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The second wave: Toward responsible inclusion of pregnant women in research

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Abstract

Though much progress has been made on inclusion of non-pregnant women in research, thoughtful discussion about including pregnant women has lagged behind. We outline resulting knowledge gaps and their costs and then highlight four reasons why ethically we are obliged to confront the challenges of including pregnant women in clinical research. These are: the need for effective treatment for women during pregnancy, fetal safety, harm from the reticence to prescribe potentially beneficial medication, and the broader issues of justice and access to benefits of research participation. Going forward requires shifting the burden of justification from inclusion to exclusion and developing an adequate ethical framework that specifies suitable justifications for excluding pregnant women from research.

Introduction

In the 1990s, prominent reports emerged indicating that women were underrepresented in biomedical research. By now, the findings are well-known: many significant studies on aging and heart disease were performed without adequate representation of women, and the health concerns of women were frequently under-investigated (General Accounting Office 1992; Merton 1996). Also well-known by now is the progress made following the establishment in the United States of the Women's Health Initiative at the National Institutes of Health (NIH) and the passage of the NIH Revitalization Act of 1993, with provisions that each NIH-funded study include representative samples of subpopulations unless their exclusion can be justified on a basis other than cost. More than a decade later, though some disparities have persisted (Chronic Disease Prevention and Control Research Center at Baylor College of Medicine and Intercultural Cancer Council 2008), women now make up the majority of participants in clinical research (General Accounting Office 2001).

Although progress was made on the inclusion of non-pregnant women in research, thoughtful discussion of how to reason about the inclusion of pregnant women in clinical research lags

²The U.S. Food and Drug Administration classifies medications in one of the following five categories: (a) adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters); (b) animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well controlled studies in pregnant women; (c) animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; (d) there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; (e) studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

³We are grateful to Andrea Kalfoglou for bringing this to our attention.

⁴Personal communication of Dr. David Grimes, Clinical Professor of Obstetrics and Gynecology, University of North Carolina Chapel Hill (Chapel Hill, North Carolina, USA) with A. Lyerly on 31 August, 2005 via email.

⁵Personal experience of A. Lyerly.

far behind. Despite a 1994 Institute of Medicine report recommending that pregnant women be “presumed eligible for participation in clinical studies” (Mastroianni, Faden, and Federman 1994), many researchers and institutional review boards (IRBs) continue to regard pregnancy as a near-automatic cause for exclusion, regardless of the costs of exclusion or the magnitude or likelihood of the risks of participation.

This reticence brings with it a profound cost. Of the more than four million women giving birth in the United States every year (Martin et al. 2007), many face medical conditions during their pregnancies that require clinical treatment, but they lack adequate data to inform their care. Indeed, chronic diseases during pregnancy are common: chronic hypertension and diabetes each complicate nearly 4 percent or 40,000 pregnancies each year (Martin et al. 2007); an estimated 500,000 pregnant women experience psychiatric illness (American College of Obstetricians and Gynecologists 2007); cancer, autoimmune disease, and a plethora of other conditions commonly occur with pregnancy and often require treatment. Further, gestation engenders a host of pregnancy-specific conditions that range from difficult (extreme nausea and vomiting) to disabling (sciatic nerve compression) to life-threatening for the woman or her fetus (preeclampsia). Pregnancy is not a prophylaxis against medical illness.

Yet only a dozen medications are approved by the United States Food and Drug Administration (FDA) for use during pregnancy. All of them are medications for gestation- or birth-related issues, such as regional anesthesia, nausea and vomiting, the prevention of congenital malformation, and the induction or delay of labor (Haire 2001). Any medication used to *treat illness* during pregnancy—be it hypertension, diabetes, depression, or cancer—is used without approval from the FDA, often leaving doctors and patients alike worried whenever they face decisions about using medication during pregnancy. Pregnancy, it turns out, is an “off label” condition.

In contemplating treatment of these conditions, an overarching concern, for providers and women alike, is of course the safety of medication for the fetus. Medications can cross the placenta and irreversibly affect fetal growth, structure, and function. Newer research has shown how environmental, nutritional, and other health factors during pregnancy can have an impact on an offspring's gene expression (Jirtle 2008). These potentially profound implications ground the reluctance in the research community to include pregnant women in clinical investigations.

Unfortunately, this conservative stance turns out to enhance neither fetal nor maternal safety. Certainly, guidelines for research in pregnancy must include careful and responsible criteria for protections. Consideration of fetal well-being will, in any framework, constitute a crucial component in shaping criteria for inclusion; further, as in any research involving a party whose capacity for consent is limited or absent, such as children, inclusion will require extra layers of protection and scrutiny of the risks, benefits, and alternatives. But currently, there are few opportunities for such a framework to be applied. With pregnant women effectively deemed untouchable in the research community, obstetricians care for their patients without meaningful data regarding the safety and efficacy of most of the medications used in pregnancy.

In what follows, we review the price of turning a blind eye to pregnancy in research and research ethics. We describe both the knowledge gaps around the use of medication during pregnancy and their costs, highlighting four reasons why ethically we are obliged to confront the challenges of including pregnant women in clinical research studies: the need for effective treatment for women during pregnancy, considerations of fetal safety, the harm from reticence to prescribe potentially beneficial medication, and the broader issues of justice and access to the benefits of research participation.

The costs of exclusion

Effective medical treatment for women during pregnancy

The first reason to confront the challenges of including pregnant women in research is a simple one: women need effective treatment during pregnancy. Without adequate research on how drugs are metabolized during pregnancy, we have very little evidence on how to treat illnesses when they occur in the pregnant body.

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. Pregnancy-related changes in the gastrointestinal tract, the cardiovascular system, the kidneys, and other organs may profoundly alter the ways that drugs are processed by the body (pharmacokinetics) or the ways that drugs act on the body (pharmacodynamics) (Mattison and Zajicek 2006). For instance, a 30–40 percent increase in blood flow through the kidneys means that some medications are cleared at much higher rates during pregnancy (Mattison and Zajicek 2006). Increases in blood volume, decreases in gastric emptying time, changes in the concentrations of sex hormones, alterations in liver enzymes, the presence (to say the least) of a fetal-placental unit, can all alter the activity of a drug. In the end, the pregnant body processes and eliminates drugs in ways that may differ both surprisingly and substantially from the non-pregnant body processing the same substance.

Indeed, evidence suggests that pregnancy often acts as a significant wild card in clinical management. In a 1999 review of the literature reporting pharmacokinetic differences between pregnant and non-pregnant women, the sixty-one studies reporting on pharmacokinetics during pregnancy revealed little or no consistency of results in studies during pregnancy, even for the same class of drugs or the same drug (Little 1999). Sometimes the pharmacokinetic parameters increase, sometimes they decrease, and sometimes they stay the same, suggesting that intuition and even clinical experience may not be trustworthy.

Opportunistic studies of drug metabolism and activity during pregnancy corroborate. In 2003, the Obstetric-Fetal Pharmacology Research Unit (OPRU) Network was founded through the United States National Institutes of Health to identify, characterize, and study drugs of therapeutic value in normal and abnormal pregnancies (Zajicek and Giacoia 2007). Initial studies generated findings that are of concern. For instance, pharmacokinetic measurements on a pregnant woman receiving chemotherapy during pregnancy revealed that the drug was so quickly and thoroughly metabolized and excreted by her pregnant body that the drug never approached a therapeutic range, despite the fact that she and her fetus were exposed to its toxicities.¹

Of potentially even broader applicability are the implications of knowledge regarding amoxicillin pharmacokinetics during pregnancy. Given heightened concern about bioterrorism, the American College of Obstetricians and Gynecologists (ACOG) recommended using amoxicillin for post-exposure prophylaxis in pregnant women in the setting of penicillin-sensitive bacteria (American College of Obstetricians and Gynecologists 2002). Yet a 2007 OPRU study revealed that concentrations of amoxicillin adequate to prevent anthrax may be unachievable during pregnancy due to altered kidney function and that amoxicillin ultimately may not be an appropriate antibiotic for post-anthrax exposure prophylaxis (Andrew et al. 2007).

With regard to dosing medications, our best predictions can be disastrously wrong. But predictions are largely all that physicians and policymakers have for making decisions. The

¹Personal communication with M. Little during meeting of the Obstetric-Fetal Pharmacology Research Unit (date?), Washington DC.

same 1999 review that highlighted the variability in pharmacokinetic parameters also highlighted standardized pharmacokinetic studies as a major area of need (Little 1999). Of more than one thousand articles published on pregnancy pharmacokinetics, only sixty-one reported relevant pharmacokinetic data, and only two synthesized data into guidelines for clinical care. When physicians prescribe medications during pregnancy, they do so in the absence of data regarding the dosage required to achieve the desired therapeutic result.

As often is said in research ethics, there is no one-size-fits-all research subject. Children are not just small adults; women are not just men with a bit less on-average muscle. Developmental stage and gender make a difference in how drugs act in the body and how the body acts on drugs (Mattison and Zajicek 2006). So, too, with gestation—a pregnant woman is not just a woman with a bigger belly. The maternal-fetal-placental system brings its own pharmacokinetics and dynamics. 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.

Fetal safety

The second reason to address the challenges of including pregnant women in research is the very same reason that is given for excluding them—fetal safety. Given their medical needs, pregnant women *do* use medications during pregnancy. The average woman receives 1.3 prescriptions per obstetric visit (Lee et al. 2006), and two-thirds of women use four to five medications during pregnancy and labor (National Institute of Child Health and Human Development 2003). More than 40 percent of pregnant women use drugs classified as C or D by the U.S. FDA risk classification (Food and Drug Administration, 2006) (Cragan et al. 2006; Andrade et al. 2004). Further, given that almost half of pregnancies are unintended (Finer and Henshaw 2006), exposure to a fetus can occur when a woman taking medication unexpectedly becomes pregnant. Without information on the fetal safety of these medications, we are left with the variable predictive value of animal studies (Brent 2004), considerable anxiety, and a paucity of data with which to reason about the trade-offs that mark decisions about the use of medication in—or continuation of—pregnancy.

Indeed, a 2002 review of fetal risk associated with all 468 of the medications approved in the United States for use in humans between 1980 and 2000 revealed just how little we know (Lo and Friedman 2002). Only 6.4 percent were recognized as safe in pregnancy (in that their teratogenic risk was considered as “none, minimal or unlikely”); and 2.5 percent were associated with some risk, ranging from small or moderate (fetal growth restriction with cyclophosphamide chemotherapy, goiter with amiodarone) to high (severe limb abnormalities with thalidomide). This leaves us without any substantive guidance regarding the risk to the fetus of more than 91 percent of the drugs on the market. Worse, this percentage has shifted very little over the last two decades. More than 80 percent of drugs are classified as “undetermined” with respect to fetal risk, whether approved 15–20 years ago (96%), 10–14 years ago (83%), 5–9 years ago (88%), or 0–4 years ago (95%) (Lo and Friedman 2002).

Of obvious concern here is that some of the medications currently prescribed to pregnant women may in fact be unsafe for the fetus. Consider ACE inhibitors—a medication widely prescribed for the treatment of hypertension. ACE inhibitors were of known contraindication in the second and third trimesters but had unknown risk status in the first trimester until a 2006 study published in the *New England Journal of Medicine* linked the antihypertensive drug to a small but statistically significant increased risk of fetal cardiovascular and neurological abnormalities (Cooper et al. 2006). The rub, in this case, is that if researchers had studied the drug in pregnancy earlier on, the congenital anomalies that resulted from the three decades of use since the approval of the drug could have been prevented.

For another example, consider the thalidomide disaster. Some of the resistance to the idea of clinical research with pregnant women almost certainly can be traced to the long shadow cast by this devastating episode. But the thalidomide example is in fact instructive. We must remember that the widespread birth defects experienced from its use were *not* the result of women's participation in research trials, but rather the result, at least in part, of inadequate research standards preceding distribution and marketing (Levine 1993). Careful and responsible research might well have attenuated the magnitude of the disaster. Yet the response of policymakers was instead to exclude nearly all women of reproductive potential from future research.

Reticence to use: The cost of uncertainty

Worries about fetal safety obviously loom large not only for researchers, but for pregnant women and their health care providers. These concerns have led some clinicians or patients not to treat, or to undertreat, illnesses that continue or emerge during pregnancy. But the failure to treat illness *also* can lead to significant harm to women and their fetuses—indeed, harm that easily can outweigh the possible risks that might accompany use of medication during pregnancy. These issues point to the third reason that responsible research in pregnancy is required: lack of information can lead to worrisome reticence to treat dangerous medical conditions.

Consider depression, for example. Treatment for depression during pregnancy has been characterized by considerable reticence, despite significant harm that untreated mental illness can entail. The Web site for the National Alliance on Mental Illness (NAMI) admonishes women to “if possible, stop using the drugs before trying to conceive [and] do everything possible to avoid medication in the first trimester of pregnancy” (National Alliance on Mental Health 2008). Yet women who discontinue medication have significantly higher rates of relapse of major depression than those who continued medication (68% compared to 25%) (Cohen et al. 2006). Untreated depression is problematic for pregnant women and the fetuses they carry: it is associated with premature birth, low birth weight, fetal growth restriction, and postnatal complications. It also is associated with decreased social support, poor weight gain, and alcohol and drug use, all of which adversely affect outcomes for women and infants alike (Orr et al. 2007; American College of Obstetricians and Gynecologists 2007).

Women with asthma, too, sometimes are treated suboptimally for fear of fetal exposure to medications (Dewyea and Nelson 2005). Halting medication brings many dangers to maternal health: poorly controlled asthma places a pregnant woman at higher risk of hypertension, preeclampsia, and uterine hemorrhage (Dombrowski 2006; American College of Obstetricians and Gynecologists 2008). Moreover, halting medication for the mother is risky for the fetus. Poorly controlled asthma is associated with fetal growth restriction, premature birth, and low birth weight; in contrast, women with asthma that is well controlled by medication have perinatal outcomes as good as comparable groups without asthma (Tan and Thomson 2000). And sometimes, the results of undertreatment are tragic: women—and the fetuses they carry—have died in emergency situations because physicians are insufficiently aggressive with medications out of concerns for fetal harm.

Here we see 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 woman and the fetus of *not* intervening (Lyerly et al. 2007). A classic example is the trainee who hesitates, in the midst of resuscitating a pregnant woman who has had a heart attack—a woman whose small chance for life depends on decisive and optimal care—over concerns about whether a cardiac drug is teratogenic. Another example is that of the radiologist who hesitates or refuses to perform standard imaging on a pregnant woman with suspected appendicitis, despite the fact that delayed diagnosis and appendiceal rupture carries a ten-fold risk of

miscarriage (Mazze and Kallen 1991). When a medical problem emerges or persists in pregnancy, many—sometimes patients, sometimes providers—feel concern about taking a medication, without appropriately weighing the risks of *not* taking it.

Pregnancy is in this respect no different than other arenas of life. The need to make calculated risks and trade-offs in the context of pregnancy is inevitable. Indeed, even for medications with known teratogenicity, calculated trade-offs may still be a fact of life. For instance, a pregnant woman with a mechanical heart valve who is insufficiently treated with heparin, may be strongly recommended to take warfarin (a blood thinner with a 30% risk of fetal anomaly), given the high risk of maternal (and needless to say, fetal) death entailed by inadequate anticoagulation (James, Abel, and Brancazio 2006).

The third reason to move toward responsible inclusion of pregnant women in clinical trials, then, is to counter unreasoned opposition to treating important medical conditions. If research is important to tell us when medications are unsafe, it is also important to reassure us when drugs *are* safe. The point is worth underscoring. For every drug that is found worrisome, it is likely that many more will bring news of welcome reassurance. Of the 468 drugs approved by the U.S. Food and Drug Administration in the last twenty years, only three drugs approved were judged to pose a “high” teratogenic risk; only eleven are believed to pose any teratogenic risk (Lo and Friedman 2002). Further, for the 6.4 percent of medications categorized as safe, it took an average of more than nine (ranging from two to nineteen) years from the time of FDA approval to ascribe a designation of low or minimal risk (Lo and Friedman 2002). And of course, research also can help us to quantify the risks of medications like warfarin or ACE inhibitors, so that we can proceed with more confidence when faced with the need to make difficult trade-offs in risk.

Access to the prospect of direct benefit

The fourth reason to enhance clinical research of medical treatment during pregnancy has to do with an important subset of trials: those that carry the prospect of direct benefit to participants. Some trials, especially Phase I trials, are designed primarily to gather preliminary information, such as data about the safety, pharmacokinetics, and pharmacodynamics of a drug. These trials, although important for the advance of scientific knowledge, present no prospect of direct medical benefit to participants. But other trials do. Many Phase II and III trials are meant to see whether a given drug is, as hoped, therapeutic for a given medical condition. Those who participate in the active arm of these trials could end up with a significant medical benefit. This means that restriction of trials to non-pregnant individuals excludes a class of potential beneficiaries and places them at an unfair disadvantage when it comes to health and well-being.

Consider an example from current international HIV/AIDS research. Vaginal microbicides were identified as a promising means for women in developing countries to protect themselves from sexual transmission of HIV (Doncel and Mauck 2004). Because pregnancy is a marker of unprotected sexual activity, understanding the effects of a medication aimed at mitigating the risks of such exposure is particularly important for this group. Indeed, any possible teratogenic risk from the gel must be considered in the context of a very clear, real, and life-threatening risk that microbicides aim to prevent—namely, maternal and fetal exposure to HIV infection. Yet pregnant women have been summarily excluded from microbicide trials. In fact, high pregnancy rates in study populations were accompanied by *increased* efforts to exclude pregnant women and to terminate enrollment for participants who do become pregnant (Raymond 2006)—this despite the fact that animal studies have not shown adverse effects of microbicides on fetal development, and the vaginal products do not seem to be systemically absorbed (Lard-Whiteford et al. 2004). And finally, given that pregnant women will certainly

be among the consumers of microbicides if they prove effective, reassurance of the product's efficacy, as well as safety, would be useful.

In this example, the prospect of medical benefit extends to woman and fetus alike. If the microbicide turns out to decrease the transmission of HIV, both women and fetuses in the active arm will benefit. Other trials present more difficult issues, offering the prospect of direct medical benefit only to the fetus or only to the woman. Clearly, there must be strong limits on the risk that research may impose on the fetus, who cannot consent, for the potential medical benefit of the woman. But the current practice—the de facto exclusion of women from participation, even when participation holds a genuine prospect of direct benefit—goes beyond what would be considered reasoned limits and suggests alarm at the prospect of *any* fetal risk whatsoever.

Indeed, some theorists have noted a “cultural anxiety” about the very idea of placing risk on the fetus for the sake of the pregnant woman (Merton 1996). Often, of course, the idea of a conflict is overstated to begin with. Physically, the woman and fetus are interconnected, the health or illness of one influencing the same in the other. More than that, the future well-being of each is, in the usual case, deeply connected. Children are affected by their parents' health and happiness; parents are affected by their children's well-being—and not just contingently, but constitutively. The fact that stopping anti-depressant use during pregnancy increases the woman's chance of severe post-partum depression is not just a “maternal” risk; the fact that lead exposure during pregnancy increases a child's risk of learning disabilities is not just a “fetal” risk.

Nonetheless, just as the bodies are not identical, neither are the goods, projects, and interests. Trade-offs between risks to the woman and the fetus can be real, and decisions about responsible and reasonable trade-offs are critical. Yet the need for thoughtful criteria has been eclipsed by a social tendency to regard the very idea of trading off risks between the woman and her fetus—however well demonstrated and large the former, however theoretical or small the latter—as anathema. Exposing a fetus to a small, even miniscule, risk in the context of research that may entail even a large direct benefit to a woman (and probably to both woman and fetus) has seemed an unreasonable risk to some researchers and policymakers contemplating categories for inclusion.

This form of reasoning carries a worrisome double standard. It holds pregnant women to a standard we do not hold fathers to; more than that, it holds pregnant women to a standard we do not hold mothers to. We accept small risks to our children for our own sakes every day. We believe it reasonable to impose the small risk of fatality introduced every time we put our children in the car (safely restrained in a car seat), even if our errand is mundane. To be sure, balancing such risks can be among the most challenging tasks of parenthood. But as parents and members of families, we recognize that reasoning about risk is inevitable, that thoughtful, responsible trade-offs are a fact of life, and that there are times when benefit to one member of a family comes at the price of a risk to another.

The fourth reason to address the challenges of responsible inclusion of pregnant women in clinical trials, then, is an issue of justice. As scholars have noted in discussions of other underrepresented populations, *access* to research, not just protection from its risks, is a constitutive part of the ethical mandates governing clinical research (Mastroianni, Faden, and Federman 1994). Whereas no one would suggest that justice requires admitting pregnant women to all trials regardless of their risks and benefits, justice does call into question the de facto summary exclusion of pregnant women in research without justification in terms of those risks and benefits.

Risk and responsibility

We suggested that there are profoundly important reasons to enhance clinical research of medical treatment in pregnancy. We also noted that such research raises significant cultural unease: the intersection of risk and the fetus is an uncomfortable one.

Of course, part of the concern has to do with the fetus's inability to consent. But pregnancy is not the only context that raises this ethical issue. Pediatrics has a long history of confronting the need to study a population that cannot consent meaningfully. The fact introduces complexity, and the need for special safeguards, to be sure; what it does not mean is a firewall against research on the population. As a recent report of the Institute of Medicine on research with children pointed out, studies involving that vulnerable population are “essential to the health of future children—and future adults” (Field and Berman 2004). After all, young children also do not consent to being treated with medication that has not been adequately tested on physiologies resembling their own and thus, whose efficacy and risks, for them, are largely unknown. Whereas the details are complex, the bottom line is simple: if a population is going to use a drug, then we need to study that drug *in* that population (Brent 2004; Field and Berman 2004; Zajicek and Giacoia 2007).

But when it comes to reasoning about risk and the pregnant body, the cultural tendency is to retreat from the idea of risk rather than confront the need to make reasoned and responsible decisions about it. The specter of risk can cast an eclipsing shadow over rational decision making. For example, in discussions about pregnancy, evidence that one thing or behavior carries quantifiable risk—say, exposure to oil-based paint or moderate caffeine consumption—can quickly taint another where there is no such evidence—for example, exposure to latex-based paint, or again, modest caffeine consumption. Indeed, the effect can persist even in the face of reassuring findings. For a recent example, we can look to the well-publicized findings of a study designed to explore the possible link of caffeine consumption and early pregnancy loss (Xiaoping, Roxana, and De-Kun 2008). Evidence of a modest increase in miscarriage risk with moderate caffeine consumption in the first trimester was touted as reason to “stop or reduce caffeine intake during pregnancy,” even when the self-same study found that caffeine consumption under two cups was found to carry no increase in the miscarriage rate. Rather than reporting reassurance that low caffeine use was demonstrated to be safe, researchers took the finding of risk associated with moderate consumption and extended it against findings of safety.

Cultural reasoning about risk in pregnancy, in short, tends to invoke the precautionary principle in a particularly unfettered way. “Better safe than sorry” is a fine aphorism in general, and a particularly good one to take during pregnancy, where untoward effects on the fetus can be permanent. But when applied without sensitivity to evidence or appreciation of the *cost* of caution—when applied myopically, without due recognition of the long-term price of one's policy—it could turn out that a policy of “better safe than sorry” is the opposite of safe. It can, in fact, lead to significant harm to women and fetuses alike. Applied here, it collides with the animating purpose of the enterprise of clinical research, which is to take responsible, limited, and calculated risks in order to *garner* evidence, lest we visit more risk on more people in the future.

Going forward

Confronting the challenges of research with pregnant women is a critical if complex project. Going forward will require a number of steps. Some are obvious and morally straightforward. These include increasing funding for the OPRU and other groups to perform opportunistic studies involving women already taking medication during pregnancy. Because women in

opportunistic studies already have made a decision to take medication outside of the research context, simple blood draws to measure pharmacokinetic and pharmacodynamic parameters introduces minimal risk and none of the onerous trade-offs that demand a novel ethical framework for inclusion. Also required is funding for research to determine the public health impact of the current lack of knowledge around medications in pregnancy. Such funding could help to answer questions critical to decision making about research priorities: what is the current burden of disease for both pregnant women and their babies that results from the need to make treatment decisions in the absence of any relevant data? What are the emotional and psychological burdens of the anxiety and stress that treatment decisions in pregnancy engender? As newer approaches to treatment in the non-pregnant population are developed, what is the comparative cost of restricting pregnant women to the older medications that obstetrical providers are accustomed to using? For example, is there a health-related cost to the usual practice of replacing new antihypertensive medications with older medications such as methyldopa, which has been prescribed during pregnancy for decades? In both of these efforts, moving forward will involve developing legislative strategies modeled on those that have created incentives for women and children to participate in research.

Other steps will be considerably more complex and controversial. For instance, addressing the liability concerns that animate so much of the behavior around research and drug development during pregnancy will require substantial efforts at both state and federal levels. Just as importantly, considerable efforts will be required to develop guidance for IRBs. Although IRBs are often and understandably focused on safety and protection from the harm of participation, in many ways they are the gatekeepers of access to research. As others have noted, IRB members may lack training or guidance regarding how to recognize or respond to the potential harm of exclusion (Chronic Disease Prevention and Control Research Center at Baylor College of Medicine and Intercultural Cancer Council 2008).

To make progress, we need an adequate ethical framework for determining what are and are not suitable justifications for exclusion of pregnant women from research. Some criteria can be borrowed from approaches to disparities in other underrepresented research populations. For instance, as with women generally, considerations of cost are not adequate justification for exclusion of underrepresented populations. When population-specific evidence is required to treat a particular group, the cost of research is one that must be borne in order to provide responsible, safe, and effective medical care to those who need it. For instance, the fact that sample size must be increased to adequately power a study that includes pregnant participants should not be accepted as valid criteria for their exclusion.

Other issues, though, will require a framework specific to pregnancy. Given the intermingled physiologies distinctly present in pregnancy, and the implications for what are potentially two rather than one person, thoughtful analysis is required to sort through the complex questions of the levels of risk the fetus—or for that matter, the woman—can be subjected for purposes of research that may benefit the other. A number of factors will be relevant, including the applicability of data from animal studies on fetal safety, data about the degree to which “borrowed knowledge” is possible, the balance of direct benefits of participation to the woman and the fetus with any potential harm, and the prevalence and seriousness of the condition in the pregnant population.

Details notwithstanding, we believe the core lesson is a simple one. As with other traditionally excluded populations, progress will not happen until we shift the burden of justification from inclusion to exclusion. There are many trials in which that burden may be met. To give an obvious example, pregnant women are not needed in trials of hormone therapies for prostate cancer. More broadly, and as with pediatric research, we do not include a population that introduces special ethical complexities into trials for medications of marginal medical

importance (pharmacologic treatments for fungal infections of the nail bed). Special attention always must be given to the relevance of the goal in the population under consideration—for instance, new lipid-lowering drugs, of potential benefit to the broad population, are inappropriate for testing during early pregnancy, when the body significantly and importantly increases the production of cholesterol and triglycerides, high levels of which are considered adaptive to maternal and fetal nutritional needs and placental functioning. The claim then, is not that pregnant women belong in all trials. Rather, the claim is that decisions about whether pregnant women belong in a given trial, or type of trial, should be just that—*decisions*—made on the basis of reasoned criteria, reflecting balanced consideration of not only the risks of teratogenicity, but the potential importance of the medication for the health of women and the fetuses they carry. As with other underrepresented populations, it is exclusion, not inclusion, that requires justification.

But such justification is not currently required. Presently, Department of Health and Human Services regulations outline ten criteria that must be met if pregnant women are to be included in research protocols (United States Department of Health and Human Services 2005). Without any legislative or regulatory pressure to include pregnant women, all the incentives line up in favor of excluding pregnant women from clinical research. It is easier for researchers to simply side-step the questions and regulatory burden they represent by not including pregnant women. Until *that* decision *also* requires justification, we will continue to lack data on how to effectively and safely treat pregnant women.

In the absence of information about the safety and efficacy of medications, pregnant women and their providers are left with two unsavory options—take a drug, with unknown safety and efficacy; or fail to treat the conditions, thus leaving the woman and fetus vulnerable to the consequences of the underlying medical problems. They deserve better. Clinical research with pregnant women is morally challenging, but it is a challenge we must confront. For the alternative to responsible research in pregnancy is relegating pregnant women to second-class medical citizens—something, it turns out, that is not good for pregnant women nor the fetuses they carry.

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