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Pregnant women & medical research: a moral imperative

_Original article

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Abstract_French and German abstracts see p. 64

Each year, millions of pregnant women are confronted with serious medical illnesses. Yet the evidence base for treating them is distressingly poor. Due in part to ethical concerns about conducting research with pregnant women, researchers and institutional review boards continue to regard pregnancy as a near-automatic cause of exclusion, even in studies carrying no additional risk to the fetus. As a consequence, pregnant women and their doctors are often forced to make difficult, anxiety-filled decisions about whether to use or continue a medication in pregnancy, guessing about what medications to use, what doses to prescribe or take, or whether to use medications at all. In this article, we outline four reasons why we must confront the challenges of including pregnant women in medical research: the need for effective treatment for women during pregnancy, considerations of fetal safety, the harm from reticence to prescribe needed medication, and the broader issues of justice and access to the benefits of research participation. We then outline three steps that legislators, regulators, and health advocates should take to advance the responsible inclusion of pregnant women in research critical to evidence-based therapeutics during pregnancy. A few small changes can make an immediate and significant difference.

Introduction

Each year, millions of pregnant women are confronted with serious medical illness: hypertension, diabetes, autoimmune diseases such as arthritis and lupus, influenza, significant psychiatric illness, even cancers. In the United States, over 400,000 pregnant women a year face significant medical illness (1, 2); in Western Europe, approximately one in twelve women enter pregnancy with a chronic medical condition requiring pharmaceutical treatment (3). 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, in short, is not a prophylaxis against medical illness.

Yet as clinicians well know, the evidence base for determining how to treat the medical conditions of pregnant women is distressingly poor (4). Indeed, some have argued that there is no group of patients for whom the evidence base is weaker. For instance, only a dozen medications are approved by the United States Food and Drug Administration 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 (5). Any medication used to treat illness during pregnancy – be it hypertension, diabetes, depression, or cancer – is used without data adequate to guide dosing, make decisions about safety, or inform differential decisions about which medicine to prescribe (6–9).

A significant problem, the cause is a simple one: pregnant women have been overlooked in medical research. Researchers and institutional review boards continue to regard pregnancy as a near-automatic cause of exclusion, even in studies carrying no additional risk to the fetus. Registries for post-marketing monitoring are spotty at best; and with no incentives to design studies tailored to accommodate the specific ethical and scientific complexities gestation represents, pregnant women are virtually absent from the social investment in medical knowledge. As a consequence, pregnant women and their doctors are often forced to make difficult, anxiety-filled decisions about whether to use or continue a medication in pregnancy, guessing about what medications to use, what doses to prescribe or take, or whether to use medications at all.

An overarching concern for researchers, of course, is the fetus. Medications can cross the placenta and irreversibly affect fetal growth, structure, and function. The possibility of teratogenic and mutagenic effects grounds a deep reluctance in the research community to include pregnant women in medical research. Unfortunately, this position has done more harm than good for women and their babies. Certainly, guidelines for research in pregnancy must include careful and responsible criteria for protections for fetal well-being; and, 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 ignoring the need for responsible research with pregnant women has brought profound costs, to women and fetuses alike (10–12).

In this article, we outline four reasons why we must confront the challenges of including pregnant women in medical research: the need for effective treatment for women during pregnancy, considerations of fetal safety, the harm from reticence to prescribe needed medication, and the broader issues of justice and access to the benefits of research participation. We then outline three steps that legislators, regulators, and health advocates should take. The good news is that a few small changes can make an immediate and significant difference.

The costs of exclusion

Effective treatment for pregnant women

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

Pregnancy adds a wild card to the ways in which the body and medicine interact. Dramatic changes in physiology – in blood flow, digestion, kidney function, enzymatic activity – change the way that the body works on drugs (pharmacokinetics) and the way that drugs act on the body (pharmacodynamics) (13). Standard doses can be processed so quickly that therapeutic levels are not achieved, leaving woman and fetus exposed to the dangers of the underlying illness.

For instance, measurements of drug levels on pregnant women taking oral medication for diabetes revealed that the drug is metabolized and excreted so rapidly that considerably higher doses than currently recommended will likely be needed to treat them effectively (14). And a recent study revealed that amoxicillin, prescribed routinely to pregnant women, and recommended by the American College of Obstetricians and Gynecologists as post-exposure prophylaxis for anthrax during pregnancy, may in fact be metabolized so quickly as to prevent its reaching concentrations adequate to prevent anthrax (15). If the threat of anthrax had been realized, pregnant women and their babies would have died for lack of adequate prophylaxis.

There is reason to be concerned that we may make a similar mistake with regard to H1N1 influenza. Pregnant women have been among the hardest hit in this pandemic (16) and are being prioritized for both antiviral treatment and vaccine (once available). Specifically, noting that H1N1 is responsive to the antiviral drugs Tamiflu and Relenza, public health officials currently advise pregnant women to take these drugs as prophylaxis upon exposure at standard adult dosages (17). Unfortunately, however, as with most drugs on the market, there are virtually no data on how Tamiflu and Relenza work in a pregnant body and thus no evidence base for making judgments about what doses are required during pregnancy – something that could have dire consequences for women and their babies.

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, many pregnant women *do* use medications during pregnancy. In the US, the average woman receives 1.3 prescriptions per obstetric visit (18), and two-thirds of women are prescribed at least one medicine other than a vitamin or mineral supplement during pregnancy (19). Medication use is similarly widespread in Western Europe. A registry study of drug use in Italy, France, Great Britain and the Netherlands reported that 64% of women use at least one drug other than a vitamin or mineral during pregnancy (3); similarly, a Finnish study reported that 46% of women purchase at least one prescription drug during pregnancy, and 12% purchase 3 or more (20). Nearly every woman in one French database study received a prescription during pregnancy, and on average women received 13 prescriptions over the course of gestation (21). Further, given that almost half of pregnancies are unintended (22), exposure to a fetus can occur when a woman taking medication unexpectedly becomes pregnant.

The lack of carefully structured safety research leaves us without data to guide decisions about which medicines are safest for the unborn, leaving fetuses exposed to unknown risks when pregnant women do take medication, as often they must. For instance, after nearly thirty years on the market, researchers have just discovered that if pregnant women take a commonly prescribed hypertension medication during the first trimester, their newborns are more likely to be born with heart and nervous system problems (23). 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.

The thalidomide tragedy is perhaps the example that comes first to mind when considering medication use during pregnancy. 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 (24). Careful and responsible research might well have attenuated the magnitude of the disaster.

Reticence to use needed medication

The third reason is a powerful one. In the absence of reassuring data, clinicians and patients often undertreat or discontinue medications necessary to manage medical conditions that continue or emerge during pregnancy. But the failure to treat illness can *also* lead to significant harm to women and their fetuses – indeed, harm that easily can outweigh the possible risks that might accompany medication use.

Women with asthma, for example, sometimes are treated sub-optimally for fear of fetal exposure to medications (25). But halting medication is dangerous for both women and

fetus. Poorly treated asthma places a pregnant woman at higher risk of hypertension, preeclampsia, and uterine hemorrhage (26, 27); it is also associated with fetal growth restriction, premature birth, and low birth weight. In contrast, women with asthma that is well controlled by medication have maternal and perinatal outcomes as good as comparable groups without asthma (28).

Untreated depression, too, 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 (2, 29). Women whose diabetes is poorly controlled in the first trimester face a one in four chance of serious birth defects, while the risk of such birth defects is near that of the general population if their disease is adequately treated (30). And when a woman dies from cancer that went untreated during her pregnancy, the wrenching implications of life without a mother may be far more devastating to her baby than the medical risks of exposure to maternal chemotherapy.

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 research will bring news of welcome reassurance for others (31). And of course, research also can help quantify the risks of medications when they occur so that women and their physicians can proceed with more confidence when faced with the need to make difficult trade-offs. Indeed, even for medications with known teratogenicity there may good reasons to consider going forward with treatment once the risks to the fetus are well characterized. 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 very high risk of maternal and fetal death entailed by inadequate anticoagulation (32).

Access to the benefits of research participation

The fourth reason to address the challenges of responsible inclusion of pregnant women in clinical trials 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 (33). While many trials are aimed at background knowledge, many Phase II and III trials hold out the prospect of direct benefit for those who participate in their active arm. 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 have been identified as a promising means for women in developing countries to protect themselves from sexual transmission of HIV (34). 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, and 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 faced broad exclusion from microbicide trials. In fact, high pregnancy rates in study populations have often been accompanied by increased efforts to exclude pregnant women and to terminate enrollment for participants who do become pregnant (35). But for several microbicides, animal studies show no adverse effects on fetal development and no systemic absorption of vaginal gels (36). Especially 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, in this population is critical.

Going forward

Concerns about the ethics of research involving pregnant women mean we know far less about how to treat diseases during pregnancy than in other adults and children. In many cases, these ethical concerns have been misguided. Illnesses during pregnancy put both mothers and baby at risk, and ignorance about how to treat those illnesses only makes matters worse. If it is sometimes unethical to do research, it is sometimes unethical *not* to conduct it. As we learned in pediatric research, if a population is going to use a medication, it must be studied *in* that population (37–39). Certainly, guidelines for research in pregnancy must include special safeguards. But the central lesson is a simple one: pregnant women and the children they bear are best protected through responsible inclusion in research, not broad-based exclusion from it.

Confronting the challenges of research with pregnant women is a critical if complex project. Some needed steps are straightforward, such as increased funding for research. Others will be more complicated: addressing liability concerns and developing guidance for IRBs, including, most critically, a framework for managing and limiting risk-benefit trade-offs between woman and fetus. Fortunately, several steps can be taken immediately.

1. *Pursue innovative study designs.* While bioethics and policy discussions often focus on the difficulties of study designs that impose risk, a wealth of information can be procured from innovative study designs that involve no additional risk to the fetus. «Opportunistic» studies, such as those pioneered by the Obstetrics-Fetal Pharmacology Research Unit Network, involve simple blood draws to measure the pharmacokinetic and pharmacodynamic parameters of medication that pregnant women are already taking (39). Such research represents no added risk, and involves none of the onerous trade-offs that demand a novel ethical framework for inclusion. Indeed, just such an OPRU-sponsored study will gather critical information about the pharmacokinetics of the antiviral drug Tamiflu by enrolling pregnant women who will take the drug for prophylaxis or treatment in coming months of the pandemic (40). Increased funding for opportunistic research of this sort could go a long way

to helping us understand how to administer medications when pregnant women need them, as often they do.

Other study designs that involve no added risk include population-pharmacokinetic studies, cohort registries, and non-invasive longitudinal studies, such as the Norwegian Mother and Child Cohort Study (41) and potentially the US National Children's Study (42); such study designs should receive immediate funding and development priority.

2. *Index levels of acceptable fetal risk to the severity of need in pregnant women.* While innovative study designs can often procure needed information without imposing risk, there will be times when research designs that impose additional risk, such as certain kinds of randomized clinical trials, are often needed to answer specific key questions. What dose of vaccine against novel H1N1 will protect pregnant women and their babies against the flu? Are there medications, such as aspirin, that will help prevent preeclampsia in women at risk for the disease (43)? Can oral medication be used safely and effectively in pregnant women with diabetes (44)? In delineating how much risk to the fetus is acceptable, regulations in the US (45) often use bright line criteria rather than indexing allowable risk to the severity of need in pregnant women. More specifically, such regulations appropriately distinguish criteria of risk for trials that offer the prospect of direct benefit to the pregnant woman and those whose benefits would only accrue to future populations of pregnant women and fetuses. In neither case, however, do regulations index acceptable risk to severity, prevalence, and need for the research. These issues are instructive for the proposed regulations currently being discussed in Switzerland. For research offering the prospect of direct benefit, Article 29 specifies that research may be conducted during pregnancy only if «the ratio between the risks and burdens for the pregnant woman and for the embryo or foetus, on the one hand, and the expected benefit, on the other hand, is not unbalanced.» This well-intentioned proposal is problematic. Without addressing the question of how the risks and benefits are distributed across the two entities – the pregnant woman and the fetus – the proposed regulation gives no guidance to ethics review committees for determining which trade-offs of maternal benefit for fetal risk (and vice versa) are acceptable. But acceptable some of them are. While there must of course be limits, risks to the fetus must be judged in the context of protecting a pregnant woman's access to possibly life-saving medication. Modest or merely theoretical risks to the fetus may be acceptable in the context of research that may save a woman's life. For research that does not offer the prospect of direct benefit, the current proposed regulation in Switzerland (Article 30), in a move similar to US (45) and other EU regulations, specifies that such research may be conducted in pregnancy only if «research-related risks and burdens to the embryo or foetus are no more than

minimal.» As intuitively appealing as this criterion may sound, it is in fact highly problematic. Notoriously plagued by vagueness, the phrase is generally interpreted as equivalent to the risks of «everyday life», which often translates in practice to excluding all but the most minor interventions, such as anonymous questionnaires and blood draws. Instead, judgments about «minimal» risk should be made against a baseline of what risks are usual for an entity in that situation – in this case, a fetus living in the womb of a very sick woman. In that context, what constitutes a minimal risk begins to approximate what is an acceptable risk in light of the seriousness of the pregnant woman's medical condition and the risks to the fetus and to her of alternative treatment options, including the risks of no treatment.

3. *Balance justificatory burdens.* All will agree that regulations should restrict when and how research can be conducted on pregnant women. But without any legislative or regulatory pressure to include pregnant women in some fashion, a powerful, systemic incentive structure is established. It is easier for researchers to side-step the regulatory burden that pregnant women currently represent by excluding them wholesale from all research, including research that imposes no risk, or risk that is clearly reasonable in its context. Without changing the burdens of justification, all the incentives to the research community line up in favor of simply ignoring pregnant women. This is unfair on several levels. First, adequate study of a drug must include adequate data for all who will use it. With pregnant women, this requirement will often mean development of adjunct studies. Such studies certainly increase the cost of research, but as is widely agreed when considering other under-represented research populations, cost is not an adequate basis for exclusion when population-specific evidence is required to determine safety, efficacy, and dosing in that group (33). And for trials involving the prospect of direct benefit, the lesson learned from other under-represented groups is clear: researchers should have to justify, by publicly agreed-upon criteria, exclusion of a population. Exclusion often will be justified: the point is that researchers should have to assess whether a given trial meets those standards of justified exclusion. No one would suggest that justice requires admitting pregnant women to all trials carrying the prospect of direct benefit, regardless of risk; what justice does call into question is the summary exclusion of pregnant women in such research without positive justification in terms of those risks. The mere fact that a woman is pregnant should not be an automatic veto on access to potentially life-saving medication. Decisions about whether pregnant women belong in a given trial should be just that – decisions, made on the basis of reasoned criteria, reflecting balan-

ced 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. More than that, decisions about how to design a trial – including how adjunct studies for specific populations might be fashioned – need to address the needs of all whose medical care will be dependent on the findings of the trial.

Conclusion

In the absence of information about the safety and efficacy of medications, pregnant women and their clinicians are left with two unsavory options – take a drug with unknown safety and efficacy; or fail to treat the condition, thus leaving the woman and fetus vulnerable to the consequences of the underlying medical problem. 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 with pregnant women is relegating pregnant women to second-class medical citizens – something, it turns out, that is good for neither pregnant women nor the fetuses they carry.

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Résumé

Femmes enceintes & recherche médicale: un impératif moral

Chaque année, des millions de femmes enceintes sont confrontées à des maladies graves. Pourtant, les données sur la base desquelles les traiter sont terriblement rares. En partie en raison de soucis éthiques concernant la recherche avec des femmes enceintes, les chercheurs et les comités d'éthique de la recherche continuent à considérer la grossesse comme une clause d'exclusion quasi automatique, même dans des études ne comportant pas de risque additionnel pour le fœtus. En conséquence, les femmes enceintes et leurs médecins sont souvent forcées de prendre des décisions angoissantes et difficiles sur la poursuite ou l'introduction d'un médicament pendant la grossesse, et de deviner quelle substance choisir, quel dosage prescrire ou prendre, voir s'il est indiqué ou non d'employer des médicaments d'aucune sorte. Dans cet article, nous décrivons quatre raisons pour lesquelles nous devons confronter les défis de l'inclusion des femmes enceintes dans la recherche: le besoin de traitements efficaces pour les femmes durant la grossesse, des considérations pour la sécurité du fœtus, les dommages causés par la réticence à prescrire des médicaments nécessaires, et les enjeux plus large de justice et d'accès aux bénéfices de la participation à la recherche. Nous esquissons ensuite trois étapes que les législateurs, les instances régulatrices, et les acteurs de la santé devraient suivre pour promouvoir l'inclusion responsable de femmes enceintes dans la recherche, nécessaire au développement de thérapies basées sur les preuves durant la grossesse. Quelques changements mineurs pourraient conduire à une différence immédiate et significative.

Zusammenfassung

Schwangere Frauen & medizinische Forschung: Ein moralischer Imperativ

Jedes Jahr sind Millionen von Frauen von ernsthaften Krankheiten betroffen. Die Evidenzbasis für die Behandlungen und Therapien ist aber erschreckend schmal. Schwangere Frauen werden aufgrund ethischer Bedenken über die Forschung an schwangeren Frauen von Wissenschaftlern und institutionellen Aufsichtskommissionen fast automatisch von der medizinischen Forschung ausgeschlossen; dies sogar bei Forschung, die kein zusätzliches Risiko für den Fötus beinhaltet. Schwangere Frauen und ihre Ärzte sehen sich deshalb oft gezwungen, schwierige Entscheidungen über medikamentöse Behandlungen in der Schwangerschaft zu treffen, die die Auswahl und Dosis der Medikamente, oder sogar die grundsätzliche Verabreichung von Medikamenten betreffen. In diesem Artikel umreißen wir vier Gründe, warum wir die Herausforderung annehmen müssen, schwangere Frauen in die medizinische Forschung mit einzubeziehen: Das Bedürfnis nach einer wirksamen Behandlung in der Schwangerschaft, die Sicherheit des Fötus, der Schaden einer Zurückhaltung beim Verschreiben von benötigten Medikamenten und das breitere Thema der Gerechtigkeit und des Zugangs zu den Vorteilen einer Teilnahme an der Forschung. Im Anschluss diskutieren wir drei Schritte, die Gesetzgeber, Behörden und Gesundheitsakteure unternehmen sollten, um den verantwortungsvollen Einschluss schwangerer Frauen – zur Entwicklung evidenzbasierter medikamentöser Therapien während der Schwangerschaft – in die Forschung voranzutreiben. Einige wenige, kleine Veränderungen können bereits einen unmittelbaren und bedeutenden Unterschied bewirken.

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