hesitates to treat a seizure disorder because of the risk of fetal anomalies associated with the preferred therapy [21]. Consider also the desire to remove pregnant women from *all* medications, regardless of the underlying condition or the fact that failure to treat a pregnant woman's asthma or depression (for example) increases the likelihood of poor outcome for the fetus and woman alike [17, 22, 23, 40]. Internationally, there has been "significant underinvestment by pharmaceutical companies in maternal health," which is at least partly attributable to the risk-averse stance of society [41].

Without question, there needs to be careful consideration of how best to include pregnant women in research; it is no accident that Lyerly et al. use the word "responsible" in every publication referring to this "second wave" of inclusion of pregnant women in research. Yet rather than work collaboratively to create such a framework, "the cultural tendency is to retreat from the idea of risk rather than confront the need to make reasoned and responsible decisions about it" [17, p. 15]. Lyerly et al. argue that what we need in research is not simply an avoidance of risk, but a careful consideration of the costs that accompany such an attitude of avoidance—costs for both the pregnant woman and her fetus. Fisk and Atun argue that a system that promotes wide-spread use of off-label drugs, as is the case in maternal health, discourages the creation of clinical trials, especially when there are other market disincentives (e.g., limited market size and industry model) [41]. Instead, closing the "regulatory gaps" that permit off-label use, coupled with the creation of incentives for investing in research and development of drugs for maternal health will create a culture of responsible and acceptable care for the health of all members of society [41].

Implications of vulnerability for all women in clinical research

Until fairly recently, women—whether pregnant or not—have been excluded from participation in pharmacologic research. In fact, it was not until 1993 that the FDA withdrew restrictions on the participation of women in clinical trials. The rationale cited was that the "risk of fetal exposure can be minimized by patient behavior and laboratory testing, and … initial determinations about whether that risk is adequately addressed are properly left to patients, physicians, local IRBs, and

sponsors, with appropriate review and guidance by FDA…" [42, p. 39408]. Note here the deferential concern for the risk of the fetus, which is particularly concerning since none of the women in question are actually pregnant; the existence of the fetus remains hypothetical. However, this is the first explicit regulatory statement that gives women, in consultation with their physicians, authority over decisions about the appropriateness of research participation. Yet it was not until 1997 that the FDA actually *encouraged* researchers to include women in clinical trials, a move that was largely based on the 1994 report by the Institute of Medicine Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Research that recommended the inclusion of women in clinical trials [32].

Historically, women were included in research only to the extent that their inclusion gave important information about others: most frequently, their sexual partners and their fetuses [33]. Ruth Faden, Nancy Kass, and Deven McGraw refer to this view as valuing women as "vessels and vectors" of disease [43]. In these instances, women are not viewed as research ends in themselves, but rather, as a mechanism for obtaining data about others with whom they are in intimate contact. To the extent that a research intervention can give us information about protecting or benefitting others, women were valued as research participants.

While women now constitute roughly half of all participants in NIH-funded clinical trials [44], analyses of published trials consistently demonstrate low enrollment of women and lack of reporting of gender-based subgroup analysis [45]. Despite encouragement from both the FDA and the IOM to include women in clinical trials, sponsors and investigators remain wary. In 2007, a review article appeared in the *Journal of the American Medical Association* about the eligibility criteria of randomized controlled trials published in high-impact medical journals. Conditions related to sex were grounds for exclusion in 47 % of trials—male sex only accounts for 7.8 % of those exclusions [46]. The authors recommended that the inclusion of women could allow the safety and efficacy of investigational agents to be determined *prospectively* in a highly monitored setting, which could result in increased generalizability to those at risk.

Hesitation on enrolling women of childbearing potential in clinical trials stems from two fronts: (1) the difference in women's physiology introduces an added variable to the study, and (2) the harm that might come to a fetus should the woman become pregnant while in the study [47]. The first concern is one of scientific rigor. Women and men are physiologically different so it is difficult or impossible to obtain "clean" data from gender integrated trials. This is, essentially, a bias towards the universality of the male body over the female body for the purposes of scientific investigation: research should be done on the paradigmatic form of the human, and then extrapolated to the variant. However, the assertion that "clean data" is preferable refutes itself: if the data obtained from a mixed population (men and women) is so different from that generated by studying only one population, then how can it later be extrapolated to a real world with multiple populations? From the point of view of the women, the data are not "cleaner," they are inadequate [18]. The Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies of the Institute of Medicine had the following recommendations for researchers [32, pp. 57–58]:

1. Medical research must be more gender balanced in order to facilitate the "health and well-being of women and men;"
2. Preferential research attention may be justified in areas where research has been lacking as a way to rectify injustice; and
3. Clinical trial recruitment should not discriminate based on gender, race, ethnicity, or age in order to increase the generalizability of results.

It is with the second concern, however, that we get the parallel to the concerns for clinical research involving pregnant women. To the extent that "all women are always pregnable and therefore always pregnant" [18], the very same concerns that apply to research involving pregnant women also have an impact on non-pregnant women. Sponsors and investigators take it as given that pregnant women ought not be included in clinical research, and as a result, many women are deprived of the benefits of participation in research because they have the *potential* to become pregnant. My colleagues and I have argued elsewhere [48–51] about the compromise investigators and sponsors often reach with participants about this issue—namely, the use of contraception in research—yet it seems to me that the real difficulty here is the overarching assumption of vulnerability. This is the true danger of classifying pregnant women as vulnerable subjects in a non-reflective sense of the term: since many investigators view women simply in terms of pregnancy (Merton's classic article title is relevant here: "The exclusion of pregnant, pregnable, and once-pregnable people (aka women) from biomedical research"), any vulnerability conferred on pregnant women necessarily is extended to *all* women.

Yet, what I have tried to show here is that by carefully analyzing the concept of vulnerability as it relates to pregnant women, it becomes apparent that the continued exclusion of pregnant women from clinical trials is the very thing that *perpetuates this vulnerability*. Regulations are not created in a vacuum; rather, they are a product of the individuals, societies, and cultures that create them as a reflection of the operant value system. To the extent that many pregnant women find themselves valued instrumentally in a culture (after all, what else are we to make of the regulations that focus exclusively on the risks to the fetus without consideration of risks to the pregnant women in whom the fetus resides?), the vulnerable character of their existence depends upon the deferential value placed on the fetuses that they carry. Only by recognizing that the well-being of the fetus and the pregnant woman are often integrally related will we be able to address the value and social structures that support the continued vulnerability of pregnant women.

Conclusion

It is beyond the scope of this paper to suggest the specific framework necessary for the responsible inclusion of pregnant women in research, although several scholars have made real progress in this arena [17, 24, 33, 52]. I agree with these commentators that researchers ought to take advantage of "low hanging fruit"—observational studies that incur no risk of harm to the mother or the fetus. However, the real regulatory challenges obtain when investigators consider prospective trials,

and this is where reform is most crucial. One step towards progress would be to learn more about how women make choices about research participation relative to reproductive risk [50, 53]. Relying on empiric data about women's decision processes may yield both improvements in the informed consent process and the bases on which new regulations can be formulated. In addition, careful analyses of the risks that are appropriate for children to assume in the context of research, as well as the appropriateness of the consent process, may also yield fruitful directions for revised policies [54–56].

What I have argued here is that the myriad vulnerabilities that obtain to pregnant women in clinical research are, in fact, merely contingent features of the society in which they reside. However, there are, one might argue, disproportionate risks that may be conferred on a pregnant woman whose fetus *does* suffer some adverse effect as a result of participating in clinical research, namely, the risk of caring for a child who may have special needs because of the effects of an investigational agent, or the burden of having to make a decision about terminating a wanted pregnancy. Yet, in no way does the concept of "vulnerability" capture these risks. Rather, I contend that the label of "vulnerability" may in fact obscure the unique risks attendant to particular populations, and therefore, makes it more difficult for IRBs to consider adequately the full range of risks of the proposed research. The concepts of vulnerability and risk are not coextensive.

Additionally, and perhaps ironically, remediation of the vulnerabilities discussed in this manuscript involves performing that very action that many have argued we avoid—namely, the responsible involvement of pregnant women in clinical research. Not only does failure to do so increase the risks to both the pregnant woman and her fetus, but it also risks the health and well-being of *all* women, as this culture of protectionism in research expands. It is clear that we need changes to the regulations in order to include pregnant women more broadly, but there first needs to be recognition of the damage that our social prejudices are having on women's health. Only then will we be ready to create a robust research framework that not only protects *all* of those at risk for harm, but also reflects an ethic of justice and respect.

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