As a case in point, a recent health study conducted in the United Kingdom reported on the health outcomes of children followed from birth to age five. The study concluded that maternal drinking "of one or two units of alcohol a week during pregnancy does not raise the risk of developmental problems in the child." However, this finding did not change official governmental recommendations. They remained unchanged that women abstain completely during pregnancy.

The Barker hypothesis has provided a model for thinking about the importance of the intrauterine environment for subsequent long term health and illnesses. Barker and his team followed a large group of men and women and looked at their birth weight in relation to adult onset of cardiovascular disease. They found a very strong correlation between low birth weight and early onset of heart disease.

The thesis that the prenatal uterine environment leads to long term epigenetic changes that have a profound effect on later health has been extended to cancer, diabetes, mental illness and other outcomes. The Barker hypothesis is potentially of major importance to improving health, but there are reasons to be concerned that it may permeate public consciousness in ways that do a disservice to pregnant women. An October 2, 2010 *New York Times* article noted that "a uterus is not a diving bell that insulates its occupants from the world's perils."

The Barker hypothesis has shifted focus away from factors such as cycles of despair, poverty, and food and physical insecurity, traditionally associated with low birth weight, to a focus on the individual uterus. In affluent countries, women are concerned that, if their babies do not fall within a relatively narrow range of birth weights, they have doomed them to a whole host of diseases. This is an injustice, and it leads to the fourth and final justice consideration, that of disrespect.

Disrespect

Social justice is about more than the fair distribution of benefits and the lifting of unwarranted burdens. It is also about the treatment of pregnant women with dignity and as deserving of equal moral concern as those who are not pregnant. At a minimum, respect for others requires the ability to see others as independent sources of moral worth and dignity. As long as women are viewed as wombs and or as diving bells when they are pregnant, they will not be fully seen as independent sources of moral worth and dignity. We need to get to the person behind the intrauterine environment. The health interests of pregnant women need to be taken seriously.

As long as women are viewed as wombs and or as diving bells when they are pregnant, they will not be fully seen as independent sources of moral worth and dignity.

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Treating Important Medical Conditions during Pregnancy

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All medicines used for non-obstetrical treatments with pregnant women are off-label. Pregnancy is the ultimate off-label condition.

Over 500,000 pregnant women in the U.S. alone face serious medical illnesses every year such as heart disease, diabetes, lupus, and cancer to name only some conditions. Only 12 drugs are explicitly approved by the FDA for use in pregnancy. These drugs are approved either to prevent premature labor or to ameliorate labor pain. All medicines used for non-obstetrical treatments with pregnant women are off-label. Pregnancy is the ultimate off-label condition. This lack of knowledge has led to a profound reticence to treat pregnant women when they do fall seriously ill, and it ends up harming the women and the babies.

There is a tendency either to think of the interests of the pregnant woman and her fetus as entwined so closely that no discussion of a trade-off of interests when considering treatment is possible. Another view is that they have opposing interests. In fact, there is a need to acknowledge the possibility of a need for trade-offs and to discuss how to confront these trade-offs in an ethically responsible manner. This need is particularly acute when making treatment decisions about a seriously ill pregnant woman. Three case studies are illustrative of reticence to treat in the face of serious illness in pregnancy.

Three Case Studies

Case 1 Acute life threatening conditions such as appendicitis occur during pregnancy. In this first case, at 15 weeks gestation, a pregnant woman presented at the hospital with severe abdominal pain, strongly suggestive of a ruptured appendix. A CT scan with dye contrast was ordered by the attending physician to make a diagnosis but the radiologist declined to do the procedure. Citing the woman's pregnancy, and in spite of clinical guidelines recommending a CT scan in pregnant women with the patient's symptoms, he conducted a sonogram. It took 18 hours and the interventions of the attending physician and hospital lawyers before the woman finally had a CT scan, which revealed a ruptured appendix, but, by that time, she was septic and lost the pregnancy.

Case 2 Depression during pregnancy is a common condition that has potentially adverse consequences for the woman and her child. In this second case, a woman in her second pregnancy and with severe, persistent, and difficult-to-manage depression decided to stop her antidepressant medication. In her first pregnancy, she had stopped medication on her clinician's advice and ended up hospitalized for a relapse. Despite the fact that by the time of her second pregnancy, much information was available about the safety during pregnancy of the older classes of antidepressants, the patient chose to stop medications out of concern for her fetus.

Without research, there is not enough information to reassure. Absent that information, the precautionary principle becomes the guiding principle.

Case 3 A pregnant woman presented with a suspicious mole and was told to wait until after she delivered for a biopsy, despite there being no evidence that punch biopsy is a risk during pregnancy. A biopsy was delayed until after the woman had delivered; at that time, the mole was found to be a melanoma, and it had metastasized during the course of the pregnancy.

Reticence and the Precautionary Principle

Practitioners, the public, and patients alike have profoundly selective vision. They tend to be riveted by worries about the risk of intervening, without noticing the risks of not intervening. They ignore the risks of not treating and the risks of not researching. Without research, there is not enough information to reassure. Absent that information, the precautionary principle becomes the guiding principle.

What medical practitioners need to remember is that, in the vast majority of cases, what is best for the baby is a healthy mother. In the vast majority of cases, the best way to treat a pregnant woman is first to ask what the treatment would be were she not pregnant. That should be the default treatment.

Pregnant women themselves are reticent to use needed medications. They are cautioned on all fronts about the dangers of the substances which they put in their bodies. Even when research indicates no risk from a modest amount of alcohol ingestion, pregnant women are still told not to take even a sip of wine. No matter that research indicates that low volatile organic compound paints pose no harm to the fetus, pregnant women are told not to paint, even with latex paint.

Ethical, Scientific, Legal, and Regulatory Challenges

The ethics of clinical research is entirely about what to do in the face of not knowing. If the precautionary principle were the sole guiding principle of clinical research, the research would never be done. In consideration of the need for more information, over the years, researchers, IRBs, and the NIH have devised ways to conduct scientifically robust and ethical research. In the case of pregnant women, the precautionary principle has run amuck. What is needed in the case of pregnancy research is the development of a thoughtful, careful framework to address a scientifically and ethically challenging situation. So one thing the *Second Wave Initiative* is attempting to do is to get creative minds in law, clinical research design, and ethics to develop the framework needed to move ahead.

What is needed in the case of pregnancy research is the development of a thoughtful, careful framework to address a scientifically and ethically challenging situation.

It is a misnomer to call pregnant women a vulnerable population. They are better referred to as a complex population. In the complex case of pregnancy, the need for an ethical framework is essential to talk about what to do in the cases where there may be trade-offs between the mother and her medical interests and the medical interests of the fetus.

Additionally, there are scientific challenges. In pregnancy, one is not only dealing with a maternal/placental/fetal unit, but a unit that is changing on a daily, weekly, and monthly basis. The challenge is not merely to consider pregnant women issues in the existing clinical trial designs, but to consider new designs. Models are emerging on how to conduct a cohort study across the trimesters in pregnancy.

There are legal challenges. They are the "elephant in the room" in pregnancy research: In pregnancy, 3 out of 100 of the babies are diagnosed with some form of birth abnormality. How can pregnant women enroll in clinical trials given this baseline without a legal framework that acknowledges this baseline and separates it out from any additional risk that the intervention itself may pose?

Finally, vague existing regulations are a challenge. Subpart B of the Federal Human Subjects Protections regulations now states that clinical research in pregnancy can be conducted, "if there is direct benefit to the fetus or mother." Otherwise, the regulations prohibit research that is more than minimal risk to the fetus. However, the definition of minimal risk is vague. Consider a single dose pharmacokinetic study, which may not directly benefit pregnant women but does involve putting something in the body. One IRB may allow this research and another may not, concluding that it is more than minimal risk.

Alternative Designs are Needed

While moving ahead with dialogue on the above topics, there is also some "low-hanging fruit" to be picked in the meantime. That is, there is much that could be learned without posing any additional risk on the fetus. Case studies and observational studies can be mined for information.

For example, 100,000 women in the National Children's Study will be enrolled while pregnant, and their children will be followed over several years. As part of the study design, women are asked about the medications they are taking and blood is drawn during pregnancy. At the time of the blood draw, a couple of questions about the dose and timing of the last medication would provide valuable pharmacokinetic data.

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In addition to opportunities in large scale studies, small scale opportunistic studies could also yield valuable information. Take the example of a pregnant woman who is facing a significant illness. She is already on medication. Her consent could be obtained for pregnancy pharmacokinetics researchers to have a sample of the blood. She could be asked what medication she is taking, what dosage, and when she last took it.

With zero additional risk to the fetus, a wealth of data could start to populate decisions about what to prioritize, decide what are the biggest problems, and get some assurance that the risks of proceeding with clinical research are much less than potential benefits. Without changes to the regulatory environment, there is much that could be learned that is crucial, not just for the health of pregnant women, but for the health of babies as well.

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Discussion

Panelists: Dr. Anne Drapkin-Lyerly, Dr. Ruth Faden, and Dr. Margaret Olivia Little

The following summary is not a verbatim transcription of all comments on issues raised in the discussion, nor does it contain a verbatim transcription of any individual comment. Rather, the summary provides highlights of discussion with special emphasis on new issues raised by the presentations and issues of general importance towards the goal of promoting the responsible inclusion of pregnant women in clinical research.

Audience comment: *Contraception requirements for participation in clinical trials.* A woman who could not become pregnant because of her social circumstances wanted to participate in a clinical trial, but as a condition of participation, she was required to provide a urine sample, despite her assurances that pregnancy was not possible. In research, how can one talk about pregnant women as a distinct population when, in fact, for a large part of her life, a woman is seen by investigators and clinicians as someone who could potentially be pregnant?

Panel Comments: The example of the woman compelled to provide a urine sample speaks to the injustice of disrespect. That was a profoundly disrespectful response on the part of the investigator. This is not to underestimate the complexities that are involved in designing studies where there is a serious concern about the possible impact of an intervention on a developing fetus. However, the burden of evidence would have to be extraordinarily high, and the concern over pregnancy extremely severe to warrant what is now very common practice, which is requiring evidence that a woman is not pregnant and informing potential participants that there is concern about including pregnant women in the trial for reasons which are described to her. The decision to participate should be left to the woman.

However, that approach is very unsatisfying from the standpoint of investigators and IRBs who often feel responsible for everything, but to do anything other than that which is not inappropriate. The question becomes one of providing better guidance for the kinds of circumstances in which it is ethically appropriate to have very strict requirements for women to participate in a study and ensure that they are not pregnant.

There are equity issues as well with regard to men. Little time is spent thinking about the possibility, for example, that certain exposures may have a male-mediated negative effect on a developing fetus or on infertility issues. Women should be treated as women and pregnancy as something that could happen to them, rather than women as potentially pregnant people.

Audience comment: *The base rate of adverse birth outcomes.* There is a base rate of 3 percent for birth defects. In the current litigious environment, how does one tease out birth defects that were going to occur anyway, regardless of drug exposure or other investigational intervention, from defects that may have been induced by the intervention? The same problem occurs in a high-risk population of people with congestive heart failure who are in a trial. Which of those people would die anyway without the intervention? Why is a birth defect, which may have happened anyway, thought about differently, from a legal perspective, and some other really serious adverse event, like death? How does one incorporate the birth defect baseline into considerations of legal liability?

Panel comments: The situation is more complicated in the case of pregnancy than in the case of other populations. Even when healthy volunteers are enrolled in a trial and there are untoward events, one might say that they might have been cultivating, for instance, cardiovascular disease, before the trial and that the disease was not caused by the trial. More frequently, untoward events happen in clinical trials with adult subjects who are already sick so that the probability of an untoward event, independent of any intervention, is much higher.

With pregnancy, the mother's health status coming into the study is known and the assumption is usually that the fetus is healthy. So adverse fetal outcomes go against that model of fetal health, and they occur in an individual (the fetus) who is not capable of consent. These circumstances raise strong standards of scrutiny. There is a need to develop special legal models for these circumstances and the difficulty of doing so should not be underestimated.

Audience comment: *Dealing with risk for adverse events in pregnancy research.* There is a tendency to conflate consent with risk. The fetus cannot consent. But a trial would not be considered ethical, if the risk was unreasonable, based solely on the fact that subjects consented to it. In pregnancy research, the idea of acceptable risk and the need for consent are conflated.

The other side of the risk issue is that, at some point in some trials with pregnant women, adverse events may happen that do cause harm but at some very low frequency. At some point, society may need to be willing to take some risk because the benefits are so important. That discussion is very difficult to have for precautionary as well as for legal reasons. Part of the problem is that when events are very rare, it is hard to measure them accurately. How does one deal with the issue of acceptable risk? Is there such a thing as acceptable risk?

Panel comments: Even if an event is rare or uncommon, and beyond legal considerations, harm to the fetus is foremost in the minds of clinicians and investigators. Having some line of responsibility with fetal harm, either as a researcher or as an obstetrician or as a pregnant woman who participates in a study or takes a drug, is something with which all involved are really uncomfortable.

Those who take care of women who have early pregnancy losses know that they often tend to think the loss was caused by something that they did. It is very difficult to think that one might have had a role in harming a baby. Attributing responsibility to the collective "all of us" may be easier than taking on the hard responsibility that the individual investigator or clinician could be doing something that may harm the fetus. That individual burden is a difficult one. Nonetheless, investigators and clinicians may still shoulder the burden because there is a greater good served, and probably, overall fewer people across time are going to be harmed.

Audience comment: *Indemnification against liability.* Worry about something bad happening to a fetus is what prevents research sponsors from wanting to include pregnant women in clinical research. Is there some kind of mechanism that could be used to protect researchers, the NIH, and drug companies, or is this even desirable?

Panel comments: Legal issues are a shared concern. Liability issues may be raised for some kinds of research that are needed to advance the health interests of pregnant women. There are also many kinds of research designs where the legal liability issue is minimal. This research is the "low hanging fruit." One action may be to promote a research agenda that moves forward the lines of research that are judged, in consultation with legal counsel, so as not to pose serious legal liability.

For over 30 years, there have been commissions and discussions about creating some sort of a system for indemnification for research risks, but that has not been successful. There is little optimism that a distinction for pregnancy concerns can be created, if it has not been done for the research human participant system overall. It is going to take some very creative and innovative thinking about that relatively narrow subset of extremely important research in which the legal liability issues are the central concern.

Legal liability is not the sole driver of reticence. Pregnant women have, in some instances, been excluded, even for studies where there is minimal risk or no risk, such as a questionnaire study. Another important issue is an asymmetry in the justificatory burdens that IRBs consider. Currently, one must justify the inclusion of pregnant women and specify what special protections are going to be put in place. That may be appropriate, but there is no requirement to justify their exclusion from a protocol. Pregnant women are the only population for which justification for exclusion does not need to be given, which makes it easy for investigators to avoid issues entirely. This has nothing to do with risk to the fetus but more with ease. Presumption of exclusion needs to be dealt with, along with the issue of legal liability.

Pregnant women are the only population for which justification for exclusion does not need to be given, which makes it easy for investigators to avoid issues entirely.