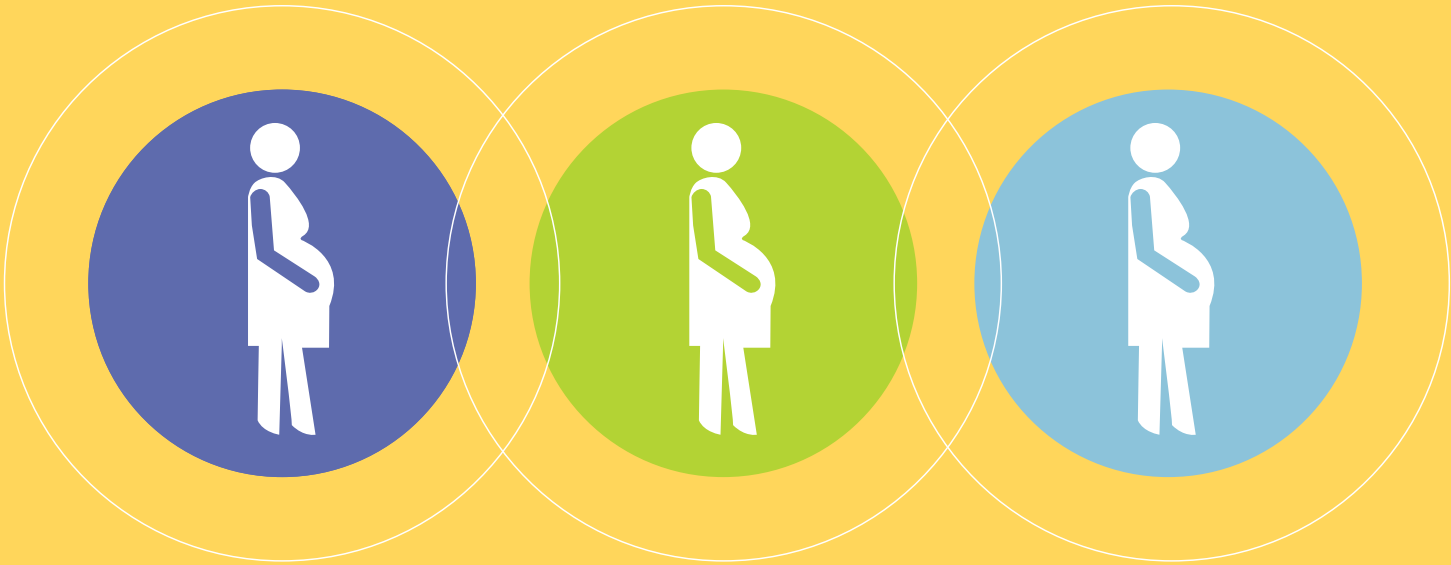
ENROLLING PREGNANT WOMEN:
ISSUES IN CLINICAL RESEARCH



An ORWH 20th Anniversary Event

Research Forum:

Ethics and Research in Pregnancy

Regulatory Requirements

Experiences in Clinical Research

ENROLLING PREGNANT WOMEN:
ISSUES IN CLINICAL RESEARCH

An ORWH Research Forum
October 18, 2010

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Sincerely,

Mary Foulkes, Ph.D.
Co-Chair
Office of Research on Women's Health
National Institutes of Health

Angela Bates, M.B.A.
Co-Chair
Office of Research on Women's Health
National Institutes of Health

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INTRODUCTION

"Pregnant women get ill, sick women get pregnant." Clinicians have meager evidence on which to base treatment of pregnant women. Clinical research investigates mechanisms of human disease and tests therapeutic interventions, but pregnant women are often excluded from clinical studies. Additionally, few studies are designed to address health concerns and questions relevant to pregnant women and this results in a lack of evidence to inform health care and treatment decisions for these women.

In October 2010, the Office of Research on Women's Health (ORWH) convened a scientific forum, *Issues in Clinical Research: Enrolling Pregnant Women* in partnership with several National Institutes of Health (NIH) institutes, centers, offices and the Food and Drug Administration (FDA), to address the ethical/Institutional Review Board (IRB) and recruitment issues that investigators face in the conceptualization, initiation, and conduct of clinical research studies that enroll pregnant women. During this forum, the audience was challenged to address gaps in knowledge about medical treatment and pregnancy, to increase the evidence base on the inclusion of pregnant women in clinical research, and to conduct appropriate scientifically-and ethically-designed clinical research. Medical ethicists, clinical investigators, academic researchers, and those with an interest in and concern about clinical research in women provided information related to risk perception, risk reasoning, and the ethics of balancing risks and benefits in the clinical arena. Additionally, examples of challenges and strategies to overcome barriers to clinical research in pregnant women with chronic or infectious diseases, or to the evaluation of preventive measures, such as vaccines, in pregnancy were presented.

Background Information

Historically, the fear that some women may become pregnant contributed to the rationale for excluding all women of childbearing potential from clinical studies. Both medical researchers and pharmaceutical manufacturers feared that if a woman participating in research became pregnant and her fetus was harmed, they might be held liable. This approach has led to gaps in knowledge about the health of pregnant women as related to metabolic activity and drug interactions. This fear was often the reason for the exclusion of women from clinical trials, despite a low reported incidence of research injuries and few reported legal cases concerning such injuries. Questions concerning liability risk are difficult to resolve, but there is growing consensus that the exclusion of women from research studies may pose just as much risk of liability as their inclusion.

While the NIH Inclusion guidelines state that "women of childbearing potential should not be routinely excluded from clinical research," the policy does not specifically address the participation of pregnant women, nor does it address liability issues. However, this issue was discussed in an Institute of Medicine (IOM) report commissioned by the ORWH, *Women and Health Research: Implications for IRBs*. In discussing this issue, the IOM report concluded that pregnant women should be presumed eligible for participation

in clinical studies. The report further recommended that pregnant woman be excluded only when the IRB finds that there is no prospect of medical benefit to the pregnant woman and that there is significant risk of harm to the potential offspring.

In moving from a paradigm of exclusion of vulnerable populations to one of inclusion, much still needs to be done to overcome some of the barriers that have prevented women from full participation, such as the widespread reticence to include pregnant women in clinical research that resulted from the thalidomide tragedy. Subpart B of the U.S. Department of Health and Human Services (DHHS) regulations for the protection of human subjects (45 CFR 46) reflects the presumption that pregnant women are as competent as non-pregnant women to weigh the risks and benefits of participation in an approved clinical study.

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Prioritizing Pregnancy Research and a Vision for Women's Health Research for 2020

Since its establishment, ORWH has had a mandated responsibility for developing and updating the NIH agenda for women's health research. In September 2010, the Office published a report entitled *A Vision for 2020 for Women's Health Research: Moving into the Future with New Dimensions and Strategies*. The report was the culmination of a two-year strategic planning process, beginning in 2008 and involving more than 1,500 leading scientists, women's health advocates, public policy experts, health care providers, federal, state, and local officials, and the general public as participants in five regional scientific meetings.

At the same time that ORWH was undertaking activities to set a new strategic plan on women's health research, the *Second Wave Initiative* at Georgetown University began efforts to focus attention on the need to increase the responsible inclusion of pregnant women in research. In a statement of the aims of the *Second Wave Initiative*, the presumption of exclusion of pregnant women from research was identified as the major factor that had led to a "troubling lack of knowledge" about how to treat their illnesses. The presumption of exclusion had also limited understanding of how illness during pregnancy affects women`s health across the lifespan. The *Second Wave Initiative* worked to develop an ethical framework to support the justice of increased inclusion of pregnant women in clinical research.

Moving Into the Future

There is clear evidence of the success of efforts over the past 20 years to increase the inclusion in clinical research of other underrepresented populations, such as non-pregnant women, minorities, and children; however, pregnant women remain, with very few exceptions, an excluded population. Investigators are now encouraged to include fertile women earlier in clinical trials. Consideration of the complexities of ethical and scientific issues that clinical research raises to address the health needs of pregnant women is needed.

This forum, *Enrolling Pregnant Women: Issues in Clinical Research*, addressed a complex set of issues regarding the persistent under-inclusion of pregnant women in clinical research and the underrepresentation of their health interests in such research. It is hoped that the presentations and discussions summarized in this report will help to guide the development of new protocols, enrich interactions with local IRBs, enhance the formulation of recruitment plans, and facilitate the conduct of clinical research in pregnant women.

WELCOME FROM THE ORWH DIRECTOR

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health, and
Director, Office of Research on Women's Health
National Institutes of Health

The NIH strategic plan for research on women's health identified six major goals for women's health research, one of which was the goal of increasing research to *"actualize personalized prevention, diagnostics and therapeutics for girls and women."* Among specific objectives listed for the goal were two objectives that directly addressed pregnancy: 1) *"encourage research on safe and effective interventions for conditions affecting pregnant women";* and 2) *"expand research on pregnancy related conditions, such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring."*

In April 2009, I had the opportunity to participate in a workshop of the *Second Wave Initiative* held at Georgetown University. That workshop provided participants with an update on progress that has been made in addressing the health needs of pregnant women by promoting their inclusion in clinical research and by developing an ethical framework from which to consider a full range of issues for pregnant women and their fetuses. At the workshop, it was determined that an important next step in the process would be to bring the issues back to NIH.

Today, we will hear discussions of the next steps needed to move forward in enrolling pregnant women responsibly in clinical research that addresses their pressing health needs, as well as the issues that NIH should consider in terms of protecting them and their fetuses. We will also hear from speakers who have been in the forefront of pioneering research on conditions affecting women during pregnancy and of the many valuable lessons from their activities. This knowledge, as well as lessons learned from NIH activities to increase the inclusion of women in clinical research, can provide a firm basis for guiding future women's health research.

We know that just because a woman is pregnant, that does not mean that she does not get sick, so there is a moral imperative to address her health needs while pregnant and to consider the implications of her pregnancy for her future health. It is critical that we work proactively to institute responsible policies for inclusion of pregnant women in our research studies.

I want to thank Dr. Mary Foulkes and Ms. Angela Bates from ORWH for taking the lead in pulling together this wonderful workshop. Thank you to all of the speakers who have come today to help us again give due attention to this issue. We are looking to you to help guide our discussions and indicate where we need to go from here.

WELCOME FROM THE NICHD DIRECTOR

Alan E. Guttmacher, M.D.
Director,
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

Thanks very much to Dr. Pinn and to the Office of Research on Women's Health for holding this workshop. I am honored to be participating in an activity that is part of the 20th anniversary celebration of the founding of ORWH, which has made so much of a difference, in the life of NIH and, more importantly, in the health and lives of women, not just across the United States but around the world. We expect even more of a contribution from the Office in the next 20 years as it reaches its adulthood.

NICHD is very proud to cosponsor this research forum because this topic is so important. It is important not just to the mission of NICHD, but to the health and well being of pregnant women and their children. There is so much we still do not know about how to treat pregnant women with health problems effectively and safely and how to prevent poor pregnancy outcomes. Clinical research could help provide that information. Yet, there remains a literally unhealthy reluctance to include pregnant women in clinical trials.

Certainly, there are unique risks and ethical issues involved in the inclusion of pregnant women in clinical studies, but my message to you is really a simple one. That is, that these barriers are not insurmountable. It is our duty, if we are to serve pregnant women and their children, to figure out how best to surmount these barriers. That is the goal for the day.

In fact, we have undertaken clinical trials involving pregnant women before and we have done them successfully. NICHD has maintained a longstanding commitment to furthering research in reproductive health, pregnancy, and pregnancy outcomes. We support a number of studies involving pregnant women, often with co-funding from other NIH institutes, centers and offices.

The Management of Meningomyelocele Study (MOMS) trial is well known. It compares the safety and efficacy of fetal cervical repair versus traditional postnatal repair for babies diagnosed in utero with spina bifida. Findings indicate that the fetal repair procedure is associated with superior postnatal outcomes.

The Prenatal Alcohol and SIDS and Stillbirth (PASS) Network, co-funded by NIAAA, investigates the role of prenatal alcohol exposure in the risk for SIDS and adverse pregnancy outcomes, such as stillbirth and, of course, fetal alcohol syndrome. The PASS Network enrolls women from two high-risk groups, Native Americans of the Northern Plains and women of color in the western cape of South Africa, and it aims to decrease fetal and infant mortality and improve child health in these communities.

The Obstetric Pharmacology Research Units (OPRU) Network is carrying out a wide range of pharmacokinetics and pharmacodynamics studies to improve therapeutics during pregnancy. The OPRU Network's current research focuses on oral hypoglycemics for the treatment of gestational diabetes, agents thought to alter uterine activity, and a broad range of other drugs used during pregnancy, such as antibiotics and antidepressants. These sorts of studies have a direct impact in clinical practice, informing medical guidelines and recommendations that improve patient outcomes.

A number of NICHD funded studies have revealed that some common practices are not beneficial for patients, despite what many had thought. For example, the Combined Antioxidant and Preeclampsia Prediction (CAPPS) study was a randomized clinical trial of 10,000 pregnant women, supported by NICHD, NHLBI, and NCRR. Findings from the study indicated that vitamin C and D supplements do not reduce the risk for hypertensive disorders and other complications that occur during pregnancy. This finding contrasted with suggestions from previous smaller studies that vitamins could reduce the risk of preeclampsia.

In two trials done by the Maternal Fetal Medicine Units (MFMU) Network, researchers found that antibiotic treatment for pregnant women with asymptomatic bacterial vaginosis did not reduce preterm delivery or other adverse perinatal outcomes. Treatment was actually associated with increased risk of preterm delivery. The results from these trials have helped lessen the indiscriminate use of antibiotics in pregnancy.

While some of these studies have stopped clinical practices, others have resulted in new preventive therapies or treatments. The Beneficial Effects of Prenatal Magnesium Sulfate (BEAM) trial, co-funded by NINDS, enrolled women who were immediately at risk for preterm birth in a randomized clinical trial to evaluate whether magnesium sulfate could prevent cerebral palsy. That study indicated that the intervention reduced cerebral palsy by a third. In other studies, the MFMU Network found that weekly injections of progesterone helped prevent recurrent preterm birth and improved neonatal outcome for pregnancies at risk.

These are just a few highlights of NIH supported studies concerning pregnant women in clinical research. There are certainly more that could be cited.

I am glad you have the opportunity today to hear a range of expert speakers, including NICHD's Catherine Spong and Heather Watts, to help us consider how best to move forward. I encourage all of you to take an active part in these conversations and to continue to talk about these topics.

We certainly hope the conversations today will provide new momentum to help us get the answers we so sorely need and to build on our past successes in improving the health of pregnant women and their children.

CHAPTER ONE: ETHICAL PRINCIPLES OF RESEARCH ON EFFECTIVE TREATMENTS DURING PREGNANCY: *PART 1*

Overview

The speakers in this session, Drs. Anne Drapkin-Lyerly, Ruth Faden, and Margaret Little, are the founders of the *Second Wave Initiative*, which advocates for the responsible inclusion of pregnant women in clinical research in order to fill the knowledge gap on treating illnesses during pregnancy. The speakers have worked to develop an ethical framework for inclusion that is based on four general considerations: (1) the need for effective treatment; (2) fetal safety; (3) harm caused by reticence to treat pregnant women; and (4) disrespect.

In the first presentation, Dr. Drapkin-Lyerly provides a brief background of the need for research in terms of the scope of illnesses that affect pregnant women and a history of earlier Federal efforts to increase the inclusion of women in clinical research from the 1990's to the present. She also discusses historical justifications for exclusion of pregnant women as participants in clinical research. Her review indicates that a persistent presumption of exclusion of pregnant women from clinical research is a major impediment. In her presentation, she presents the several reasons arguing for change in policy and practice.

The second presentation by Dr. Faden continues the development of the ethical argument for the inclusion of pregnant women in clinical research from the perspective of justice. She discusses the injustices of denial of direct benefits of clinical research to pregnant women and the underrepresentation of interests of pregnant women in the clinical research enterprise. She argues that pregnant women are unjustly burdened by the application of research findings to them from which they were excluded due to extreme reticence and the precautionary principle. These factors demonstrate disrespect for pregnant women when they are viewed primarily as vessels for a pregnancy rather than as individuals with health needs and who are capable of making informed decisions about their health care and participation in research.

The third presentation by Dr. Little provides examples of how pregnant women with extremely serious medical conditions were denied needed treatments due to misapplication of the precautionary principle and unwarranted reticence by physicians to treat pregnant women. In her presentation, she discusses the need for regulatory changes that will clarify issues of including pregnant women, current efforts to mine available data, and design of new study approaches as they relate to the pregnant women populations. Further, Dr. Little recommends considering redefining the current regulatory status of pregnant women from a "vulnerable" population to one of a "complex" population. In this way, special issues in pregnancy would be considered but would not present insurmountable impediments to needed research in all women.

Direct Benefit to Pregnant Women

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Each year, over 400,000 women in the U.S. confront significant medical illness while pregnant, but information about how to treat these conditions in pregnancy is profoundly limited. Much of what will be discussed today stems from work as part of the *Second Wave Initiative* (http://secondwaveinitiative.org). The *Second Wave Initiative* acknowledges the need for responsible inclusion of pregnant women in clinical research and confronts the challenges of such inclusion. The Initiative's work is undergirded by four reasons that such inclusion is ethically required. These include: (1) the need for effective treatments for women during pregnancy; (2) fetal safety; (3) harm stemming from reticence to prescribe potentially beneficial medication and (4) broader issues of justice and access to benefits of research participation. This presentation will focus on the first three of these principles; while the presentation of Dr. Ruth Faden, will examine the fourth.

Before discussing guiding principles of the *Second Wave Initiative,* however, a bit of history is in order. If we are now working on the "Second Wave," what was the "First Wave?" The "First Wave" refers to the activities undertaken about twenty years ago by scientists, advocates, and policymakers to ensure the inclusion of women in clinical research. In the early 1990's, women were underrepresented in clinical research–even excluded from major clinical trials of interventions for serious conditions affecting them, such as cardiovascular disease.

Justifications commonly proffered for their exclusion included the complicated nature of women's physiologies, the need to protect them and their fetuses, and difficulties in recruiting them into research. These issues were discussed and disputed, and the process culminated in a requirement in the NIH Revitalization Act of 1993 for the inclusion of women and minorities in NIH funded research. In large part because of these activities, women are now the majority of participants in NIH funded research studies, but that majority holds only for non-pregnant women. Pregnant women remain profoundly underrepresented in research.

This was not the intention of those moving forward the "First Wave." In 1994, an IOM committee issued a report on challenges and barriers to the inclusion of women in clinical research. The IOM committee authors recommended that pregnant women be presumed eligible for participation in clinical studies. Taking into account special considerations for pregnant women and their fetuses, the report specified acceptable

exclusion criteria: (1) no prospect of medical benefit to the pregnant women; and (2) risk of significant harm to offspring. Despite the report and its recommendations, in practice, pregnant women continue to be excluded from the vast majority of studies by most IRBs and researchers, even studies that hold a negligible prospect of risk to women or their offspring. This exclusion is consequential in a number of ways.

A few years ago, as a member of an IRB for Family Health International, many researchers who were studying the efficacy of a vaginal microbicide in sexually transmitted diseases (STDs) and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) prevention became concerned because of very high pregnancy rates in their study population. They sought advice from the IRB about the ethical considerations that should be taken into account when counseling patients about contraceptive options and about how hard the researchers could push subjects to use contraception. When asked why pregnant women were not included as subjects (since the high rate of pregnancy in the study population suggested strongly that pregnant women would be among its consumers if the drug was shown to be effective), the researchers offered reasons that were reminiscent of those given for the exclusion of women from clinical research prior to the NIH Revitalization Act of 1993. Reasons included complicated physiologies of pregnant women, alterations in mucous membranes, vaginas and cervixes, the effects of these changes on the interpretation of study results, and the need to protect women and fetuses from the potential risks of the drug. It was striking that the risks of HIV during pregnancy for the women and their fetuses were not on their radar screens. So, this issue was discussed with colleagues Ruth Faden and Maggie Little nothing that something needed to be done about the pervasive presumption of exclusion for pregnant women. The result has been that, over the last few years, we have developed a framework to describe the need to move forward responsibly with the inclusion of pregnant women in clinical research.

Over the last few years, we have developed a framework to describe the need to move forward responsibly with the inclusion of pregnant women in clinical research.

Reason 1: The Need for Effective Treatment

Four million women give birth in the U.S. yearly. Many of them face medical conditions when they are pregnant such as hypertension (5 percent; 190,000); diabetes (4 percent; 150,000) and psychiatric illness (approximately 15 percent, 500,000). A range of other conditions, such as nausea and vomiting, migraines, lupus, and even cancers, can also complicate pregnancy. Pregnant women with these conditions need treatment, but despite this, very few drugs are approved for use during pregnancy, and little pharmacokinetic and pharmacodynamic research is available to inform clinical treatment guidelines.

Women's physiology during pregnancy is different from the non-pregnant state and that difference provides a compelling reason to study the activity of drugs in pregnant women. Pregnant women's physiology differs from the non-pregnant state in many ways, such as increased cardiac output, decreased gastric emptying

and intestinal transport and increased renal excretion, all of which can lead to significant changes in the way drugs are metabolized. The impact of pregnancy on pharmacokinetics is difficult to predict. Pregnancy acts as a "wild card" in how drugs are processed. A review in the journal *Obstetrics and Gynecology* found only 61 articles with relevant pharmacokinetic data and two articles that resulted in evidence-based guidelines. Furthermore, there was no consistency of results, even for similar drugs.

In recognition of a need to develop more evidence, in 2003, the National Institute of Child Health and Human Development (NICHD) formed the Obstetric Pharmacology Research Units (OPRU) Network. The OPRU Network serves in part as a proof-of-concept platform to demonstrate that clinical investigations can be performed in pregnant women. Here are two examples of what researchers participating in the network have found about dosing in drugs commonly used during pregnancy.

Amoxicillin Amoxicillin is a drug known to be safe to administer during pregnancy. Amidst widespread concern over the possibility of a public health crisis from anthrax exposure, the DHHS Center for Disease Prevention and Control (CDC) and American College of Obstetricians and Gynecologists (ACOG) recommended amoxicillin for anthrax prevention in pregnancy. However, a recent study of the pharmacokinetics of amoxicillin indicated that concentrations adequate to prevent anthrax were probably not achievable during pregnancy due to increased metabolism of the drug. If the threat of anthrax exposure had materialized, pregnant women would have been undertreated because of the way that their bodies metabolize a drug that we know is safe in pregnancy.

Glyburide Diabetes is common in pregnancy and it is critical to maintain glycemic control in order to ensure optimal fetal development. A clinical trial by Cooper and colleagues found that glyburide could be used safely in pregnancy, and so the drug was added as a therapeutic option. However, until recently, the pharmacokinetics of glyburide had not been studied in pregnant women. As part of the OPRU Network, a study by Hebert and colleagues of women with gestational diabetes mellitus found that, at equivalent doses, glyburide plasma concentrations were approximately 50 percent lower than in non-pregnant women. Pregnant women in clinical trials were likely not receiving a therapeutic dose. If they had been, the results would have been even more in favor of glyburide use as an effective treatment for diabetes.

Other examples of our lack of knowledge about drug metabolism in pregnancy include chemotherapeutic agents and antivirals, such as Tamiflu or Relenza. Clearly if we are going to move ahead and use medications in pregnancy, and it appears that we are, then we need to know how to dose correctly. There is a need to know whether standard therapeutic doses will work or not. There is a need to know how to treat pregnant women when they get sick, and, right now, it is not known how to do this.

Clearly if we are going to move ahead and use medications in pregnancy, and it appears that we are, then we need to know how to dose correctly.

Reason 2: Fetal Safety

Fetal exposure to medicine is widespread. It is estimated that two thirds of pregnant women use four to five medications. More than 40 percent of women use FDA class C or D drugs and about 50 percent of U.S. pregnancies are unintended. However, the teratogenic risks of drugs are largely unknown. Furthermore there is no correlation between how long a drug has been approved and how much we know about risk profiles in pregnancy. This lack of knowledge again is potentially harmful. Two examples are illustrative.

ACE Inhibitors Hypertension is a common complication of pregnancy, and it often requires pharmacological management. ACE inhibitors are a class of antihypertensive drugs that were not recommended for second and third trimester use due to potential fetal risks, but there had been no such caution toward first trimester use. Not until 2006, nearly 30 years after ACE inhibitors were approved for use, was it finally realized that first trimester fetal exposure was associated with increased risk of major congenital malformations.

Thalidomide No talk on pregnant women in research would be complete without mention of Thalidomide, a drug approved in the 1950s in Europe for the first trimester of pregnancy which resulted in major birth defects in exposed fetuses. The experience led to an almost universal exclusion of pregnant women from research. But the lesson that ought to have been drawn from it is that the birth defects resulted not from enrolling pregnant women in research but from inadequate research standards prior to approval. The damage could have been mediated if the drug had been studied in pregnant women before its distribution acrosss Europe.

Reason 3: Reticence to Prescribe Medication

Reticence refers to a tendency for clinicians to undertreat during pregnancy and for patients to discontinue or eschew their medications out of concern for harm to the fetus. Often, however, the harm of undertreatment during pregnancy is greater than the risks of medication use.

Untreated depression is associated with suicide, premature delivery, and small-for-gestational-age infants; whereas infant outcomes of successfully treated women are about as good as for non-depressed women. Untreated asthma is associated with preeclampsia, premature delivery, hemorrhage, and low birth weight, but the outcome for infants of effectively treated mothers is equivalent to that of non-asthmatic women. Women with uncontrolled diabetes in the first trimester of pregnancy are at high risk of delivering a baby with a birth defect, but despite this, women still may stop taking oral hypogylcemics in early pregnancy due to misplaced concerns about the effects of the medication on fetal outcomes. Reticence to treat also occurred during the recent threat of a flu epidemic. Reticence to use the H1N1 vaccination was common;

this despite the fact that H1N1 infection during pregnancy conveyed especially high risk. When pregnant women were infected, there were delays in diagnosis and pregnant women were more likely to require hospitalization. Thus, once hospitalized, there were delays in the use of anti-viral medications.

In summary, the current approach to treatment during pregnancy has resulted in significant knowledge gaps and harms. Pregnant women are left with two unacceptable options: either take a drug of unknown safety and efficacy or fail to treat a condition, with consequences. Pregnant women deserve better.

Pregnant women are left with two unacceptable options: either take a drug of unknown safety and efficacy or fail to treat a condition, with consequences. Pregnant women deserve better.

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Justice in Health Research: Beyond Protection from Risks

Ruth. R. Faden, Ph.D., M.P.H.
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There is moral urgency to increase research that includes pregnant women: This urgency is all the more evident when issues are framed in the language of justice. There are four different kinds of injustice that characterize the current lack of inclusion of pregnant women in clinical research.

Denial of Benefits of Research Participation

The first injustice, and the one most commonly mentioned with regard to pregnant women, is the denial of direct benefits of research participation. This assumes that there is a prospect of direct clinical benefit to at least some patients when they enroll in clinical trials. Dr. Drapkin-Lyerly provided an example of injustice resulting from the exclusion of pregnant women from microbicide trials. The benefits accruing to pregnant woman in preventing HIV/AIDS infection, and to the fetus in preventing its vertical transmission were substantial, but even in this "win-win" situation, researchers were reluctant to include pregnant women in the research.

A more extreme case would involve an early stage clinical trial for a very serious cancer with a very poor prognosis. It would be easy to conclude that pregnant women with the cancer should not be involved because of potential risks of treatment to the fetus. However, this argument ignores a fundamental alignment of maternal and fetal interests. That is, it is in the fetus' interest to have a mother who survives her disease.

A new health care system is slated to be implemented within a decade. As part of this system, a new learning health care environment will also need to be put in place, with research findings integrated more rapidly into treatment guidelines. Comparative effectiveness research will guide treatment. This integration of research and clinical care will only increase the egregiousness of the injustice of denying the benefits of research to pregnant women.

Underrepresentation of Pregnant Women's Interests in Research

A second injustice is that pregnant women's health interests are underrepresented in the research enterprise. Here the focus shifts from the interests of individual women who are treated unjustly to the interests of pregnant women as a class. There is an assumed societal pact with science. Biomedical research is granted tremendous status and public funding. Research participants allow scientists access to health information and even their own bodies because of their belief that, as a consequence of this access, beneficial knowledge will accrue.

An injustice occurs when some groups do not benefit from this understanding as much as other groups. In recent years, there has been great progress in this regard with respect to children and women in clinical research. It is an empirical and moral point of contention whether or not minorities are now represented as a group at a sufficient level of equal and fair sharing in the benefits that should come from society's investment in biomedical research.

In biomedical research, there is probably no group that is treated less fairly than pregnant women. Another way of saying it is that no group is more underrepresented in biomedical research than pregnant women.

For pregnant women, what does "underrepresentation" mean? The simplest way to think about it is to say that pregnant women should be represented in research in proportion to their representation in the population of participants in clinical trials; and that, if that proportion is achieved, pregnant women should be considered as fairly represented. But that view is flawed. There needs to be a focus, not only on the relative numbers of pregnant women, but also on the health interests of pregnant women. An example is illustrative of the point that merely including pregnant women does not begin to address this kind of injustice. In the early days of the HIV/AIDS epidemic, it was recognized that women were at risk for contracting HIV/AIDS. They began to be enrolled in natural history studies to understand the course of the infection. But those early studies of HIV-infected women did not include gynecological outcomes. In this instance, even though women were included, their interests were not well-addressed.

There needs to be a focus, not only on the relative numbers of pregnant women, but also on the health interests of pregnant women.

Similarly, including pregnant women in clinical trials will not address the injustice of underrepresentation unless questions in those clinical trials are directed at the health needs of pregnant women and the design of the study is powered such that those questions can be asked. It is not adequate to consider only the impact on health during pregnancy. What also must be considered is the impact of treatment (or non-treatment) during pregnancy on the health of women over the course of their lifetimes.

Disproportionate Burden of Research Findings on Pregnant Women

Research findings impose a disproportionate burden on pregnant women. Extreme reticence to treat is the outcome of the application of an extreme cautionary principle to pregnancy. Furthermore, even when research findings suggest that a practice could be liberalized, the precautionary principle is maintained for pregnant women.

What also must be considered is the impact of treatment (or non-treatment) during pregnancy on the health of women over the course of their lifetimes.

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.

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.

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.

CHAPTER TWO: ETHICAL PRINCIPLES OF RESEARCH ON EFFECTIVE TREATMENTS DURING PREGNANCY: *PART 2*

Overview

The two presentations of the session continue the focus on ethical principles in clinical research for the responsible inclusion of pregnant women in clinical research. Dr. Katherine Wisner shares her broad experience as a clinician and as a researcher who has been working with pregnant and postpartum women. She asserts that questions about treatment in pregnancy must always weigh relative risks and benefits, and so can never be absolutely clear cut. Separation of fetal and maternal risks and benefits can create a false dichotomy, when in fact, these risks and benefits are entwined. In risk-benefit considerations, there is a tendency for the focus to be on errors of commission rather than omission, but the adverse effects of failure to treat can be more harmful to both mother and fetus than any adverse effects attributable to treatment. In clinical care, clinicians and patients must enter into individualized risk-benefit discussions in order to make the best clinical decisions for the individual patient. Dr. Wisner also discusses difficulties in isolating the effects of a treatment exposure from the effects of numerous other exposures.

Dr. Robert Levine's presentation provides a review of regulations governing the inclusion of pregnant women in clinical research and a discussion of ambiguities in current regulations that serve as an impediment to clinical research. In particular, ambiguity, combined with IRB conservatism in interpreting regulations and fears of legal liability, serve as major barriers to including pregnant women as participants in clinical research. He cites a survey of IRB chairs who were asked to evaluate the degree of risk for various kinds of research on children as evidence of IRB significant conservatism, as well as considerable inter-IRB variability in assigning different degrees of risk. Furthermore, similar conservatism and variability in degrees of risk pertain to research involving pregnant women as participants. For example, current proposals to require contraceptive use in women of childbearing age as a condition for their participation in clinical research may not only restrict women's participation, but may also limit the generalizabiity of findings.

Treatment During Pregnancy: Are We Asking the Right Questions?

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How do researchers arrive at the questions they ask in their studies of pregnant women? How do those questions and their answers reflect issues in treatment? Does research provide the kinds of information that women and clinicians need to determine treatment options? As a clinical researcher and as a clinician

who has treated over a thousand pregnant and postpartum women, these questions have been grappled with for many years.

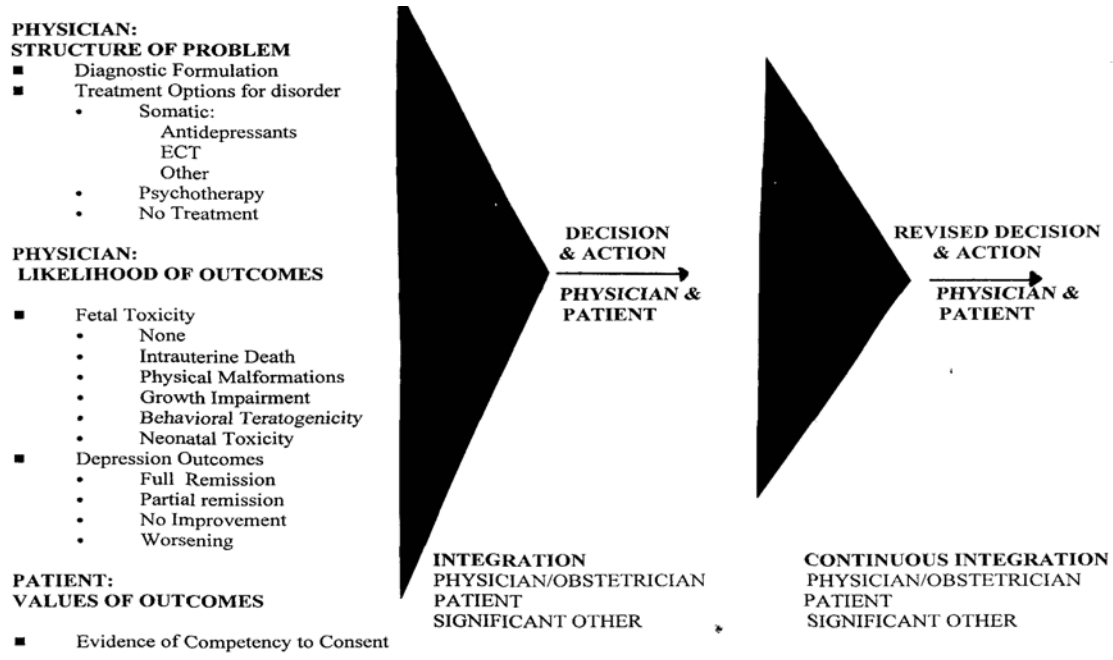
There is little doubt that, when treatment in pregnancy is at issue, the focus becomes one of the liability that could result from treating the pregnant woman and having adverse birth outcomes. There is little talk about the liability of not treating her and having adverse birth outcomes, although both outcomes are possible from a liability standpoint. Errors of commission are emphasized rather than errors of omission.

Consider the example of patient who is four weeks post-conception. She is taking fluoxetine and wants to know if the drug is "safe," by which she probably means that the drug has no adverse effects. The word "safe" has no operational definition in this context, and framing the question in this way presents clinicians and researchers with the impossible task of proving a negative effect. That is to say no effects of an exposure on any of a large number of reproductive and developmental outcomes throughout the exposed offspring's lifespan and perhaps arguably, the lifespan of his or her offspring.

A Model for Clinical Decision Making

A better way to frame issues is to ask a question about risks and benefits. About a decade ago, a work group from the American Psychiatric Association took on the task of structuring the discussion of risks and benefits for the treatment of depression during pregnancy, and they developed a model for making decisions. This model is shown in Figure 1.

FIGURE 1: MODEL FOR DECISION-MAKING: DEPRESSION DURING PREGNANCY



In this model, the physician's role is to discuss with the patient, not only what is known about the risks of different treatments and their benefits, but also the likelihood that any adverse outcomes could be related to the depression itself. The patient is asked to consider this information and place values on risks and benefits, so that she arrives, with the physician's help, at an optimized individual decision. This is a complex process, one made more so because pregnancy is a dynamic process in which the best decision at one point may not be the best at a later point.

Risks and Benefits of Exposures and False Dichotomies

How are possible risks identified? Typically, hypotheses about exposure risks are generated first by means of case studies of exposure outcomes and then by larger observational studies. Numbers of adverse events associated with exposure are based on a limited set of reproductive outcomes. For fluoxetine, which was released in 1988, it is only recently that large scale case control studies have provided better answers to questions of exposure risks.

This emphasis on exposure and risk creates false dichotomies. Consider four possible outcomes of a pharmacological treatment during pregnancy. Option 1: good for the mother and bad for the fetus, Option 2: good for the mother; and the fetus; Option 3: bad for mother, good for fetus; and Option 4: bad for both mother and fetus. Option 4 is obviously undesirable and Option 2 is a "win-win" situation, but what about option 3? This situation is clinically rare, although there are certainly treatments that are delivered to the fetus through the mother, so it is conceivable. Option 1 is the one that clinicians most often grapple with. Yet, both options 1 and 3 are based on a false dichotomy. Benefit or harm to the mother is almost always linked to benefit or harm to the fetus, since, as the previous presentations have pointed out, a healthy mother who survives her disease is of great benefit to her baby. In fact, the questions that need to be asked are whether the benefits of treatment with a medication are greater than the established risks associated with its use or with the untreated disease process. These are exceedingly complex questions.

Clinical Complexities

Regarding complexity, the case of a patient with schizophrenia is instructive. The patient was taking depot fluphenazine, a medication to treat her psychosis. Every time she stopped her medication, she saw horrible demons who were trying to consume her. She became pregnant and decided to continue her medication because she thought that her usual behaviors off medication, such as trying to jump out of a window to escape the demons, would not be conducive to good health during pregnancy. She also suspected that

In fact, the questions that need to be asked are whether the benefits of treatment with a medication are greater than the established risks associated with its use or with the untreated disease process. These are exceedingly complex questions.

her baby was at a higher risk of eventually developing schizophrenia because of her diagnosis. She asked a really interesting question, whether or not taking the medication during pregnancy might help decrease the baby's risk to develop schizophrenia later on. Patients are often the best teachers as far as questions go. The possibility that maternal treatment might improve the offspring's health is rarely considered.

Returning to the case of the pregnant patient currently taking fluoxetine for depression, she needs to know whether her pregnancy outcome is likely to be better if she continues or discontinues fluoxetine. That is a very different question than whether it is safe in absolute terms. What weight does she assign to the value of her own health or interests compared to the weight she assigns to preventing any possible risk to the well being of the fetus? She may conclude that the drug's risks are worth it since she cannot function when she discontinues medication, and if she cannot function, she may lose her job, which is an unacceptable outcome, since she is a single mother supporting her family.

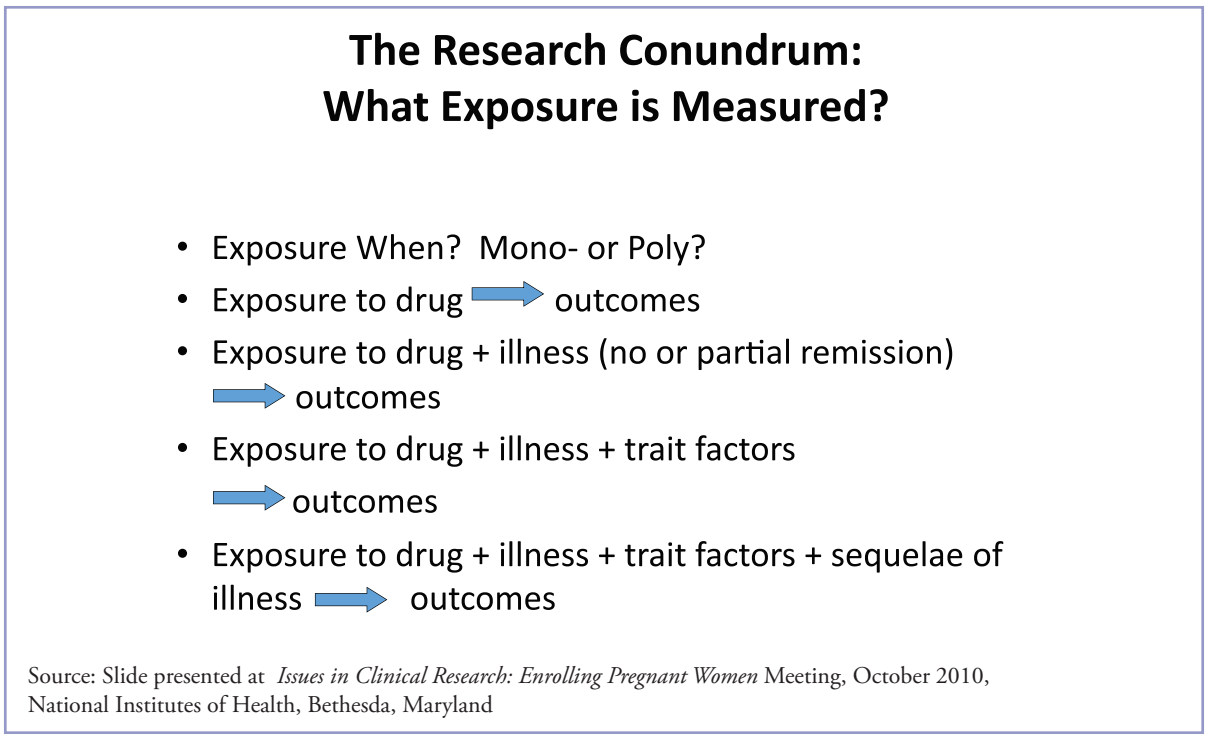
Another woman, weighing the drug's risks and benefits, may decide that no matter how small the risks, she cannot be comfortable taking this drug during pregnancy. For a clinician, the experience of monitoring a depressed woman who declines any kind of pharmacological treatment and does not respond to non-drug treatments or to electroconvulsive therapy or other kinds of somatic interventions is extremely difficult. Some of these patients become nonfunctional and suicidal. For these patients, would it have made a difference if the clinician had been able to tell them that based on findings of a research project, for women with their level of depression, treated outcomes for mothers and babies were better than for non-treated mothers? Research of this kind is needed.

Another patient asks about the risks of taking active medication in pregnancy, given that the placebo response rate in depression treatment studies is so high, around 30 percent. Why risk an active treatment when a placebo pill could work? It is conceivable that a placebo control study would provide answers about the placebo effect in pregnancy, but such a study is probably not possible given ethical concerns its design raises.

The above questions concern outcomes in groups but the individual patient wants to know about her individual risks and benefits and her baby's individual risks and benefits. These are not predictable based on population statistics, and a particular patient may not be exactly like those women who have the benefit and minimal risk. The clinician's task is to push the limit to understand from the research why and how affected members of the population are affected and non-affected members are not affected. Qualifying variables, such as nutrition, other environmental risk, genetics, and gene by environment interactions, can be garnered from population and clinical research, and they can be used to provide more personalized treatments. Such detective work is a challenge in dealing with women who are pregnant and postpartum.

Research Conundrum: Defining Exposures

Defining exposures presents pregnancy researchers with a major conundrum as outlined in Figure 2. Exposures are identified and operationalized differently by different investigators, particularly for the treatment of depression. Some investigators identify as controls, women who were on antidepressants but stopped when they found out that they were pregnant. Other investigators include in their control groups, only those women who have absolutely no exposure to antidepressants documented by either serum levels or drug screens. Because pregnancy is a dynamic state, there are different kinds of definitions of exposures. Does exposure refer to first and third trimester exposure or to second and third trimester exposure?



Source: Slide presented at *Issues in Clinical Research: Enrolling Pregnant Women* Meeting, October 2010, National Institutes of Health, Bethesda, Maryland

The simple model of comparing a drug exposed population with a non drug-exposed population, in fact, does not work very well. In many studies of a drug, such as fluoxetine, an exposed group is compared to a general population or a population not exposed. The assumption is that the outcomes are related to fluoxetine. In fact, the outcome probably reflects the exposure to fluoxetine, as well as exposure to some underlying level of the disorder that is not fully treated. Or, perhaps what the outcome reflects is exposure to the drug, exposure to some level of illness, and some type of trait factors of the psychiatric condition that heighten risk, even if the symptoms are in remission. What the outcome reflects may be all of those factors, plus the sequelae of illnesses. Chronic and prolonged depression can lead to job loss, loss of insurance, social isolation, and living in neighborhoods with high exposure to environmental toxicities, including violence. So there is a need to expand understanding of the kinds of contextual factors that are considered.

Comorbidities complicate definitions of exposure. Many pregnant women with depression also have other kinds of medical comorbidities or comorbidity with substance use disorders. This latter comorbidity is common in depressed and bipolar populations. Therefore, the complexity increases, because the exposures under consideration are not only to antidepressants, but exposures to other substances. In fact, very little is known about the pharmacokinetics and pharmacologic interactions of various drugs in pregnancy.

So where does that leave clinicians wanting to maximize the benefits of treatment? It is known that women who continue antidepressants during pregnancy have a relapse risk of about 26 percent, compared to 68 percent if they stop their drug. That is certainly a significant difference and important information; one that patients need to weigh when they consider discontinuing their medication. However, what is an adequate dose of medication to prevent relapse?

The FDA issued a draft guidance document on pharmacokinetic studies in pregnancy. It emphasized treating pregnant women so as to optimize results for the maternal-fetal pair. In order to do that, it is important to obtain pharmacokinetic data that reflects changes in drug metabolism across pregnancy. Some laboratory data indicates that serum levels for two antidepressants, sertraline and citalopram, decline across pregnancy. Many women may in fact be at risk for relapse in late pregnancy if their dosage is not adjusted to reflect pregnancy related changes in metabolism. Thus, mother and fetus may be exposed to any risks associated with these drugs during pregnancy, without also gaining the benefits of a therapeutic dose. Clinicians need to be proactive and modify dose as pregnancy advances, rather than waiting for the patient to call them when they have relapsed. To do this, they need predictive models derived from population-based research.

Researchers need to intensify the quality and the quantity of research and pose more sophisticated questions in order to arrive at more comprehensive answers to crucial questions that will impact the care of pregnant women with psychiatric disorders. Clinicians need evidence-based tools to bring more science to their art of medical practice. This is a challenging, but rewarding research area with potential immense benefit to women and their children.

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IRB Perspective on Inclusion of Pregnant Women in Clinical Research

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This presentation reviews the history of the development of policies governing research on pregnant women and discusses current guidelines and justice-based arguments for their inclusion. The conservatism of IRBs in reviewing pregnancy research is also discussed.

History of Policy Development in the Field

In 1974, Congress asked the newly formed National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to produce a report on research involving pregnant women and fetuses. In doing this, the Commission was influenced by recent major events that altered the nation's social landscape. In the aftermath of the US Supreme Court's decision in 1973 in *Roe v. Wade,* there was much ethical commentary and controversy on balancing women's recently recognized rights against the anti-abortion position. Controversy entailed a central focus on what was then called the maternal-fetal conflict.

The Commission was also influenced by the publicity surrounding such unfortunate events as thalidomide, diethylstilbestrol, and the Dalkon Shield. It is worth noting that none of these events were research. In each case, the problem was that research had not been done to validate the use of the product. This point notwithstanding, they stood as powerful metaphors for the dangers of research involving women who were or who might become pregnant. Fear of causing harm led to a protectionist stance, particularly regarding any exposure of the fetus to research interventions.

The Commission was given four months to produce its report on research involving the fetus. This timeline was not sufficient to create a credible document. Furthermore, the Commission's work was completed without benefit of the conceptual clarifications that were first presented in its 1978 *Belmont Report*. Consequently, it took many years to clarify the resulting regulations and to bring them into harmony with the rest of the regulatory corpus.

In subsequent years, there emerged a series of corrections to the federal regulations. In 1986, NIH policy was changed to encourage the inclusion of women in research. In 1990, the Women's Health Equity Act was passed, and the Office for Research on Women's Health was established. In 1993, the FDA withdrew its restriction on women's participation in early phase clinical trials. In 1994, NIH also took the next step and mandated the inclusion of women in clinical trials. In 2001, Subpart B of 45 CFR 46 was modified.

TABLE 1: THE CURRENT WORDING OF §46.204.

45 CFR46 Subpart B	Category	Explanation
§46.46.204	**Pregnant women or fetuses may be involved in research if ALL of the following conditions are met**	a. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses; b. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means; c. Any risk is the least possible for achieving the objectives of the research; d. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions; e. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy r esulted from rape or incest. f. Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate; g. For children as defined in Sec. 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of the Protections for Children Involved as Subjects (Subpart D); h. No inducements, monetary or otherwise, will be offered to terminate a pregnancy; i. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; AND j. Individuals engaged in the research will have no part in determining the viability of a neonate.

Interpretative Challenges in Subpart B § 46.204

The interpretation of some aspects of Subpart B still presents challenges to IRBs. Subpart B states that: "Pregnant women or fetuses may be involved in research if all of the following conditions are met," and it outlines ten conditions, shown in Table 1. Condition (a) specifies that, "Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses." This language leaves many open questions. IRBs wonder how much preclinical research is enough to ensure that there will be no harm to the fetus. IRBs typically interpret this directive conservatively.

Condition (d) allows for the inclusion of pregnant women, "If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions." The phrase "the risk to the fetus is not greater than minimal" is very problematic. Despite clarifications in 2005 by the Secretary's Advisory Committee on Human Subjects Research, as well as clarifications from the IOM and other organizations, arguments continue about the meaning of minimal risk and interpretations vary widely.

If participation in the research protocol holds out the prospect of direct benefit for the pregnant woman, such benefit can be a powerful justification for imposing risk on the mother or the fetus, in much the same way as is done in clinical medical practice. But the IRB is left to ponder how much direct benefit justifies the risk of the research. What if there is a small probability of a great benefit? What if the probability of a modest direct benefit is quite high?

If the research holds out the prospect of direct benefit solely for the fetus, then Condition (e) of the guidelines holds that the consent of the woman and the father (must be) obtained, except that the father's consent need not be obtained if he is unable to consent because of unavailability. This requirement has been highly controversial, for example, during the conduct of the clinical trial that established the efficacy of azidothymidine in reducing perinatal transmission of HIV.

In many ways, these guidelines are more restrictive than another set of authoritative guidelines promulgated by the Council for International Organizations of Medical Sciences (CIOMS). CIOMS Guideline 16 states: "The potential for becoming pregnant during a study should not, in itself, be used as a reason for precluding or limiting participation. However, a thorough discussion of risks to the pregnant woman, and to her fetus, is a prerequisite for the woman's ability to make a rational decision to enroll in a clinical study.

In this discussion, if participation in the research might be hazardous to a fetus or a woman if she becomes pregnant, the sponsors/investigators should guarantee the prospective subject, a pregnancy test and access to effective contraceptive methods before the research commences. Where such access is not possible, for legal or religious reasons, investigators should not recruit for such possibly hazardous research women who might become pregnant." Quite clearly under the CIOMS guidelines, the possibility of pregnancy is not a reason to exclude women from participation in research.

CIOMS Guideline 17 is directed more specifically at pregnant women. It states that: "Pregnant women should be presumed to be eligible for participation in biomedical research…. [They must be] adequately informed about the risks and benefits to themselves, their pregnancies, the fetus and their subsequent offspring, and to their fertility. "Research should be performed only if it is relevant to the particular health needs of a pregnant woman or her fetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity." Although this guideline does not require paternal consent, the associated commentary states that in research directed at the health of the fetus, it is desirable to obtain the father's opinion, when possible.

In many ways, the CIOMs guidelines are more respectful of the rights of women than those outlined by Subpart B; they have, however, been subjected to differing interpretations. Their wording has been interpreted by some as referring to "compassionate use." But the clearly expressed intent of the guidelines is to encompass the inclusion of a pregnant woman with hypertension or other medical condition in an ongoing clinical trial. This is not the same as compassionate use.

The phrase, "the health needs of pregnant women" has been construed narrowly by some as referring to problems peculiar to pregnancy. However, the language is meant to be responsive to the health needs of pregnant women with such diseases as diabetes or cancer. That means that pregnant women can be enrolled in clinical trials of treatments for these conditions. It is not necessary that the research focus on diseases that occur only, or almost exclusively, in pregnant women.

Competing Justice Arguments for the Inclusion of Pregnant Women in Clinical Trials

The argument that pregnant women ought to be included in research consists of two different justice-based claims, which are in competition with each other. The first is that it is unjust to deny access of individuals to research participation on the basis of criteria (such as gender or pregnancy) that are not morally relevant. All too frequently, the response to this injustice has been to have open enrollment. The problem with that is that it may obfuscate important distinctions. Generalizable data relevant to gender or pregnancy will most likely not be obtained from an open enrollment policy. Studies with open enrollment in the past have missed important distinctions based upon gender, race, and so on.

The second claim is that it is unjust to deprive women as a class of persons of the benefits of research. But the way to address that issue is to have clinical trials, with stratifications, so that the same number of women are included in each of the arms of the clinical trial; or to develop separate clinical trials that are adequately powered to find outcomes of interest in women.

The Conservatism of IRBs

Minimal risk Minimal risk is an elusive definition. There is no survey available from IRB chairs to address how they differ in their interpretation of minimal risk in the context of research conducted in pregnancy, but data from a survey published in a 2004 paper by Shah and colleagues aimed at research involving children may be instructive in this regard.

TABLE 2: IRB CHAIR SURVEY: PEDIATRIC RISK

Race and Hispanic Origin	Minimal Risk	Minor Increase	Greater than Minor Increase
Single Venous Sample	81%	19%	0%
MRI no sedation	48%	35%	17%
Weekly 10ml venous samples X 6 mos.	15%	51%	34%
Pediatric testing of drug found safe in adults	5%	23%	72%
Pharmokinetic study death risk 1/1,000,000	7%	30%	63%

Source: Slide presented at *Issues in Clinical Research: Enrolling Pregnant Women* Meeting, October 2010, National Institutes of Health, Bethesda, Maryland

In the column on the left, several procedures are named. IRB chairs were asked to evaluate the risk of each of the procedures as minimal, a minor increment above minimal risk, or greater than a minor increment above minimal risk. These are important thresholds in the pediatric regulations. If there is more than a minor increase above minimal risk, a protocol must undergo a more extensive review that can take up to three years to accomplish.

Testing of drugs in a pediatric population presents an analogous situation to testing of drugs in a pregnant population. The table shows that for pediatric testing of a drug already found safe in adults, only five percent of IRB chairs said that presented minimal risk. Seventy-two percent of them said that was greater than a minor increase above minimal risk. Even for a pharmacokinetic study in which the risk of death is estimated to be less than one in a million, 53 percent of IRB chairs evaluated it as greater than a minor increase over minimal risk.

Contraceptive requirements Some IRBs have already decided to apply the FDA drug categorization which is based on strength of data supporting safety for the fetus, mostly absence of birth defect, to determine when contraception should be either suggested or made mandatory for female research subjects. This policy has merit only if the focus is placed on protections where they are truly needed. However, because IRB policies and practices tend to be conservative, we can anticipate an expansion of mandatory contraceptive policies to an ever increasing number of clinical trials.

Requiring contraception for women who participate in clinical research and who have the biological capacity to become pregnant will necessarily distort the resulting data. There are well known pregnancy-related physiological and pharmacokinetic changes, and such changes may also be induced by oral contraceptives. Data from clinical trials involving only women who are using contraceptives may not be applicable to other women; in other words, generalizability may be lost. Use of effective contraceptives in clinical trials will preclude the development of any information regarding safety to the fetus. This is not to advocate for stopping contraception requirements, as appropriate, for women in clinical trials; in many clinical trials, contraceptive use is ethically obligatory. We must be cognizant, however, of the fact that use of contraceptives by clinical trial subjects will impose limitations on the nature of the information obtained.

IRBs tend to be highly conservative, regarding the review and approval of research involving women who are or could become pregnant.

Legal liability Legal liability is apparently a major consideration for many IRBs. Institutional administrators express great concern over exposure to legal liability, even though this appears to be a rare problem in actual experience. In 2005, NIH, in collaboration with several other agencies, held a workshop on alternative models of IRB review. There was a separate breakout session on legal liability for local IRBs. Nobody in that session could come up with a single example of successful litigation against a local IRB, because they had deferred part or all of their responsibility to another IRB. Nonetheless, there is still high resistance to the concept of central IRBs, because there could be liability. Pervasive anxiety about liability in many aspects of IRB activity drives them to adopt conservative policies and practices.

In conclusion, IRBs tend to be highly conservative, regarding the review and approval of research involving women who are or could become pregnant. They are influenced by the frightening history in the field—particularly the thalidomide disaster. They are influenced by the current general forces that drive IRBs to focus on documentation and on other bureaucratic details. Perhaps most importantly, they are very much influenced by concerns over liability exposure.

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Discussion

Panel: Dr. Katherine Wisner and Dr. Robert Levine

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: *Barriers to information about drugs used in pregnancy.* There are several historic barriers to information about pregnancy and drug therapies. Newly proposed contraception restrictions may limit further knowledge of the effects of drugs in pregnancy and access to needed therapies. What can be done to deal with limitations?

Panel Comments: If one is considering a drug that pregnant women with a certain disorder need, then it is probably one that is already approved for marketing. During the clinical trial leading to approval of the drug, there was at least some doubt that the drug was effective. The purpose of the trial was to find out if it is effective and safe. Such doubt makes it difficult to justify making the drug available to pregnant women prior to obtaining evidence of efficacy and safety. In the past, programs have been developed that have expanded access, using a parallel track for individuals who did not meet eligibility criteria to enter a trial. The FDA is working to clarify regulations on the use of expanded access for therapeutic use and for open label continuations of clinical trials looking for safety. Those clarifications may shed further light on the appropriateness of programs for populations such as pregnant women.

Audience comment: *Liability and lawsuits.* How common are lawsuits involving adverse outcomes for fetuses and are they more common in clinical research or clinical practice?

Panel comments: For the past 20 years, things have been fairly quiet in terms of liability claims, but recently there has been more aggressive advertising by lawyers soliciting individuals to self-identify if they had taken a drug and are affected by adverse outcomes associated with the drug. This includes individuals who have taken psychotropic drugs during pregnancy and have infants with certain adverse outcomes.

Some have argued that failure to do research that might lead to an understanding about fetal abnormalities in the aftermath of drug therapy and pregnancy might expose sponsors and perhaps investigators to a greater threat of litigation than they would expose themselves to by doing the research. This could occur

after many years, as happened in the case of DES, when use in pregnancy was found to be associated with cancer of the vagina in offspring. Findings of this type, even at times far removed from the original exposure, could still lead to litigation. Such fears are, in large part, reasons that may have influenced IRB conservatism.

Audience comment: *Inter-IRB variability.* IRBs evaluate the same protocol differently, in part because of different views of liability. There are also other factors that may underlie differences in IRB behavior, such as cultural or religious considerations. Is there a way to deal with or understand these factors so as to minimize inter-IRB variability?

Panel comments: CIOMS guidelines do allow religious, as well as legal considerations to enter into decisions to participate in research. For example, if there are religious reasons to avoid contraception, and without contraception there appears to be risk, then the guidelines conclude that the research should be done somewhere else, where religious considerations are not an issue.

The American College of Neuropsychopharmacology (ACNP) surveyed its membership about IRB issues and their policies and practices to see if they facilitated or impeded research. One member reported experiences in a multi-site study, where half of the IRBs involved had no issues with a consent form, but the other half wanted language changes to the form that were not acceptable to the first half. Another issue raised was that of IRB review of placebo control designs.

Members recognized the important role that IRBs play in protecting human safety and also provided evidence of exemplary interactions. However, they also noted that the red tape involved in obtaining IRB approval and the tendency for IRBs to be restrictive and conservative present barriers to research. In particular, novel protocols may have particular difficulty getting approval. This discourages researchers from spending the time and effort necessary to submit protocols.

Audience comment: *The need for special groups to evaluate pregnancy research.* What role could clinical research committees or subcommittees that have special expertise in maternal fetal issues or reproductive issues play in ensuring appropriate evaluation of pregnancy research?

Panel comments: IRBs are in a developmental phase, with regard to pregnancy research. At the University of Pittsburgh, the director of the IRB is a maternal fetal medicine specialist. There are also a number of special committees to review proposals where in-depth knowledge of the material is likely to be helpful. These committees are under IRB purview in a central organization. There is also increased attention to having lay community members represent the patient perspective.

The Endocrine Society, in collaboration with the Pediatric Endocrine Society, is issuing a consensus paper calling for clarifications in terminology in the overall regulatory scheme. In addition to ambiguous concepts such as "minimal risk," there are other ambiguities, such as what is meant by the term "commensurate" or what constitutes a "condition" or a "disorder."

One of the recommendations of the consensus paper is that various subspecialty groups form high-level committees to develop best practices documents. These documents could address the meaning of the terms in the regulations, when one is talking about patients in their subspecialties. For instance, when one is talking about adolescents versus toddlers, how does minimal risk differ?

Another recommendation is the development of committees by culturally-distinct groups of people who can help clarify what minimal risk means for them, or what a condition or a disorder means for them. Best practices documents can reduce the diversity of decisions by IRBs.

Audience comment: *Pregnant adolescents.* Pregnant adolescents are one group that poses complex issues for IRBs. Is there anything that can be done to address this problem in a way that allows for the inclusion of pregnant adolescents in clinical research?

Panel comments: As adolescents approach age 18, increasingly, they should be treated as adults in terms of consent. One trend around the country was for an IRB to be guided by rules that allowed researchers to get consent from adolescents to participate in certain types of research if the research was on a disease for which, in that jurisdiction, the adolescent was authorized to receive treatment without the approval, or even the awareness of parents or guardians (such as for STD's or drug abuse). However, increasingly, there is another issue that occurs when adolescents receive their medical care from a practice group, which treats the parents and covers the adolescent's treatment. In those practice groups, the parents ask for their adolescents to be covered and may also ask for notification in certain instances about adolescent health issues. Others have argued that adolescents who are being cared for in practice groups ought to be able to consent their participation in a broad range of research, not only specific research on STD's or drug abuse, without the awareness of their parents or guardians. So this issue is in flux. Pregnancy adds another layer of complexity to adolescent research.

Another example of the added complexity of research with childbearing adolescents can be found in a study conducted on postpartum depression. In that study, a consent waiver was obtained to screen adult women, but parental and subject consent were both required to screen adolescent females. This difference in consent standards can create an additional barrier to adolescent participation in clinical research. Certainly, adolescents are more reluctant to participate in research on socially sensitive issues if parental consent is required.

Audience comment: *Role of DSMBs.* The Data Safety Monitoring Board (DSMB) functions to monitor safety issues in ongoing clinical trials. What is the role of the DSMB in pregnancy research? In pregnancy research, there may be no evidence of an effect for 15 or 20 years, as occurred in the case of DES use during pregnancy.

Panel comment: DSMBs are charged with reviewing safety data during a trial, and they have independent responsibility. They do not have the power to stop a trial, but they have the power to recommend to the sponsor that they stop a trial; and most sponsors would be very reluctant to ignore the advice of the DSMB. During a trial, if a DSMB becomes aware of a signal that a drug may be problematic, they nonetheless do not want to act prematurely on preliminary data that may change when more data are accrued. They want to avoid shutting down important clinical trials prematurely. For instance, a DSMB became aware that an active drug was associated with a higher risk of atrial fibrillation, but members were not confident that the signal was important. If the sponsors had been notified immediately, then they would have shut the trial down. However, the DSMB waited to obtain further evidence, and fortunately, the treated group-placebo group difference went away.

Audience comment: *Role of IRBs and DSMBs in evolving clinical practice standards.* Increasingly, IRBs and DSMBs are being asked to pass judgment on therapeutic clinical interventions that are innovative. As an example, pediatric cardiologists were doing fetal therapy that they believed was a standard, but it was not yet an accepted standard of practice. So they asked the IRB for approval to do the intervention, and a DSMB was imposed. This is not clinical research, but as clinicians use more novel kinds of interventions, techniques and technologies for exit procedures and fetal interventions, they are asking IRBs and DSMBs to look at clinical practice. This speaks to the interface between clinical research and clinical practice and the fact that often the line is very much blurred.

Panel comments: The IRB is not constructed to determine what is acceptable clinical practice. Even in large institutions, there may be only a couple of individuals with expertise in an innovative therapy. If these individuals are also involved in an intervention under review, IRB rules exclude their participation from the IRB meeting in which the protocol is discussed. If the intervention is an NIH-funded protocol, institutions may rely on the Initial Review Group (IRG), also known as the Study Section, to evaluate the human subjects' issues raised by the intervention. An IRG is composed of a dozen experts. If one of them happens to be from an institution where the work is proposed, the individual is excused from the review of the protocol, but that leaves 11 experts still available to evaluate the protocol. They know what is acceptable in a field. If the intervention under consideration is pure practice and does not involve research, then it may be advisable to refer it to a specialty society, the State Department of Health, or to those who will convene a suitable panel of experts.

Audience comment: *Evidence needed to conduct clinical trials in pregnancy.* What evidence would suffice to move ahead with a study to get information that is needed to use a drug safely in pregnancy? What basis in prior knowledge is required so that the study is designed with adequate safety data, not only from prior adult studies in non-pregnant women, but also pre-clinical work?

Panel comments: The manufacturer of a newly-released psychotropic agent was interested in systematically collecting data on outcomes for pregnant women who were exposed to a drug. This strategy was seen as preferable to waiting for case reports, which are much more likely to lead to misattribution of a negative outcome to the drug. The protocol involved enrollment of women who became pregnant while taking the drug in question. As part of the study, the patients were characterized thoroughly. Characterization of the women included gathering information on nutritional parameters, life event markers, levels of stress, ultrasounds, urine drug screens, hair screens etc.

In this way, there was an attempt to assess the drug in pregnancy while respecting the manufacturer's legal issues and also from a scientific perspective, by gathering extensive information on other substances or life events to which each participant was exposed so as to guard against making misattributions of an adverse outcome to the drug exposure. However, this approach does not address evidence for randomized clinical trials or other types of designs.

It is very problematic to get data in an IRB-approved clinical trial that will provide information on adverse events for the fetus if the study subjects are all on contraceptives and not pregnant. In a clinical trial with a sample of 300 pregnant women, the naturally-occurring rate of fetal adverse events or birth defects is three percent. If, in a sample of 300 pregnant women, one or two adverse events occur, it will be difficult to interpret these events.

Audience comment: *Evidence needed to conduct clinical trials in pregnancy.* In thinking about clinical trials, one often does not have information on pregnancy. In the standard clinical trial, there is standard information, including preclinical studies, which may be difficult to interpret, and some clinical data on non-pregnant subjects. What evidence needs to be added that is going to ease the burden of having clinical trials in pregnant women move forward?

Panel comments: One thing that may help is to design studies so that they are more "real world." An example is a stratified equipoise design to answer the question of what pregnancy outcomes are associated with different treatments. In the real world, women go through risk-benefit decisions, and they choose among treatment options. For example, a study using this design was set up so that women had several choices for treatment, including two drug therapies, a non-drug somatic therapy, and a behavioral therapy, all delivered across eight sessions. In this type of design, personal acceptability became a component. As long as women were willing to accept at least two of the treatments, they were then randomized to one of them.

This kind of trial has its problems, but it also gets around some of the problems with a straight randomized trial. In this study, if women would only accept one of the treatment options, or did not want any treatment, the plan was to follow them with the exact same measurements used for the women who did accept two treatments and randomization to one of arms. This was in order to see whether what women actually chose might be more novel than anticipated and also again to see what were the "real world" outcomes. Such designs may also have a better balance of ethics with science, and they may be more feasible when considering moving forward with pregnancy research.

In the clinical trial world, the gold standard is the randomized double blind trial, but the reality is that that standard cannot be met all the time. Double blind studies cannot be done for many types of major surgery interventions, for instance, for thoracotomies or pneumonectomies. In several other areas, like cancer chemotherapy, single-blind studies are more the norm than double-blind studies. Perhaps there is a need to acknowledge that there are limits on the researchers' ability to get perfect information and to concede that, given current conditions, there will never be data on what the real risk is to the fetus in certain types of studies where new drugs are introduced into the population of women.

Morning Wrap Up

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This morning's panel on Ethical Principles of Research on Effective Treatments during Pregnancy has introduced the notion of the need for a "Second Wave" to move women's health research forward to include research on the health needs of pregnant women. What can be done to move the "Second Wave" forward? Below are eight ideas that have emerged from the panel presentations and discussions.

1. Keep in mind that the goal of all research is to generate useful knowledge to solve or resolve uncertainties in a responsible and scientifically rigorous way, while always bearing in mind the need to protect and respect the study participants.

2. Redefine pregnant women as a "complex" population rather than a "vulnerable" one. "Vulnerable" is a misnomer. Pregnant women are capable of making informed decisions about their treatment and their participation in research and capable of weighing risks and benefits to themselves and their fetuses.

3. Develop a research agenda, with the assistance of ORWH. Among elements to be included in that agenda are the following:

   - Prioritize the "low hanging fruit" and to see what questions can be addressed with existing data and through ongoing studies, without adding any additional risk to the fetus.
   - Plan innovative new studies that ask the most important questions and employ sophisticated designs.
   - Focus on what needs to be known so that good evidence-based clinical practice can be moved forward. Consider context and real world settings.

4. Eliminate the exclusion presumption for pregnant women. There is a need to talk about inclusion from a perspective that is very different from the one in the current guidance documents. When planning research, a first consideration should be to invite scientifically appropriate people, including pregnant women, to participate, and only then exclude groups or individuals if there is a good reason.

5. Make funding for the research agenda a priority. Funding for mining existing studies and developing new knowledge on treatments for use during pregnancy is critical to move the research agenda forward and to change the presumption of exclusion.

6. Develop more transparency in discussions about the trade-offs that need to be made in moving forward with an agenda for research on pregnant women. The trade-offs are multiple. There are trade-offs in deciding to treat or not to treat pregnant women with conditions, when there is no research. There are trade-offs in deciding which research questions will be answered and what study designs will be used.

7. Clarify regulations governing the inclusion of pregnant women and fetuses in clinical research and the decision making procedures of IRBs that approve such research. From regulatory bodies, there needs to be more guidance on how to interpret words like "minimal risk" and on how to think of vulnerability in research. IRBs, too, should be asked to make their decision processes and trade-off considerations concerning research involving pregnant women more transparent. Comparative data about differences in IRB decision making in research with pregnant women should be obtained.

8. Tackle the legal challenges. They have to be dealt with because reticence of medical professionals to treat women during pregnancy and reticence of researchers and sponsors to include pregnant women in clinical research stem, to a significant degree, from fears of legal liability. That needs to be dealt with.

CHAPTER THREE: REGULATORY REQUIREMENTS AND GLOBAL HEALTH ISSUES

Overview

This panel considers regulatory and regulatory science issues affecting clinical research involving pregnant women and their fetuses. In their presentation, Drs. Sara Goldkind and Karen Feibus argue for a need to increased consideration of pregnant women's health needs in the drug approval process and in post-marketing studies. Reasons why pre-marketing clinical trials in pregnant women are difficult to carry out include lack of established efficacy, and relatively limited experience of safety and efficacy of the drug in non-pregnant populations. Post-marketing studies, including database studies and registries, are the most common methods used to obtain information on the impact of a drug on pregnant women. Increasingly, pregnancy registries are being established if an approved drug is likely to be used widely by women of childbearing potential. Two hypothetical scenarios of clinical trials are presented: one of a trial involving women who become pregnant while in the trial and the second of a trial that is designed to include pregnant women. Ethical issues are discussed in these cases.

A second presentation from Dr. Duane Alexander provides an extensive history of the development of regulations governing the inclusion of women and fetuses in clinical research, with emphasis on the social context in which the regulations were initially developed. Modifications of 45 CFR46, Subpart B, were approved in 2001 in response to widespread concern that paternal consent requirements for fetal research were unduly restrictive and served as an impediment to studies of the effects of drugs in preventing vertical transmission of HIV-AIDS from mother to fetus during pregnancy. Dr. Alexander concludes that, despite continuing limitations, current regulations have made it increasingly possible to expand research in pregnancy into wider and wider areas of inquiry.

Pregnant Women in Clinical Trials: Scientific and Ethical Considerations

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There are numerous questions that a practitioner needs to ask when considering therapeutic options for a pregnant woman with a medical condition requiring treatment with pharmaceuticals and biologics. Among them are questions of how well her current medications control the condition and maintain her quality of life. What fetal and developmental risks are associated with her current medications, as well as with alternative medications, and how do these risks compare to those associated with her condition, if it is untreated? All too often the practitioner cannot answer these questions simply because medication use has not been routinely studied in pregnant women.

The widespread presumption of exclusion of pregnant women in clinical research can no longer be justified, and, as has been heard today, there are a number of ethical reasons to increase their inclusion. In a 2010 Lancet publication, Macklin stated that "the most compelling reason to justify the inclusion of pregnant women in a greater number of studies is the need for evidence gathered under rigorous scientific conditions that place fewer women and their fetuses at risk than the much larger number of pregnant women who will be exposed to the medications once they come to market."

When considering moving ahead with greater inclusion of pregnant women in studies of the efficacy and safety of drugs, there are also a number of scientific considerations that need to be addressed. An essential step in drug regulatory science is to identify the target populations for a drug. In drug regulatory science, who are pregnant women? Pregnant women are not a separate and distinct population, except in situations where the condition for which a drug is developed is unique to pregnancy. Pregnant women are a dynamic subset of the adult and adolescent female population who use drugs and biologics. It is important to consider whether, how, and when to study pregnant women in the drug development process.

Only a handful of drugs are specifically approved for use in pregnancy. If a woman has lupus or asthma or hypertension and is being treated for her condition with drugs that are intended for the condition, is she suddenly using all of her drugs "off-label" if she becomes pregnant? The answer is no. She is still using those drugs to treat the condition that they were meant to treat. However, because of her pregnancy, she is now a member of a more "complex" subset of women, and there are more issues that she and her healthcare provider need to consider with regard to the risks and benefits of her drug treatments during the course of her pregnancy. Pregnant women are also an especially dynamic subset of the population of women, one in which physiological changes occur that can alter a drug's efficacy and pharmacokinetics. Dosing recommendations established for non-pregnant women cannot automatically be extrapolated to pregnant women.

In contemplating larger numbers of clinical studies in pregnancy, there are a number of issues to consider. When in the drug development process should pregnant women be studied? Should they be studied in the pre-marketing or the post-marketing stage? Which designs should be employed? Randomized controlled trials or cohort and case-control epidemiological studies? Among pregnant women, who are the potential subjects? Which women are most likely to experience direct benefit from participation in the research? What data and endpoints will be obtained?

When in the drug development process should pregnant women be studied? Should they be studied in the pre-marketing or the post-marketing stage? Which designs should be employed?

Post-Marketing Studies

Currently, the most common way of obtaining information about the efficacy and safety of drugs for use in pregnant women is to conduct post-marketing research. This is because for marketed drugs there is an established body of non-clinical toxicology data and clinical information about the effects of the drug in non-pregnant women. Possible designs for post-marketing studies include case-control and prospective studies, as well as clinical trials.

Exposure Registries Exposure registries are currently available for some conditions, and for some drugs, to monitor their impact in pregnant women. Studies of exposure registries typically involve a prospective cohort design with an internal or external control group. The 2007 FDA Amendments Act provided the FDA with authority to require pregnancy exposure registries for drugs that are expected to be used extensively in women of child-bearing potential. A list of pregnancy exposure registries is maintained by the FDA Office of Women's Health at: http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm#Specific_Medical_Products.

Database studies For drugs that have already been marketed for an extended period of time, database studies that link mother-baby records and case-control studies are options. When correctly designed, such studies can be quite informative.

This utility can be seen in an example of the approval process for Coartam, an anti-malaria drug, which was approved by the FDA in 2009. This drug has been used worldwide for a long time, and the drug application came into the FDA with published and unpublished human data in pregnant women. Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Coartem tablets (including a third of patients who were exposed in the first trimester), and published data of over 1,000 pregnant patients who were exposed to derivatives of a compound in the tablet, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rate. This information was included in the drug's pregnancy labeling.

Clinical Trials Clinical trials are another option. Clinical trials have generally not been done in pregnant women in the post-marketing phase, but due to the ethical arguments, they are increasingly likely in the future. What are some considerations when clinical trials are contemplated? When an active treatment currently exists, can a new drug be compared to a placebo? The extent and duration of use of the drug among pregnant women is also a consideration. How will that influence study design? Are data collection mechanisms adequate to capture maternal, fetal, and neonatal outcomes of interest? Will maternal variables such as gestational timing, duration of drug exposure, ultrasound reports and results of other prenatal testing be obtained? Are study outcomes appropriately planned? Will records of maternal complications be obtained? Will other information on pregnancy outcomes be obtained, such as gestational age at delivery, delivery complications, and the condition of the neonate?

Pre-Marketing Studies

Pre-marketing studies of pregnant women are very limited in number. Reasons for this include ones already mentioned today, such as liability concerns and concerns over harm to the fetus. For pre-marketing studies, it is also less likely that a large body of information concerning the efficacy and side effects of a drug in women of childbearing age can be drawn upon. In certain instances, where there has been urgent need to test therapies for serious endemic conditions affecting pregnant women such as HIV, malaria and tuberculosis, or for life threatening illnesses such cancer, exceptions have been made, and pregnant women have been studied to some degree.

Questions to ask when considering the inclusion of pregnant women in pre-marketing phase studies include whether pre-clinical reproductive and developmental toxicity studies are complete and adequate. Are there positive findings of developmental toxicity in animals? If so, that information needs to be incorporated into the informed consent process. Are there planned pharmacokinetic (PK) assessments early in the study to ensure adequate systemic exposure to achieve efficacy (e.g., nested PK study in a Phase 3 clinical trial)?

Are effective alternative therapies available, and do they have better developmental toxicity profiles based on animal data and/or any available human data? If so, can women get access to the alternative drugs? If there are alternative therapies, but the only therapy that a woman can get when she is pregnant is the one available through a clinical trial, then does she not deserve access to that treatment?

As with post-marketing studies, one needs to ensure that study measures and outcomes are adequately thought out to measure maternal, fetal, and neonatal risk. Risk-benefit considerations are complex because pregnant women are a complex subset of women. There are risks and benefits for the mother and risks and benefits for the fetus. They are intertwined, because the health of the mother determines the health of the intrauterine environment, and a healthy intrauterine environment is what that fetus needs to develop well.

Ethical Considerations: Two Clinical Trial Scenarios

When thinking about the ethical issues for including pregnant women in clinical trials, there are two scenarios to consider: women who become pregnant while participating in a clinical trial and pregnant women who actually enroll in a clinical trial.

Pregnancy while enrolled in a clinical trial In this scenario, a woman becomes pregnant during a clinical trial. What ethical considerations pertain in this scenario? Should the woman be allowed to continue in the trial? In making such a decision, what needs to be considered is whether the potential benefits of continued treatment outweigh the potential risks of ongoing fetal exposure to the study drug. What are the risks of discontinuing maternal therapy and/or the risks of exposing the fetus to additional drugs if the mother is placed on an alternative therapy? Such risk-benefit issues become especially germane when one is considering serious endemic or life-threatening illnesses that affect pregnant women, such as malaria, tuberculosis, and cancer.

If a woman enrolled before pregnancy, she probably received contraceptive counseling or potential embryo-to-fetal toxicity counseling during the informed consent process. If she becomes pregnant during the study, she would need to have pregnancy management counseling, and a new informed consent process should also include a discussion of the alternative therapies and comparative therapeutic risks and benefits, the risk of fetal exposure to the study drug, or, if she is removed from the clinical trial to any new alternative therapy, the risk of that removal and new therapy or the risk of being untreated for her maternal disease.

Enrollment of pregnant women in a clinical trial In this scenario, a clinical trial involving pregnant women is planned. Several issues need to be addressed in this scenario. Many of these issues are the same as those for post-marketing clinical trials. They include enrolling those pregnant women most likely to derive direct benefit from the drug. Are there alternatives to clinical trials? Are there available alternative treatments? Has the pregnant woman failed to respond to other available therapies, or does she have a drug allergy, drug intolerance, or drug resistance to alternative therapies? Other considerations include risks to the fetus. Is the risk to the fetus greater than minimal? Will important knowledge result from the study that cannot otherwise be acquired? Are there adequate pre-clinical studies?

Other Challenges to Participation

There are many challenges to studying pregnant women in clinical research, and recruitment and retention are among them. In order to recruit suitable subjects, a strategy to work more closely with obstetricians and/or gynecologists is needed.

In order to recruit and retain pregnant women in clinical research, they need to be made aware of the current paucity of information, the value of research participation, and what they and other women may get out of pregnancy registries and clinical trials.

Concerns about sharing and the security of personal information also present challenges to recruitment and retention. Only about 50 percent of women who make contact with pregnancy registries ultimately sign the consent form, because there are concerns about access to personal information in medical records. Providing information about how personal information will be secured is critical.

There is a need to understand how social and demographic factors influence a woman's decision to enroll in a study and how those factors also influence the attitudes of her health care practitioner, because the support and encouragement of the practitioner to enroll in a study will likely affect her final decision, as well.

Finally, in recognition of the need to address issues of importance to pregnant and lactating women, the FDA has issued or is in the process of issuing a number of guidance documents. They are listed in Figure 1 below.

FDA Guidances

- **Pregnancy Exposure Registries:**
  - Guidance for Industry, Establishing Pregnancy Exposure Registries, final published August 2002
- **Pharmacokinetics:**
  - Industry Guidance (draft), Pharmacokinetics in Pregnancy - Study Design, Data Analysis, and Impact on Dosing and Labeling, draft published October 2004.
  - *Final guidance in clearance* – Pharmacokinetics During Pregnancy and the Postpartum Period.
- **Clinical Lactation Studies:**
  - Industry Guidance (draft), Clinical Lactation Studies-Study Design, Data Analysis and Recommendations for Labeling, draft published February 2005.
  - *Final guidance in clearance*
- **Pregnant women and clinical trials:**
  - Industry Guidance, Pregnant Women in Clinical Trials: Scientific and Ethical Considerations, *draft in clearance*

Source: Slide presented at *Issues in Clinical Research: Enrolling Pregnant Women* Meeting, October 2010, National Institutes of Health, Bethesda, Maryland

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Global Health Issues and US Regulation 45 CFR46, Subpart B

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This presentation provides a historical overview of issues and events that led to the development and issuance, in 1975, of the Federal regulations (45 CFR46, Subpart B) governing the inclusion of pregnant women in clinical research. It also discusses a 2001 revision to the regulations, which guides research today.

Initial Impetus for Regulations: The Thalidomide Tragedy

The initial impetus for regulations governing research involving pregnant women and their fetuses came from the thalidomide tragedy, in which fetal drug exposure led to severe birth defects. In Europe, thalidomide had been introduced in late 1950s and quickly became very popular there as a treatment for nausea in the first trimester of pregnancy. In the U.S., however, the FDA had delayed its introduction, citing a need for further studies prior to approval. Within a few years after thalidomide's introduction in Europe, an epidemic of limb reduction birth defects was linked to its use during pregnancy. Thalidomide was found to be a very potent teratogen, with a high frequency of stillbirth and abnormalities. The President of the United States presented medals to the FDA officials responsible for withholding U.S. approval of the drug, and Congress held hearings to ensure that similar tragedies could be prevented in the future.

The hearings were chaired by Senator Estes Kefauver of Tennessee. They led to congressional passage of the Kefauver-Harris Amendments Act of 1962, which codified and strengthened FDA rules with regard to drug approval, including requirements for animal studies and evidence of safety and efficacy, and licensing for specific indications and for specific populations.

Women and Children as Therapeutic Orphans

The implementation of the revised FDA regulations had unintended consequences. In order to protect "vulnerable" populations such as children and pregnant women, but still get new drugs out to the general population, labels were issued with statements indicating that safety for children or for use in pregnancy had not been established. As a result, as of 2001 more than 75 percent of the drugs used in children were not studied or labeled for use in children; more than 95 percent of the drugs used in pregnant women were not studied or labeled for use in pregnant women.

The paradox is that, even though concerns for pregnant women and their fetuses were instigating factors in the codification of FDA rules for drug testing, women were effectively left out of the solution. Why were women excluded from drug testing?

Pregnant women and women who might become pregnant during a clinical trial were excluded due to fears of legal liability if any problems occurred with the fetus. By extension, women of child-bearing age were excluded from many drug studies out of concern that they could become pregnant while in a study. A second paradox was that, at the same time that pregnant women were excluded, they were prescribed treatments that had not been tested in pregnancy.

The controversy over fetal research came at the same time that the U.S. research enterprise was under siege, due to revelations of the Tuskegee syphilis study and other research on prisoners and the mentally ill.

Social Controversies Complicate Issues of Inclusion and Consent

Issues of inclusion and consent of pregnant women in research were further complicated in the early 1970s by social controversies surrounding the Supreme Court's decision on abortion. The *Roe v. Wade* decision in 1973 brought out deep divisions on the issue. Research conducted in Scandinavia on aborted fetuses was widely publicized in the U.S. and heightened concern over the possibility that similar research could be conducted here. There was a call for legislation to ban research on the fetus.

The controversy over fetal research came at the same time that the U.S. research enterprise was under siege, due to revelations of the Tuskegee syphilis study and other research on prisoners and the mentally ill. To allow these issues to be discussed in a public fact-finding and solution-generating forum, a National

Commission for Protection of Human Subjects of Biomedical and Behavioral Research was established in 1974. The Commission was charged with studying issues in vulnerable populations, as well as general issues in clinical research protections.

The National Commission's Recommendations: Women and Fetuses

The Commission was specifically tasked with developing guidelines for research in pregnancy and was given a four-month time frame to do so, after which time it was to send its recommendations to the Secretary of Health, Education, and Welfare. In its deliberations, the Commission attempted to differentiate between research directed toward the pregnant woman and research directed toward the fetus. The Commission further distinguished between therapeutic and non-therapeutic research. The ensuing report was the first ever to formally address how research during pregnancy, whether directed to the mother, the fetus, or both, could be carried out ethically and appropriately. Distinct recommendations were made for research on mother or fetus. However, the interdependence of the maternal-fetal unit was also acknowledged in considerations of risks and benefits.

For therapeutic research directed toward the pregnant woman, the research had to be evaluated for possible impact on the fetus and had to place the fetus at the minimum risk, consistent with meeting the health needs of the pregnant woman. For this research, consent of the pregnant woman alone was sufficient. For non-therapeutic research directed toward the pregnant woman, research had to pose minimal or no risk to the fetus, and the woman had to be told about possible impact on the fetus. For this research, the woman had to give her consent, and the father had to "not object."

Therapeutic research directed toward the fetus was encouraged. This research had to conform to appropriate medical standards. The mother's consent was sufficient, as long as the father did not "dissent." Non-therapeutic research directed toward the fetus was limited to no risk or minimal risk. The consent of the mother was required. The father had to "not object".

DHEW Regulations 45 CFR46, Subpart B

In 1975, the recommendations developed by the National Commission for Research on Pregnant Women and Fetuses were incorporated into the federal regulations for research with human subjects (45 CFR46, Subpart B). The regulations took a proscriptive approach in the language used. The wording was "No pregnant woman may be involved in research unless…", but the content followed the Commission's recommendations very closely.

Under the Federal guidelines, if the research addressed a woman's health needs, the wording called for the risk to the fetus to be the "least possible", consistent with meeting those needs. Otherwise, she could participate only if the risk to the fetus was minimal.

If the research addressed the woman's health needs, only her consent was required. If it did not address her health needs, the father also had to consent to her participation, even if the risk to the fetus was minimal, unless his whereabouts could not reasonably be ascertained, he was not reasonably available, or the pregnancy resulted from rape.

Research directed toward the health needs of the fetus had to pose the least possible risk to the fetus, or, if the research was not therapeutic, it could be no greater than minimal risk. The mother's consent was required, as was the father's, with the same exceptions as for research in pregnant women.

The Department explained that the reason for the more explicit requirements for the father's consent was that the terms "not dissent" or "not object" used by the Commission were not specific enough for a document issued for regulatory purposes. The only way to ensure non-dissent or non-objecting was to ask the father.

These regulations were generally viewed positively in the research community because they were reasonable and allowed important research to proceed with appropriate safeguards. An exception was the requirement for the father's consent. For example, the regulations, if strictly interpreted, would not allow a pregnant woman even to give a blood sample for a new study unrelated to her health without the father's consent, even though there was no risk at all to the fetus. He also had to consent to any research directed toward the fetus.

Modification of 45 CFR46, Subpart B

The AIDS epidemic and efforts to prevent mother-to-child transmission of the HIV virus with drug treatment during pregnancy highlighted problems with paternal consent. The antiretroviral drugs were often given when the pregnant woman did not meet the current guidelines for HIV infection treatment, because her CD4 count was not low enough, so it could not be argued that the treatment was for her, and that the fetus was an incidental recipient.

The treatment was clearly for her fetus and was potentially life-saving, as well as urgent. But by the letter of the regulations, it was therapeutic research directed toward the fetus and required the informed consent, not only of the mother, but of the father, as well, except if he was not available.

Some research sites quickly decided that the father was not "reasonably available" if he was not present at the time the mother gave consent, but others did not and it rapidly became an issue with women demanding that the regulations be changed.

This request was supported by reports from the Institute of Medicine and the President's AIDS Advisory Panel. In 1995, meetings were convened to address this and other concerns for research on fetuses and pregnant women covered by Subpart B of the regulations.

Proposed revisions were published for public comment in 1998, as part of the regulation revision process. The major change proposed was to make maternal consent sufficient for all research in pregnancy, regardless of whether it was directed to the mother or the fetus, regardless of whether it was therapeutic or non-therapeutic, and regardless of the degree of risk.

Following further revision and public comment, the revised regulations were published in November 2001. At the outset, the revised regulations begin with a different tone. Rather than a proscriptive approach, saying that no pregnant woman may be involved in research unless certain conditions are met, the language states that "Pregnant women or fetuses may be involved in research if all the following conditions are met…."

The new regulations continue the requirement for preceding animal research and human clinical research. They contain the same risk directives for research on pregnant women and limitations for the fetus. No more than minimal risk is acceptable for non-beneficial research and higher levels of risk are permitted only as required in efforts to benefit the fetus or the pregnant woman.

The major change proposed was to make maternal consent sufficient for all research in pregnancy, regardless of whether it was directed to the mother or the fetus, regardless of whether it was therapeutic or non-therapeutic, and regardless of the degree of risk.

With regard to consent, that of the pregnant woman alone is sufficient for research intended to benefit the pregnant woman and research intended to benefit both the pregnant woman and the fetus. If the research is not intended to benefit the pregnant woman or the fetus, the mother's consent alone is adequate as long as the risk to the fetus is minimal. The only research requiring consent of the father is research intended solely to benefit the fetus, with the same exceptions with regard to his availability.

Generally, these changes to the rules continue to facilitate research on the health of pregnant women. Their evolution over 35 years has left researchers in a position to move ahead with investigations to further improve pregnancy outcomes for the pregnant woman and her fetus.

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Discussion

Panel: Dr. Sarah Goldkind, Dr. Karen Feibus, and Dr. Duane Alexander.

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, it provides highlights of discussion with special emphasis on new issues raised by the presentations and issues of general importance to the goal of promoting the responsible inclusion of pregnant women in clinical research.

Audience comment: *The clinical trials gold standard and the FDA.* The field of research and drug development in pregnant women, particularly when there is also already a known effective drug, may be impeded if the FDA accepts as evidence only the results of a double blind placebo-controlled clinical trial. Is this situation changing?

Panel comments: The FDA encourages drug developers to come in for consultation prior to submitting an investigational new drug application and prior to finalizing a protocol, so that they can talk to the review division about study design considerations, etc. Within that context, there can be a very robust and helpful discussion about alternative trial designs to placebo-controlled randomized trials. In the FDA, there are a variety of opinions about non-inferiority trials. Many non-inferiority trials are being conducted in drug development research and are being used to support drug approval in a variety of FDA review divisions. Depending on the group of drugs, and the group of conditions that a review division has to deal with, they may be more or less likely to employ a non-inferiority design.

There are FDA guidance documents under development that deal with non-inferiority designs. There are internal courses that train reviewers in how to look at non-inferiority designs and how to statistically analyze them, and there have also been adaptive trial design courses. Over the past several years, there has been increased willingness to consider alternative trial approaches and alternative sources of data. There is more willingness, compared to a few years ago, to put epidemiology study-based data into labeling. There is a growing realization that no data may be worse than data that is silver or copper standard, instead of gold standard.

Audience comment: *The FDA Sentinel Initiative.* The FDA Sentinel Initiative is an effort to obtain information on pharmaceutical use in larger populations than are currently represented in rarified, randomized controlled trials. Among the millions of people on whom data will be collected in the planned large scale epidemiologic studies, are there plans to include pregnant women and women who are childbearing age and who become pregnant, or will they be excluded from the sample? Is there a plan for pregnant women to be tracked in the populations that the Sentinel Initiative will track?

Panel comments: The Sentinel initiative has to do with actively acquiring post-marketing data on drug use and drug use outcomes. A network is being set up to do this through the Office of Surveillance and Epidemiology, in the Center for Drug Evaluation and Research. The Office of Surveillance and Epidemiology is also currently conducting a pilot study called Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP). The program involves a collaboration among the FDA and researchers at the HMO Research Network Center for Education and Research in Therapeutics (CERT), Kaiser Permanente's multiple research centers, and Vanderbilt University.

The intent is to link mother-baby records, in order to be able to query this linked set of databases about medications used in pregnancy and look at maternal outcomes, look at information pulled off of birth certificates, and ultimately, if the study goes into a full production, to attempt to look at death certificates to get information about fetal deaths and those outcomes.

So, studies of the pregnant populations are currently being done in a separate program, but that is not to say that, ultimately, the Sentinel Initiative program could not also start to collect data on pregnant women.

Audience comment: *Pharmacokinetics data in pregnancy.* There is great deal of pharmacokinetic data from non-pregnant, mostly male populations. Can this data be used to inform the pharmacokinetics of drugs in pregnancy? What comparisons are acceptable with data from pregnant women?

Panel comments: Fortunately, because women have been enrolled in clinical research now for a number of years, at least at the rates of men, there is usually some clinical pharmacology data that is available in women as well. Certainly, if there are data on non-pregnant women, it is preferable to compare them to pregnant women, rather than using data from men, just in case there are population differences based on gender.

Specifically, if there is clear understanding of whether males and females have similarities in pharmacokinetics under non-pregnant conditions, and if population PK methods are used, it may be possible to use non-pregnant women data as important covariate information. For example, if the pharmacokinetics of a drug is defined primarily by body weight, that aspect can be incorporated into the population PK analysis methodology, so that one can then compare non-pregnant to pregnant data, even in a historical case. That is commonly done during regular review work at the FDA.

Audience comment: *Changing human subjects regulations.* A review of the history of Subpart B is very informative. Is it worth trying to change Subpart B again? How difficult would it be to change it, particularly since it is the common rule and all the agencies would have to buy into changes?

Panel comments: The internal process of reviewing a regulation in one area opens up all of the rest of it at the same time. Any proposed changes to Subpart B need to be put out for public comment, which has to be very carefully analyzed, response by response. These responses are taken into account in what the final regulation/publication looks like. A department needs to demonstrate that it has carefully considered, and been responsive to, public comment. Any effort to make changes to subpart B would have to be carefully thought out and carefully organized to ensure that, when the public comment opportunity comes about, the community that is interested in changes responds promptly and actively.

CHAPTER FOUR: *PANEL 1:* CLINICAL RESEARCH EXPERIENCE IN ENROLLING PREGNANT WOMEN-INFECTIOUS DISEASES AND MATERNAL FETAL MEDICINE

Overview

This panel provided examples of successful research undertaken to address the health needs of pregnant women. In three of the presentations (The H1N1 Trial; MFMU Network and H1N1 Registry; Antiretrovirals), the research described was undertaken utilizing the resources of extended research networks. In the fourth presentation (HIV-Malaria Co-infections), data sharing among sites with similar protocols is described.

Dr. Richard Gorman presents an overview of H1N1 vaccine studies undertaken in pregnant women in anticipation of an H1N1 pandemic. In work to establish that vaccines under development were effective in pregnant women, NIAID enlisted its network of Vaccine and Treatment Evaluation Units (VTEU's) to supplement their expertise with the specific expertise needed to conduct research involving pregnant women. Dr. Gorman also discusses factors which generally contribute to the success of a clinical trial.

Dr. Catherine Spong outlines several major activities of the NICHD-funded Maternal Fetal Medicine Units Network (MFMU), including a major study of the effect of progesterone in the prevention of preterm birth and of magnesium sulfate in the prevention of cerebral palsy when administered during imminent preterm birth. The findings from these studies have led to changes in clinical practice in obstetrics and gynecology.

Dr. Myaing Nyunt describes the challenges involved in conducting research in sub-Saharan Africa on a condition, such as malaria complicated by HIV infection. Treatment of malaria during pregnancy is common in the region, using drugs such as Coartem, but insufficient pharmacokinetic data are available to address correct dosing requirements. Dr. Nyunt describes how social and logistical challenges, as well as the weakened condition of potential subjects, present impediments to research, while emphasizing the importance of developing sensitivity to cultural norms and values.

Dr. Heather Watts describes several protocols investigating HIV/AIDS in pregnant populations. Early studies by a series of NIH funded networks have provided information on the effects of antiretroviral agents in pregnancy, including findings that have changed dosing recommendations. Dr. Watts also describes challenges in obtaining informed consent and in protecting subjects participating in HIV/AIDS research.

The H1N1 Trial

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National Institutes of Health

Clinical research can be conceived of as a dynamic system in which four interrelated elements influence chances of success. The elements are: planning and preparation, people, presentation, and providence or luck. How these elements influenced three H1N1 clinical vaccine studies, conducted in 2009-2010 with pregnant women, will be discussed.

Preparations for coping with a looming threat of an H1N1 influenza pandemic in 2009 had been ongoing for almost a century. In the influenza pandemic of 1918-1919, 50 million people were infected with an H1N1 virus, with 20 to 40 million deaths worldwide, 50 percent of them in young adults. In the U.S., over 500,000 individuals died. Influenza was scarred into the public consciousness. In the early years of the 21st century, H5N1 influenza, otherwise known as bird flu, exploded onto the public health scene and reignited fears of a pandemic.

The inevitability of another pandemic was addressed in 2005 in a U.S. Department of Health and Human Services planning document entitled, "HHS Pandemic Influenza Plan." The Plan identified four tiers of individuals for whom vaccines would be administered as a public health priority. Pregnant women were included in the first tier.

In 2009, on the eve of a possible H1N1 pandemic, what was known about pregnant women in terms of their response to influenza vaccines? There was abundant safety data, since seasonal influenza vaccine has been recommended for them since 1997. However, there was little and conflicting data on efficacy.

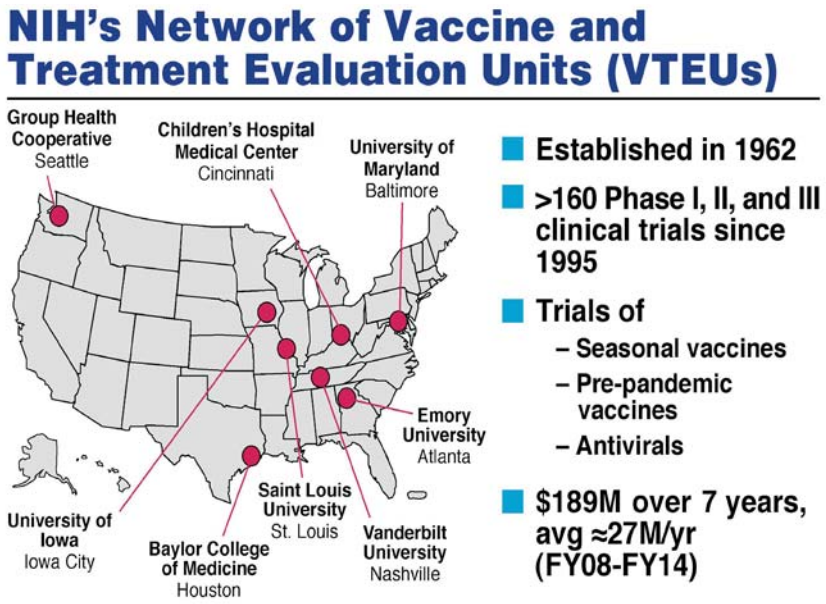
Research Infrastructure is Critical

When the threat of a H1N1 pandemic loomed in 2009, the Division of Microbiology and Infectious Diseases (DMID) at NIAID was prepared to undertake studies of H1N1 vaccination of pregnant women. Two other DMID studies of pregnant women were already underway and had provided experience in designing, writing, and implementing clinical trials in pregnant populations. The first was a study of the Tdap vaccine in healthy pregnant women. Tdap vaccine protects against tetanus, diphtheria and pertussis. The second was a study in a sample of pregnant women of Praziquantel, a vaccine for the treatment of Schistosomiasis japonicum. DMID was thus well-prepared to study optimal H1N1 vaccine dosing strategies in pregnant women.

The second element needed for the success of a clinical trial is getting the right people. To do research with pregnant populations it is obviously necessary to engage, interest, and excite such groups as obstetricians, midwives, and nursery, and labor and delivery staff.

It is also necessary to have in place a network of the right people who are experienced at carrying out clinical trials in a timely way and who are situated in environments where they have access to needed infrastructure and patient resources. NIH has such an existing network in place, the Vaccine and Treatment Evaluation Units (VTEUs). There are eight sites, which are shown in Figure 1.

FIGURE 1



Source: Slide presented at *Issues in Clinical Research: Enrolling Pregnant Women* Meeting, October 2010, National Institutes of Health, Bethesda, Maryland

The VTEUs are extremely mature and capable sites, but they had limited capacity to perform studies in pregnant women. It became apparent in March and April of 2009 that clinical trials that included pregnant women would be performed by the NIH. The VTEU sites reached out to their obstetrical colleagues. Several subcontracts were activated from the VTEUs to expand their access to a pregnant population and expand their capacity to perform studies in pregnant women.

NIAID Influenza Studies in Pregnancy

The VTEUs performed three studies in pregnant women. The first was a study of the seasonal inactivated trivalent vaccine. The second was an H1N1 study involving one or two vaccinations with two different dose levels. The third was an H1N1 study of one vaccination and two dose levels.

Seasonal trivalent vaccine study This study enrolled 104 pregnant women in the second or third trimester of pregnancy between June 2009 and September 2009. The aim was to determine immunogenicity in pregnant women. There was an active ethical debate at DMID prior to starting this study. The possibility of direct benefit to the women in the study was remote since it was started after the influenza season of 2008-2009. However, DMID prepared a letter for IRBs explaining how the information gained from the study would guide future studies of the novel H1N1 vaccine. Results of the trivalent vaccine study indicated that immunogenicity in pregnant women was equivalent to that of historical controls. There was no safety signal. The results suggested that whatever dose was found to be immunogenic for the general population would be equally immunogenic for pregnant women.

H1N1 study 1 For this initial study of the H1N1 vaccine in pregnancy, 120 pregnant women were enrolled between September and October 2009. The design included two vaccinations, since at the time it was unknown whether one "shot" would be sufficient to acquire the necessary level of immunity. Two different dosage levels were also incorporated into the design. Results indicated that immunogenicity reached generally accepted levels for protection shortly after the first dose, and no safety signal was found. Pregnant women receiving the H1N1 vaccine had an immune response that was equivalent to the general population.

H1N1 study 2 After determining that one dose of the H1N1 vaccine provided adequate immunogenicity, a second study tested two different dose levels. Ninety-four pregnant women were enrolled between November 2009 and May 2010. Their immunogenicity generally reached accepted levels for protection shortly after the first dose. There was no safety signal.

Pregnancy outcomes were monitored in an ongoing way during the studies. In a group of 300 second and third trimester pregnancies, there is an expected rate of spontaneous abortions and stillbirths, and spontaneous abortions and stillbirths occurred during the studies. The NIH Safety Monitoring Committee, which included a number of thoughtful obstetricians, provided assurances that these events did not exceed what was normally to be expected.

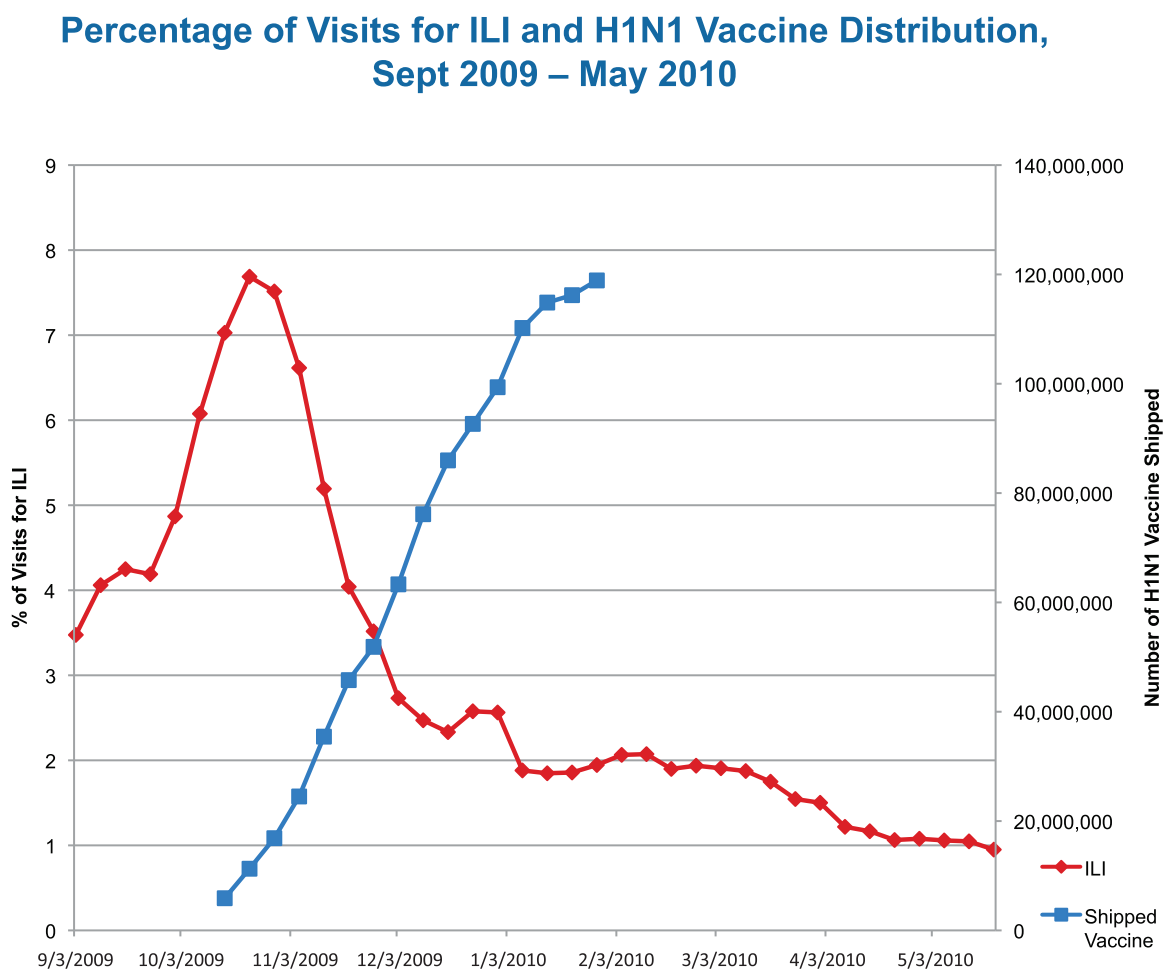
Rather than talking about doing research on pregnant women, a better way to frame a study is to talk about how its results will help meet the health needs of pregnant women.

Presentation is an important element in successful clinical research. Professionals and experts develop their own specific vocabularies full of acronyms and words that have meanings understood inside specialized groups. Often, they use phrases or words that are shorthand for longer thoughts. They use them for so often and for so long that they become unaware of what they sound like to people outside of their profession. Although such language may be convenient shorthand among colleagues, it can sound highly insensitive to the individuals who are the subjects of clinical research and is to be avoided outside of one's own research circle.

How the aims of research are presented also matters. Rather than talking about doing research on pregnant women, a better way to frame a study is to talk about how its results will help meet the health needs of pregnant women. Care should be taken in framing the introduction of studies, not only to potential study subjects, but also to institutions, institutional review boards, and the general population.

The timing and impact of a clinical trial can be influenced by variables that are not under the researcher's control. This can be attributed to providence or luck, depending on one's belief systems. An example of how providence or luck can affect a trial, Figure 2 depicts seasonal influenza occurrences between September 2009 and May 2010 in relation to vaccine availability to the general public.

FIGURE 2



Source: CDC ILI and Vaccine Distribution Data

Influenza like illnesses including H1N1 peaked in the fall of 2009 at a time when the availability of H1N1 vaccine in the general population was at its lowest. Enrollment into these studies made vaccine available to the human volunteers before it was available, or when it was still in short supply to the general public. Would the vaccine's availability be too late to prevent serious consequences in the general population? With early reports from Mexico indicating that the strain was of unusual virulence and high transmissibility, this was a major concern. However, by providence or luck, the strain turned out to be only slightly more transmissible than seasonal influenza, and reports of infections were falling off significantly by winter. The World Health Organization declared an end to the pandemic by August 2010.

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MFMU Network and H1N1 Registry

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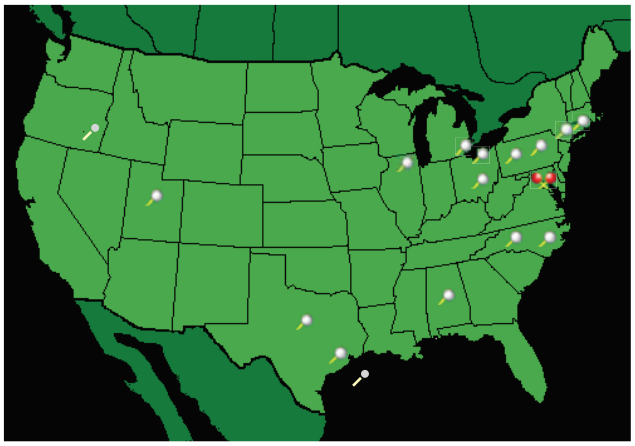
The NICHD Maternal-Fetal Medicine Units (MFMU) Network began in 1986 and is openly and actively re-competed every five years. There are 14 clinical sites in the Network, (listed in Figure 1) and an independent data center, along with NICHD. The Network identifies priority clinical issues and conducts studies and trials in pregnant women. The current network encompasses about 140,000 deliveries each year.

FIGURE 1

NICHD's MFMU Network centers 2006-11

- 14 Clinical sites
- Data coordinating center
- NICHD
- ~140,000 deliveries/yr
- Re-competition: 5 yrs

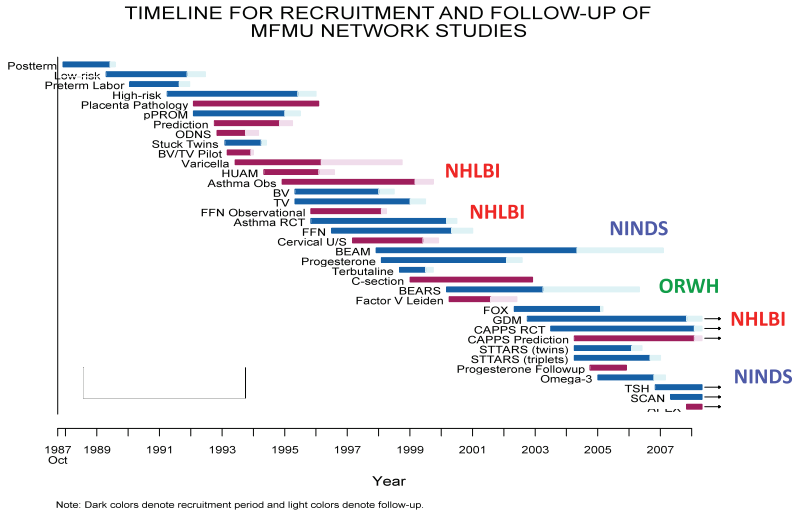


- Columbia
- Case Western
- U Pittsburgh
- Northwestern
- Ohio State
- Oregon HSU
- U Alabama
- U North Carolina
- U Texas-Houston
- U Texas SW-Dallas
- U Utah
- UTMB Galveston
- Wayne State
- Women and Infants

Source: Slide presented at *Issues in Clinical Research: Enrolling Pregnant Women* Meeting, October 2010, National Institutes of Health, Bethesda, Maryland

FIGURE 2

NICHD MFMU Network: Studies & Trials



Source: Slide presented at *Issues in Clinical Research: Enrolling Pregnant Women* Meeting, October 2010, National Institutes of Health, Bethesda, Maryland

Figure 2 highlights the observational studies and clinical trials that have been done in the Network since its inception. As the Network has matured, it has become common for four to six studies to be ongoing at a given time. In addition to NICHD, Network studies have been supported by ORWH, NHLBI and NINDS.

There are special considerations in doing research with pregnant women, and one of the most important considerations is how the stage and the status of pregnancy affect the way the potential subject needs to be approached for study participation. If a study is preventive and a drug can be given early in pregnancy, the patient can be approached in a non-emergency context. At other times, an experimental intervention must be done in an urgent situation, while a woman is in the hospital for a condition that poses a threat to her or her fetus, or even while she is in labor. At such times, patient stress is quite high. An approach for study participation must reflect sensitivity to that stress, while at the same time consent needs to be obtained under time constraints inherent in research on rapidly progressing obstetrical conditions.

Preterm Birth Prevention: Progesterone Study

Prevention of preterm birth is clearly a public health priority. One out of eight infants in the United States is born preterm, accounting for about half a million preterm births each year. Preterm birth is the leading cause of neonatal mortality. For those who survive, it accounts for one of five children with mental retardation, one in three children with vision impairment, and almost half of all children with cerebral palsy. In the long term, these children, who are usually born at a low birth weight, as well, have higher risks of heart attacks, strokes, hypertension, and diabetes as adults.

A MFMU study was designed to determine if progesterone during pregnancy could reduce the risk of a subsequent preterm birth in women who had previously had a preterm birth. This was a double-masked, placebo-controlled trial of women with singleton pregnancies between 16 and 20 weeks. The patient population was highly select and highly motivated. Progesterone was administered intramuscularly for up to 16 weeks. Results indicated that progesterone significantly reduced preterm births of less than 37 weeks, which is the common definition of preterm birth, and deliveries less than 35 weeks, as well as less than 32 weeks.

There are special considerations in doing research with pregnant women, and one of the most important considerations is how the stage and the status of pregnancy affect the way the potential subject needs to be approached for study participation.

Preterm birth is much more common in African-American women. For these women, progesterone was found to be as effective in reducing preterm birth as in other women. The availability of an intervention was a significant breakthrough to clinicians who previously had little to offer a pregnant woman at risk for preterm birth by virtue of having previously delivered a preterm infant. The progesterone intervention could reduce recurrence by about one third. The effectiveness of this therapy was such that only five to six women with a prior preterm birth would need to be treated to prevent one preterm birth at less than 37 weeks.

A 2005 March of Dimes analysis used parameters from the MFMU Network study to estimate how many preterm births could have been prevented in 2002 if all women at risk for preterm birth had received progesterone. The figure derived at was that 10,000 of the 30,000 recurrent preterm births in 2002 could have been prevented.

These findings have been translated into clinical practice. A 2008 Committee Opinion issued by the ACOG recommended that progesterone be offered to women who have had a prior preterm birth to prevent a subsequent preterm birth.

Preterm Birth Prevention: BEAM Study

The Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) Trial was undertaken by the MFMU Network to determine whether antenatal magnesium sulfate could reduce cerebral palsy in the offspring. This was a double-masked, placebo-controlled trial done in women who were in preterm labor, or had ruptured membranes with a planned delivery. They were between 24 and 31 weeks pregnant.

Women were randomized to magnesium sulfate or placebo. This was a population who had to be recruited at a critical time. Not only were they recruited when preterm labor was imminent, but the protocol required that they and their children be followed up for two years, in order to obtain the primary study outcome. Over 2,000 women were randomized and almost 96 percent were followed up. A significant reduction in moderate to severe cerebral palsy was found in the group receiving magnesium sulfate, from about 3.5 % to 1.9 %. The risk of death overall was not different between the two groups. It was estimated that one case of cerebral palsy could be prevented for every 63 women who received the treatment.

These results were incorporated into a 2010 Committee opinion from ACOG, which concluded that the evidence for the efficacy of magnesium sulfate in reducing risk of cerebral palsy was strong enough that obstetricians should consider its use in high risk preterm deliveries for fetal neuroprotection.

H1N1 Registry

In 2009, the MFMU Network established an H1N1 registry to look at the severity of influenza-like illness in hospitalized, pregnant, and immediately post-partum women. Women hospitalized with influenza-like illness were identified by intensive monitoring of patients in critical care units, on medical floors, and in labor and delivery units. Analysis of data is ongoing.

Since its inception, the activities of the MFMU Network have been directed toward the identification of key clinical issues for pregnant women, the design and conduct of studies to address priority issues, and the rapid translation of study results into improvements in clinical practice and, ultimately, in the health and wellbeing of mothers, children and families.

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Malaria-HIV Co-Infections

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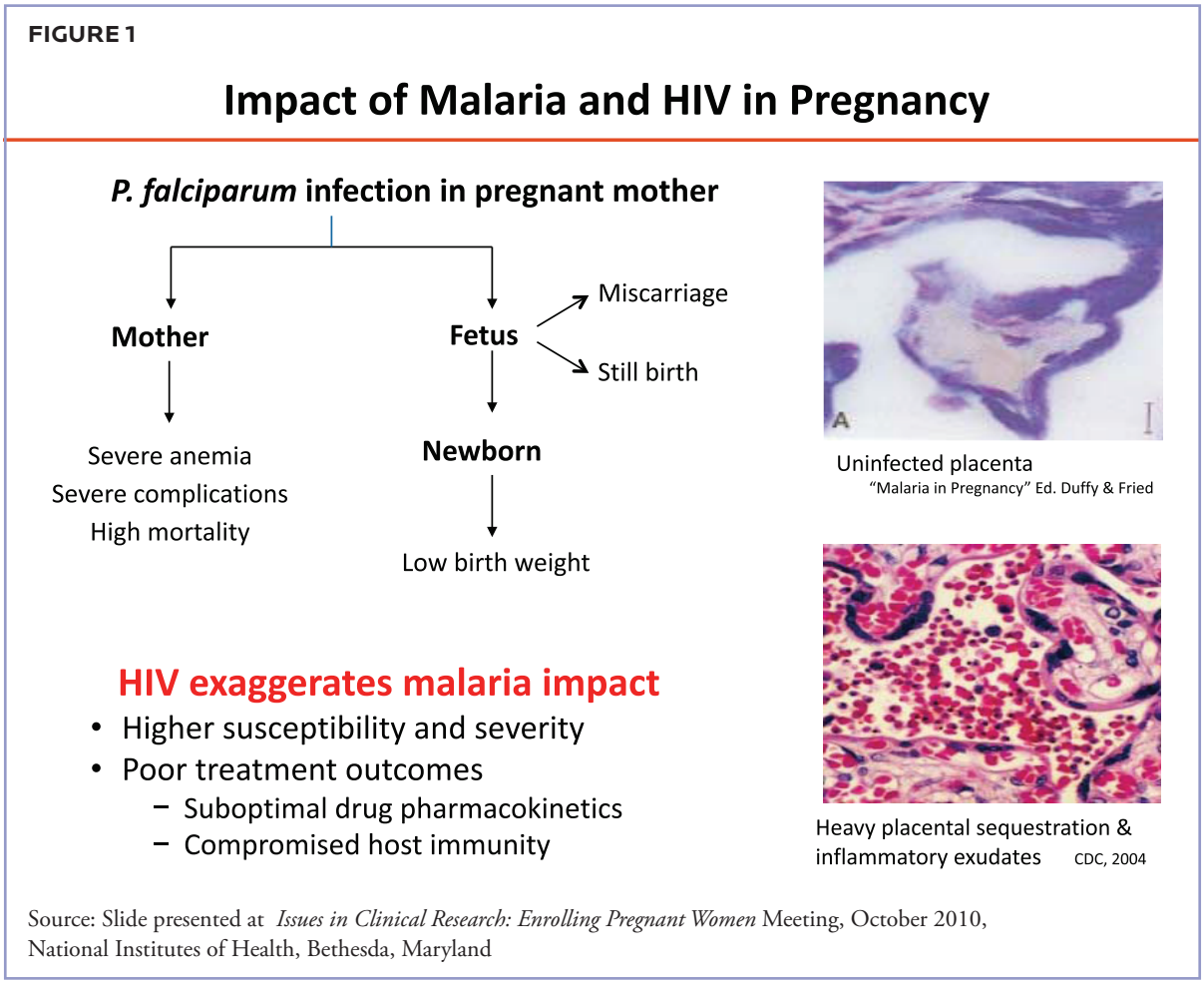
Plasmodium falciparum infection during pregnancy is strongly associated with maternal morbidity and mortality. Plasmodium falciparum infection increases risk for fetal loss, stillbirth, and delivery of a newborn with a low birth weight. HIV infection exaggerates the negative impact of malaria on pregnancy. The impact is illustrated in Figure 1.

FIGURE 1



Source: Slide presented at *Issues in Clinical Research: Enrolling Pregnant Women* Meeting, October 2010, National Institutes of Health, Bethesda, Maryland

There is evidence to suggest that there are poorer treatment outcomes in pregnant women with HIV and malaria. Among possible contributory factors are pregnancy-related changes in drug pharmacokinetics, interactions between malaria and HIV drugs, and compromised host immunity. There is public health urgency to support clinical studies addressing the medical needs of these pregnant women, but there are also significant barriers. Two studies, one published and the other currently underway, are illustrative of the special challenges involved in research with pregnant women with malaria in the developing world.

Study 1: SP Pharmacokinetics in Pregnancy

Sulfadoxine-pyrimethamine (SP) is widely used in Africa as an intermittent preventive treatment of malaria in pregnancy. SP is typically given to pregnant women twice, one month apart, during the 2nd and 3rd trimester of pregnancy. The dosing regimen was based on pharmacokinetic and pharmacodynamic information that originated from the non-pregnant adult population, mostly male.

Only limited data are available on the pharmacokinetics of Sulfadoxine and Pyrimethamine (SP) during pregnancy. A prospective, self-matched, multicenter study of 98 pregnant women was conducted in four African countries, in order to determine the effects of pregnancy on SP pharmacokinetics. The study design was complex and labor-intensive. It involved two overnight hospital stays for the subjects, one during pregnancy and the second postpartum, since women were used as their own controls. A woman was dosed while pregnant and then again two months following delivery, at the end of the postpartum period. The protocol also involved four weekly outpatient visits.

Study 2: Quinine versus Coartem in HIV Positive Pregnant Women

HIV co-infection greatly complicates malaria and its treatment. There is significant geographic overlap between the global distribution of HIV and malaria, and both conditions have a disproportionately negative impact on pregnant women. Both are associated with infant morbidity and mortality, and both conditions demand specialized care throughout pregnancy. Quinine is the oldest anti-malaria drug in existence. It is still widely-used, particularly for pregnant women. Coartem is a more recently available anti-malarial drug, which combines artemether and lumefantrine. It is increasingly popular throughout sub-Saharan Africa. The aim of this study is to look at efficacy and pharmacokinetics of quinine and Coartem in a sample of HIV positive women with malaria. It is an open label comparison of 7 days of quinine versus 3 days of Coartem. The single-site study is ongoing in Mali.

There is public health urgency to support clinical studies addressing the medical needs of these pregnant women, but there are also significant barriers.

As in the previous study, the study design is complex and labor intensive. It involves a multi-day hospital stay during which there will be multiple blood draws; and, from day 7 to 28, 4 weekly safety and efficacy follow-ups and blood draws for pharmacokinetic studies on days 7 and 14.

Challenges in Research in Sub-Saharan Africa

By its very nature, research is very focused. Some researchers study HIV and others malaria but there is often no connection, even though the conditions frequently co-occur in the same individuals. HIV studies tend to have well established resources, but they are not located where malaria is endemic. There is fragmentation in the way that clinical care for the conditions is delivered; and there is fragmentation of the clinical research infrastructure to study them. These issues have captured the attention of many individuals and organizations, and solutions are actively being sought. Currently, they still impose limits on research feasibility, as well as on clinical care.

Resources for the hospital monitoring of patients during pharmacokinetic studies are often quite distant from the villages where women live. Transportation is a major issue, as are issues of childcare. Multiple blood draw requirements are logistically demanding and may place other health burdens on the women. While these problems are not confined to pregnant women, they are more pronounced for them because they have underlying health fragility and physiologic vulnerability.

Cultural sensitivities need careful consideration. Approaching women for study of HIV and comorbid malaria is difficult and challenging for social reasons. There are unusual social sensitivities and prejudices about sexually transmitted diseases throughout the world, including in West Africa and South Africa. Informed consent often involves culturally sensitive interactions with more individuals than the individual study participant. In order to obtain permission to approach pregnant women for potential research participation in rural areas of Mali, community consent or permission to enter a village often had to be obtained from village elders.

Cultural sensitivity and sensitivity to fears and concerns must be an integral part of the individual consent process. Among fears the pregnant women expressed were those of the research process itself. Education was very important in this regard. Much effort needed to be directed toward communicating the reality of their illnesses, the need for treatment, and the risks versus benefits. Given the nature of HIV, confidentiality was a special concern. The consent forms had an entire section devoted to the promise of confidentiality, and significant time was also spent in individual discussions of the issue.

Lessons learned

Scientists tend to be perfectionists. They want a perfect set of data, but in the developing world, logistical impediments can place limits on what is possible. How can research be done without compromising patient safety or data quality, while at the same time minimizing research burden on pregnant women? There are a number of strategies to consider.

Investigators working in close geographic areas and on similar diseases should work to harmonize protocols so that data sharing is possible. Study 1 was harmonized with a similar study that was planned in Mozambique and Sudan. The resulting data set was much larger and more powerful than the two data sets would have been separately analyzed. Data were analyzed together, and results were published together.

Frequent blood collection is a potential research burden on the pregnant women for multiple reasons. Modeling and simulation can be used to determine the most efficient schedule without compromising data quality. Volume of blood drawn may also be reduced. Work is currently ongoing to develop methods to analyze very low volumes of blood.

Scientists tend to be perfectionists. They want a perfect set of data, but in the developing world, logistical impediments can place limits on what is possible.

Another way to reduce burden on women is to enable them to participate by providing childcare. In Study 1, when women were asked to come to hospital for a follow-up visit, their children were also invited. What could have been a burden was turned into a pleasant respite. Other options to reduce burden include the use of mobile clinics and home visits to meet the patient where she lives.

In the developing world, the process of engaging patients in research requires outreach, determination to overcome language and cultural barriers, cultural sensitivity, detailed disclosure and discussion in the consent process, and transparency in the study aims and goals. Training and educating the larger community, in particular health care workers and investigators participating in research, is a useful part of the larger work to be done, if the health outcomes of pregnant women are to be improved and health care capacity developed. Training and education are ongoing processes rather than a one-time event. Outreach to health care systems will be necessary to overcome the current fragmentation of health care. While there are many barriers, both major and subtle, in the conduct of research in the developing world, the task is difficult but not impossible.

In the developing world, the process of engaging patients in research requires outreach, determination to overcome language and cultural barriers, cultural sensitivity, detailed disclosure and discussion in the consent process, and transparency in the study aims and goals.

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Antiretrovirals

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This presentation discusses barriers to antiretroviral research with pregnant women. Problems are noted with the regulatory requirements for paternal consent for therapeutic research targeted at the health needs of the fetus. In addition, studying agents in pregnancy not already approved for use in non-pregnant adults provides another level of difficulty. Three retroviral study protocols are discussed, in particular as they illustrate issues in IRB review.

Paternal Notification and Consent Issues

Early studies of the prevention of maternal-child transmission of HIV involved clinical trials of zidovudine. One study was conducted by the NIH-funded Pediatric AIDS Clinical Trials Group (PACTG), which is now called the International Maternal Pediatric Adolescent AIDS Clinical Trials Group. The intervention, oral zidovudine, was considered to have potential therapeutic benefit for the fetus, but not for the mother, since, at that point, zidovudine was indicated only for people with CD4 counts less than 200.

The father's consent was therefore required in a trial of an intervention offering what, at the time, was the only hope for preventing HIV infection in the baby. The mother's HIV status had to be disclosed to him. That setting brought to the forefront difficulties with the paternal consent regulations.

When a woman tested HIV positive, study personnel had to help her deal not only with her own concerns and her concerns for the health of her fetus, but they also had to work out a plan for partner notification and partner consent.

Partner notification and consent in HIV studies raised a number of issues not encountered in other protocols. If the father learns that the mother has gestational diabetes, it does not have direct implications for his health. But if a pregnant woman finds out that she is infected with HIV, the odds are high that she got it through sexual activity. It also means that her partner is at risk, and it usually means that she got it from

Partner notification and consent in HIV studies raised a number of issues not encountered in other protocols.

the partner. There were often very disturbing issues to be dealt with.

In some cases, because of concerns about domestic violence, that plan involved notifying the partner when she was in the hospital having the baby, because then she was in a safe place and was not at risk for assault when her partner found out that she had HIV, even though he may have given it to her.

In 2001, changes to Subpart B improved the consent process. Nonetheless, and especially in the field of HIV/STD research, requirements for partner consent may still constrain maternal- fetal studies.

Antiretroviral Study Protocols: IRB Challenges

NICHD co-funds several networks that are primarily funded by NIAID, looking at treatment and prevention of HIV. One of these is the International Maternal Pediatric Adolescent AIDS Clinical Trials Group and another is a Microbicide Trials Group.

These networks conduct a range of studies of antiretrovirals (ARVs) in pregnant women. These studies have presented a range of challenges in obtaining IRB approval.

Three study protocols representing increasing levels of challenge in IRB approval are:

1. ***PACTG1026S***: an opportunistic PK study of ARVs that pregnant women are already receiving as part of their clinical care.

2. ***PACTG076*** *and multiple others*: evaluations of ARVs for reduction in perinatal transmission of HIV and for maternal health.

3. ***MTN008:*** PK and safety study in HIV-uninfected women of a 1 % tenofovir vaginal gel in late stage pregnancy and lactation.

PACTG1026S

P1026S is an opportunistic intensive PK study in pregnant women already on antiretroviral drugs. The drugs are already prescribed, so the study risks are the blood draws, not the drug prescription. IRB approval was not problematic. There have been almost 500 women enrolled on various antiretrovirals. Very important data has been obtained from this study and results have led to changes in dosing recommendations for some of the protease inhibitors.

PACTG076

The next level of studies are trials in HIV-infected pregnant women, primarily aimed at reducing perinatal transmission of HIV, but sometimes also looking at maternal health issues. Subjects in these studies were HIV infected pregnant women, so there were clear indications for the drugs. Some of the trials were initially controversial with IRBs. However, PACTG076 was not as controversial with the IRB as with the activist community.

In the process of addressing activist concerns, a very productive relationship with the community has come to exist. Community advisory boards now provide advice to study investigators on the development of studies, and then they also help with the presentation to the communities.

MTN008

Many in the microbicide field have advocated for pregnant and lactating women to be able to stay in studies of microbicides. But there were also barriers and resistances, because questions existed about the efficacy of the microbicides and the appropriateness of exposing pregnant women to these drugs in the absence of a clear indication of benefit. In African countries, there was even more reluctance to approving studies of microbicide agents in pregnancy.

In anticipation of IRB concerns, members of the Microbicide Clinical Trials Group developed a stepwise agenda. As part of this agenda, MTN008, which is a PK and safety study in late pregnancy, was proposed.

The protocol went to the local IRB, and they decided that they could not approve the study in pregnant women, and that it needed to be referred to the Office of Human Research Protections for their review. The outcome of that review is pending.

In African countries, there was even more reluctance to approving studies of microbicide agents in pregnancy.

A previous study had involved giving a single dose of the gel to women who were having a scheduled caesarean delivery, obtaining blood levels, and looking at the absorption of the drug, because a topical drug in the vagina might be absorbed at higher levels in a pregnant woman than in a non-pregnant woman.

Design The proposed study would include 45 healthy pregnant women who would receive the microbicide gel at 37 weeks gestation. They would get once daily dosing for seven doses; and absorption, tolerability, and safety would be examined. If there were no problems, such as toxicity, or increased risk of ruptured membranes, women at 34 to 36 weeks gestation would then be studied.

There are also plans to include a lactation cohort of 15 women who will receive seven daily doses. A lactation cohort is very important especially in African countries where women breastfeed on average

longer than they do in the US. If safety and PK data are not obtained for lactating women, then they may be excluded from potentially beneficial trials. The protocol includes plans to examine safety and drug levels in the babies and the mothers.

Background data. What background data are available to support this study? Oral tenofivir has been studied extensively in animals. There were concerns at higher dose about bone changes, but the drug is well-tolerated at human exposures. There are over 1,400 cases of oral tenofivir exposure in pregnancy reported to the Antiretroviral Pregnancy Registry. No increase in birth defects with oral tenofovir use has been detected. It is being studied for reduction of maternal-fetal transmission.

Plasma drug levels are a hundred-fold lower after topical dosing than they are after oral dosing. A study had already been done in pregnant women who were undergoing C-sections.

Importantly, the IRB did not have the results of the CAPRISA 004 study of tenofovir when they initially reviewed the protocol. Those study results, which came out in the summer of 2010, suggest a 39 percent reduction in HIV acquisition with tenofivir gel use.

If a topical microbicide does become available for STD and HIV prevention, it is going to be widely used by reproductive age women. Some of these women will become pregnant. It is important to know about the effect of the gel in pregnant women before it is widely prescribed.

Unanswered Questions

This raises several other questions. What constitutes minimal risk? Obviously, the IRB that reviewed this MTN008 protocol believed that it was above minimal risk for pregnant women, and that is why they referred it on.

Is it always necessary to have evidence of efficacy in non-pregnant adult before a drug is studied in pregnant women? Can a proactive approach be taken, so that if it is anticipated that a drug is going to be widely used by women of reproductive age, then some data in pregnancy can be obtained before licensure?

If a drug does have to be FDA-approved first, then how can safety data in pregnancy be acquired once a product is approved and used widely?

Adequate post marketing surveillance may be difficult, especially in those settings where widespread use of microbicides is anticipated. These include disadvantaged settings in sub-Saharan Africa where surveillance systems are not well-established and reporting to registries is not common.

Other questions can be asked. When can PK data from non-pregnant women be extrapolated to pregnant women? When are specific studies in pregnancy required? What are the best methods for identifying which drugs deserve the highest priority for pharmacokinetic and safety studies in pregnant women?

In conclusion, risk/benefit considerations in studies of antiretroviral agents in pregnant women are complex; but the inclusion of pregnant women in such research seems fully warranted based on the potential direct preventive and therapeutic benefit for a large number of women and their children from the drugs tested.

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Discussion

Panel: Dr. Richard Gorman, Dr. Cathy Spong , Dr. Myaing Nyunt, and Dr. D. Heather Watts

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, it provides highlights of discussion with special emphasis on new issues raised by the presentations and issues of general importance to the goal of promoting the responsible inclusion of pregnant women in clinical research.

Audience comment: *Collaborative efforts to share data.* Much data that could be gathered from clinical trials is basically being lost because of a lack of cooperative effort and the ability to combine data sets. What progress is being made in this area?

Panel comments: NIH-funded researchers are required to report outcome data and the clinical trial result data, which then will be available through the National Library of Medicine at http://www.clinicaltrials.gov/.

Data-sharing and data coordination are good ideas, but one must avoid comparing apples and oranges. To move in the direction of combining data sets, one has to start from the level of study design, analytical methods, and statistical planning.

NIAID is moving towards a single clinical research platform. Other Institutes may do so, as well, to encourage data sharing and coordination.

NICHD is working with FDA to try to merge some data sets. It is a very difficult endeavor because of the difference in how the data are collected. It would behoove researchers to forwardly think to create data elements and data structures that can be easily merged. NICHD did an influenza vaccine study in HIV-infected pregnant women at the same time that NIAID was doing one in non-infected pregnant women, and the two institutes are sharing data and comparing levels of antibody response and other parameters.

At NICHD, there are units that do obstetric and fetal pharmacology research and other units that conduct maternal fetal medicine research. More collaborative activities might be devoted to developing a shared rationale for deciding which drugs to study, and which drugs are less of an issue for pharmacokinetic studies.

At the Society of Maternal Fetal Medicine in early 2010, there was an effort to bring together the groups internationally that were doing research in obstetrics and in maternal fetal medicine, to promote collaboration and the planning of studies and trials so that similar data elements can be collected, even if the trials were different and had different endpoints. The group is now called *GONet* for Global Obstetrics Network, and hopefully it will provide another forum to improve collaboration internationally.

CHAPTER FIVE: *PANEL 2:* CLINICAL RESEARCH EXPERIENCE IN ENROLLING PREGNANT WOMEN-CHRONIC DISEASES

Overview

Presentations from the panel on Clinical Experience in Enrolling Pregnant Women with Chronic Diseases dealt with a diverse group of conditions ranging from cancer to opioid dependence. Dr. Elyse Cardonick describes her experiences in developing a registry for pregnant women with cancer, a population on which very little information was available to inform clinical treatment strategies or regarding the likelihood of favorable fetal outcomes following maternal treatment with chemotherapeutic agents. Ways to gain knowledge in this understudied population are discussed.

Dr. Kimberly Yonkers describes her experiences in dealing with the complexities of a prospective cohort study involving pregnant and postpartum women. Differences among IRBs in their evaluation of the study protocol is discussed, as are a number of specific issues that may present as impediments to research on mental health conditions in pregnant women. The issue of stigma in particular requires particular sensitivity in the way the study is presented to potential subjects, as well as to the larger community.

Dr. Donald Coustan presents findings from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study. HAPO was a multi-site program undertaken to clarify the risk associated with various degrees of maternal glucose intolerance less severe than that in overt diabetes mellitus. The challenges posed to the study due to differences among sites in standard clinical practices are discussed, as are a number of other issues that arose among the multiple sites involved in the multinational effort.

Dr. Hendree Jones discusses the challenges of conducting research on the treatment of opioid dependence in pregnancy. Use of opioids in pregnancy can be associated with adverse outcomes in the newborn, including withdrawal syndromes requiring infant stays in neonatal intensive care units. The findings of the study provide evidence that buprenorphine may lead to more favorable newborn outcomes than another commonly used maintenance agent, methadone. Ethical issues in this area are discussed.

Cancer

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The Value of Registries

The Pregnancy and Cancer Registry at Cooper Hospital includes pregnant women with cancer treated internationally. Two hundred seventy eight women with diagnoses of cancer, among them patients with leukemia, Hodgkin's disease, and breast cancer are currently in the registry.

A registry is the first step toward accumulating safety data that can then be used in support of prospective studies, or at least to reassure patients and their physicians that pregnant women with cancer can be treated. It is fortunate that physicians, whose pregnant patients were exposed to chemotherapy, published information on maternal and fetal outcomes, so that the information could influence another physician's decision to treat a pregnant woman. It is also fortunate that a pregnant patient with cancer can now be told what is known about the effects of chemotherapy on pregnancy outcomes.

The National Transplantation Pregnancy Registry (NTPR) at Thomas Jefferson Medical College provides further evidence of the benefits of registries. Women with organ transplants do not have the option of stopping anti-rejection medication during pregnancy, because they will lose their organs. The NTPR has collected information on more than 1800 recipients and 3100 pregnancies and now may be in a position to propose a prospective study of pregnancy outcomes in kidney transplant patients on two different anti-rejection medications to determine which medication is less likely to be associated with hypertension or preeclampsia, which often occur in pregnant patients with renal transplants.

A registry is the first step toward accumulating safety data that can then be used in support of prospective studies, or at least to reassure patients and their physicians that pregnant women with cancer can be treated.

Information on Cancer Treatments in Pregnancy: Early Studies

Among the first women to be treated for cancer in pregnancy were those with acute leukemia. For these pregnant women, the clinician's first instinct was to recommend terminating the pregnancy, but some of the women were too sick to undergo a termination prior to treatment. They would have died from infection or perforation of the uterus and hemorrhage. So the initial plan was to give them chemotherapy to stabilize them, and then perform a termination.

That happened in some patients, but other patients felt better following the chemotherapy and since the baby looked healthy on ultrasound, they wanted to continue the pregnancy. Treating physicians, originally in Mexico, reported either how the fetus looked at termination or how the neonate looked at birth, and some information became available on those chemotherapy exposures.

Thanks to those brave physicians, data were available to advise pregnant women about the outcome of pregnancies where there were exposures to chemotherapy.

In the second scenario, pregnant women with acute leukemia had such prolonged amenorrhea that no one even considered that they were pregnant, and so they received chemotherapy, often in the first trimester. Again, their clinicians published outcome data.

In the third scenario, pregnant women with acute leukemia were told that if they did not get chemotherapy both they and the fetus would die; the women received chemotherapy, and the outcomes of the pregnancy were published.

Thanks to those brave physicians, data were available to advise pregnant women about the outcome of pregnancies where there were exposures to chemotherapy. Based on that information, other physicians were then able to treat pregnant women with less life-threatening cancers, such as Hodgkin's disease and breast cancer.

Clinical Experiences with Registry Information: Physicians

As a result of that accumulation of data, in 1997, I was able to take outcome information to my Hospital Ethics Committee, which was considering the treatment course for a pregnant patient with Hodgkin's disease. The oncologist, the risk management team of the hospital, and the nuclear medicine physician were at first unwilling to treat. When they reviewed the available data, however, the patient was able to get treated. There are many remaining obstacles to overcome.

A major obstacle to treatment of cancer in pregnancy remains fear of legal liability. In the case of the woman with Hodgkin's disease, the oncologist actually expressed this fear to the patient, her husband, and the committee.

Another obstacle to overcome is the emotional factor in physicians' decision making. In one example, when a pregnant woman with a breast mass was sent to a radiologist for a mammography, the radiologist was reluctant to do this test, even though she acknowledged that the radiation dose fell within safe limits for pregnancy. Emotionally, she could not bring herself to expose this fetus.

In the first 10 years of the registry, it was hoped that the recommendation by clinicians to have a patient terminate her pregnancy would decrease, as evidence of positive fetal outcomes accumulated. Available data, for instance, suggests that pregnant women with breast cancer who terminate have outcomes no more

favorable than those women who continue their pregnancies. However, there is no significant difference between the first five years and the second five years of the registry in terms of physician recommendations for termination.

Nonetheless, when women are given a recommendation to perform a termination, often they will seek out other information independently. When they find out about the Cancer and Pregnancy Registry, they often call and ask for information about pregnancy outcomes; they also ask what they can do to help another pregnant woman who has to face a similar crisis.

Clinical Experiences with Registry Information: Patients

Pregnant women with cancer are so blind-sided by this diagnosis that they want to do something positive. The enrollment in the cancer registry is mostly patient-, not physician-driven. At enrollment, they give their consent, not only to provide information on pregnancy outcomes, but also to allow contact with their pediatricians and oncologists on a yearly basis. Clinician burden is eased by having registry staff extract details of treatment and other information from the records ourselves.

It seems easier to enroll women in registries when it is a rare event, because there is so little information. When a pregnant patient and her husband ask the oncologist how many other pregnant women he has treated, and he says one or two, they are very motivated to get more information, to provide more information, and to help prevent other women from not facing the same information vacuum.

Confidentiality of information is stressed to patients. They are assured that their names are not given out. They are told that if other patients call about the registry, they want to know they are not the only pregnant woman with cancer. When they call the registry and find out that 15 other women with Hodgkin's disease have received chemotherapy in the last few years, and that their babies are relatively healthy, they have more confidence when they walk into the chemotherapy suite, and they are very motivated, again, to participate in the registry.

The patient is often told that she has to be healthy in order to have a healthy baby, and the goal is for her to live beyond the pregnancy. So the importance of keeping herself healthy is strongly stressed. This is not to suggest that pregnant women use the newest drug that is on the market, but that they look at older studies of efficacious drugs that do have safety data. If two drugs have equal efficacy for survival, and one has more information on safety, then the patient will usually chose the drug with more information.

Patients are allowed to withdraw at any time. In over 13 years of the registry, only two women have withdrawn. One woman said it was too sad to relive that time in her life, and the other woman said that she never told her daughter she was pregnant with cancer at the time, and she did not want her daughter to find out.

Future Needs

In 1997, the patient who got treatment for her Hodgkin's disease asked me in the delivery room to take a sample of her breast milk to analyze it for levels of her chemotherapy agent, dacarbazine. She was not going to breastfeed since she was on the agent, but she wanted to contribute to knowledge about its levels in breast milk. When the drug company was contacted, they were unwilling to perform an assay for fear that if the medication did not show up in the breast milk, then that would encourage pregnant women to breastfeed while on it.

That was in 1997. Pharmaceutical companies have come a long way and now embrace post-marketing registries. The FDA required Genentech to start a pregnancy registry for herceptin following case reports of oligohydramnios in pregnant women with breast cancer, treated with the agent.

Pharmacokinetic studies are needed to make sure that pregnant women are receiving a therapeutic dose of chemotherapy agents.

In the future, researchers, clinicians, and journal editors need strong encouragement to publish findings of normal fetal and infant outcomes following chemotherapy. Currently, it is much more likely that a study showing abnormal outcomes will get published, and this tendency may skew the literature. My job was made easier, because physicians were able to publish studies indicating that babies could have normal outcomes despite their mothers' taking chemotherapy.

Pharmacokinetic studies are needed to make sure that pregnant women are receiving a therapeutic dose of chemotherapy agents. Over 100 cases of breast cancer treatment in pregnancy with Adriamycin and Cytoxan have been accumulated, and those experiences are useful in encouraging other women and their physicians to treat. However, treated women often say that chemotherapy has little effect on nausea and hair loss during pregnancy but that, following delivery, the same dose causes these side effects. This suggests that pregnant women may metabolize the drugs differently and pharmacokinetic studies would be very important.

In this regard, a study was recently approved in Belgium to look at pharmacokinetics in pregnant women, and hopefully we will be adding to that study information about a pregnant patient with non-Hodgkin's lymphoma who is getting chemotherapy.

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Depression

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This presentation discusses challenges encountered in the course of a prospective study of depression in pregnant and postpartum women.

Background

The burden of depression to society is substantial. Depression can be a chronic and/or recurring disorder, and it is associated with significant social and functional disability. During pregnancy, it is estimated that 12 to 16 percent of women are affected with clinically significant depressive symptoms. In addition to functional impairment in the affected women, depression during pregnancy has been found to be associated with worse infant outcomes, such as preterm delivery or low birth weight.

The Prospective Cohort Study

A prospective cohort study investigated whether significant depressive symptoms or antidepressant treatment in pregnancy were associated with adverse perinatal outcomes. The study attempted to disentangle the effects of untreated depressive symptoms from the effects of pharmacological treatments for depression.

Women were recruited into the study before 17 weeks of gestation from 137 obstetrical practices or hospital-based clinics throughout Connecticut and western Massachusetts. They were followed up through the postpartum period. The multi-site aspect of the study required 12 IRBs to approve the protocol.

Inclusion criteria included: women who had a depressive disorder or posttraumatic stress disorder during the last five years before recruitment or who were undergoing antidepressant treatment in pregnancy. A non-exposed control group was included as well.

Exclusion criteria included: women less than 17 years of age; plans to move outside of the geographic area, intent to terminate the pregnancy, no telephone access, non-English or Spanish speaking, diabetes, and known multi-fetal gestation.

Nearly 10000 women were screened and, of these, 3500 were identified for participation. About 2800 completed a postpartum interview, and pregnancy outcomes were obtained on 2751 women.

IRB Challenges

Use of Psychiatric Screeners Initial case finding was required in order to find sufficient numbers of women with the conditions of interest. IRBs were asked to give permission for case finding using a brief screener, instead of a six-page consent form.

The screener included questions about depression, stress, or trauma. Although all IRBs approved the screening procedure, they expressed differing degrees of reservations about the screener questions.

In particular, IRB concerns centered on institutional responsibilities and liabilities. If a woman who was questioned about depression on the screener was later found to have committed infanticide or otherwise harmed her infant, would the institution be liable?

There is no evidence that asking about suicidal ideation increases risk of suicide; in fact, such questions are important in making a diagnosis of depression. Nonetheless, some IRBs expressed concerns over questions about suicidal ideation for fear that such questions would increase the probability that vulnerable women would in fact attempt suicide.

> **Concerns about influencing subjects adversely by asking them questions about psychiatric symptoms are not unique to studies of pregnancy, but it seemed that IRBs were much more attuned to, and fearful of, such issues when the sample consisted of pregnant women.**

As part of the study, it was also essential that participants identified as having depressive symptoms be followed closely and that measures were in place for women to have interventions should they develop clinical depression.

Pregnancy termination and contraception Another IRB issue concerned questions about plans to continue or terminate the pregnancy and about past terminations and questions about contraceptive use.

Some IRBs expressed concerns that questions about terminations would be interpreted as endorsement of the practice. However, the protocol called for follow-up of the women through the postpartum period. It would obviously not be suitable to enroll subjects who planned to terminate their pregnancy.

Furthermore, it was important to date gestational age as precisely as possible in order to determine eligibility for enrollment in the study. Questions about contraception were important.

Contacting the subjects There were other challenges that arose in the course of contacting subjects for the study. The study could not be described as focused on depression for fear of stigmatizing the women who were participating. Study personnel had to parse their words about the study very carefully both to the public, as well as in consent forms. Any contact had to be couched in a way that no information about depression or post traumatic stress disorder would be revealed to a third party.

Messages about the study could not be left on the phone or by mail in such a way that a third party could find out that the subject was pregnant, because she might have been living in a household where her partner or other family member did not know that. The name of the study "Pink and Blue" could not be mentioned in these communications, because the name could indicate that the subject was participating because she was pregnant.

Informed consent Some hospitals would not allow the inclusion of participants who were under the age of 18. At others, the status of a participant could change. Some hospitals would allow a pregnant 17-year old woman to enroll, but once she delivered, she had to be re-consented.

The study included a very thorough medical record review, which created a host of other issues. Various hospitals wanted their own release-of- information form to be used, in addition to the study consent form. Because the baby's records as well as the mother's records were reviewed, sometimes that meant that two sets of consent forms had to be obtained.

Moreover, the timing of initial consent, which was at the beginning of pregnancy, often presented challenges. Women were followed through pregnancy and into the immediate postpartum period. For some hospitals, the consent form, according to their rules, would only be in effect for a year. It meant that it was often necessary to go back and re-consent participants and consent them for the baby.

Barriers to Participation

There were other barriers to participation, these stemming from the women themselves. Depression is often a debilitating illness, and some women were just trying to get through the day. The notion of participating in a study on top of getting meals prepared, or taking care of children, could be daunting.

Stigma was a major issue for participants. It was important that participation in the study was not stigmatizing. This was a concern, both for women who were depressed, as well as for the asymptomatic controls.

Some women were also concerned that, if they were identified as depressed, protective services might be contacted, because someone thought that they were unable to take care of their other children at home.

Another participant issue was that some women would not participate if their husbands or partners did not provide consent. There were cultural issues with regard to participation.

Solutions

Clinical studies of pregnant women are complex and challenging. In order to conduct a successful study, several steps can be taken.

Suggested Steps for a Successful Study

- It is important to work with individual members of the IRBs in advance, in order to vet difficult issues.
- Participant safety is central, and it is critical to have plans in place for different scenarios.
- Careful staff training is a must to protect patient privacy, identify patients at risk, and to develop sensitive means of contact and follow up.
- In a study of perinatal depression, it is extremely important to develop explanation procedures that do not stigmatize the subject or raise concerns about the possibility that endorsing psychiatric symptoms could lead to unwarranted intervention by social service agencies.
- Site selection is critical. It is often possible to work out accommodations to the concerns of individual sites, for instance, by changing inclusion and exclusion criteria. At other times, it may be better to restrict site inclusion.

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Hyperglycemia and Adverse Pregnancy Outcomes Study

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Diabetes mellitus during pregnancy is associated with significantly increased risks of adverse perinatal outcomes. Risks associated with hyperglycemia, which is less severe than the diagnostic of overt gestational diabetes mellitus (GDM), are uncertain. Furthermore, there are no uniform international standards for the ascertainment and diagnosis of GDM. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study was conducted to clarify the risks of adverse outcomes associated with various degrees of maternal glucose intolerance less severe than that in overt diabetes mellitus

HAPO study

HAPO was an observational multisite (15 centers), multi-country (9 countries) study. Over 23,000 pregnant women and their offspring completed the study.

Study protocol Women underwent a standard oral glucose-tolerance test, with the use of a 75-gram dose of glucose, blinded between 24 and 32 weeks of gestation. Height, weight, and blood pressure were measured at the test visit. Data concerning smoking and alcohol use, history of diabetes and hypertension among first-degree relatives, and demographic characteristics were collected. Race or ethnic group was self-reported by participants. A blood specimen was also collected between 34 and 37 weeks of gestation for a random evaluation of plasma glucose level, as a safety measure to identify cases with hyperglycemia above a predefined threshold.

The 75-gram glucose tolerance test was unblinded at a field center level if fasting glucose was >105 or the two-hour glucose was >200, because it was thought that these levels likely indicated a need for intervention. If the random glucose test was > 160, the patient was unblinded because again treatment might be needed.

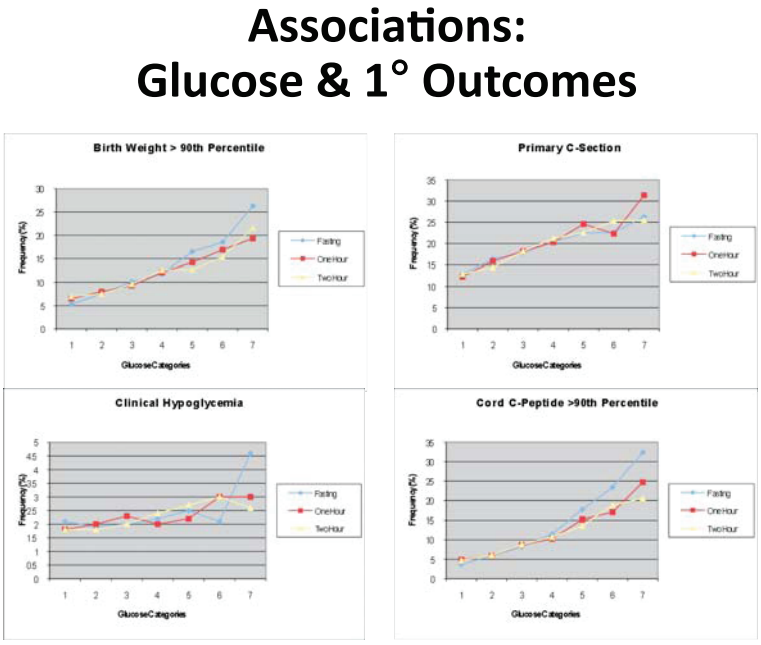
The study patients underwent standard care at their field centers. Study personnel were blinded to the results of the glucose tolerance tests. Cord glucose and C-peptide, neonatal glucose, and a number of other things, including neonatal anthropometrics (such as skin fold thickness) were recorded.

Outcomes The primary outcomes of the study were: newborn birth weight >90th percentile, delivery by primary Cesarean section, clinically evident neonatal hypoglycemia, and neonatal hyperinsulinemia as measured by cord serum C-peptide. Secondary outcomes included: newborn body fat > 90th percentile,

preterm delivery (< 37 weeks gestation), preeclampsia, shoulder dystocia/birth injury, and Neonatal Intensive Care Unit admission or hyperbilirubinemia.

Results The four panels in Figure 1 illustrate associations between increasing fasting, 1 and 2 hour plasma glucose concentrations, and each of the four designated primary study outcomes: birth weight >90th percentile (top left), primary Cesarean section (top right); clinical neonatal hypoglycemia (bottom left), and cord serum C-Peptide > 90th percentile, (bottom right). It is clear that the frequency of each outcome increases progressively across the ranges of each increasing glucose concentration. There was no inflection point, which made it difficult to identify a diagnostic cut point. The relationship was linear and, even down to the lowest levels, there was a relationship between maternal glucose and neonatal outcomes.

FIGURE 1



Source: Slide presented at *Issues in Clinical Research: Enrolling Pregnant Women* Meeting, October 2010, National Institutes of Health, Bethesda, Maryland

Study Challenges and Lessons Learned

Fifty-nine thousand eligible subjects were identified by reviewing records. Thirty-two thousand, or 54 percent, consented to be in the study. Of those, 25,700 had glucose tolerance tests done, which is 43 percent of the eligible subjects. Eighty percent of the patients who consented actually finished their glucose tolerance test. Of those 25,000-plus, 23,000, or 39 percent, were ultimately eligible for analysis.

Site recruitment challenges There were large differences in the number of enrollees at the different field centers. Bellflower, which is a Kaiser hospital in California, was the American center that had the most success in enrolling, but centers at Northwestern, Brown, and Cleveland had similarly lower numbers of enrollees. For foreign sites, the Bangkok, Thailand site was very successful. Hong Kong would have been very successful, except that during a threat of an influenza epidemic, the hospital that was part of the study was at the epicenter and was closed for quite a while.

Clinical practice differences were related to site differences in enrollment success. In some centers around the world, such as Bangkok, there was no ongoing screening for gestational diabetes. Some centers in the U.S., such as Bellflower, were already using a 75-gram glucose tolerance test, whereas at the Northwestern, Brown, and Cleveland centers in the U.S., a 100-gram glucose tolerance test was used.

To recruit a patient or a subject into this study in Bangkok, it was a matter of informing the patient that the test was going to be offered, but it was not a practice change. In Kaiser, it was a continuation of existing practice, except for the blinding to it; whereas in Providence and Chicago and Cleveland, it meant that a detailed explanation to the prospective patient was necessary in order to gain consent for a 75 gram test, when the 100 gram test was standard practice.

TABLE 1

BARRIERS TO RECRUITMENT

EXISTING PRACTICE	RECRUITMENT SUCCESS RATE
NO SCREENING	74%, 65%
75 GRAM TEST	60%
100 GRAM TEST	24%, 43%, 38%

REPRESENTATIVE DATA FROM 6/15 CENTERS

Source: Slide presented at *Issues in Clinical Research: Enrolling Pregnant Women* Meeting, October 2010, National Institutes of Health, Bethesda, Maryland

What can be seen in Table 1 is that the highest recruitment was in those foreign sites with no established screening, but in the U.S., those sites where the 75-gram test had been adopted, which was the same as the study test, had higher recruitment rates than those sites where the study test required additional justification. This provides some lessons in terms of planning studies.

Practice setting also influenced recruitment. Recruitment from private practices was more complicated and labor intensive than recruitment from clinic settings, because the clinics tended to have larger patient populations so that one research nurse could do a great deal of recruiting in one day. By contrast, private practices were typically smaller, and recruitment from them was not as efficient. However, private practices were included in recruitment in order to have as wide a demographic representation in the sample as possible.

IRB challenges IRBs were another challenge. IRB practices were variable, not only within the U.S., but internationally; the international design of the study added another cultural and linguistic layer of complexity to IRB review. IRBs at different sites wanted consent forms to contain different wording, and these differences took considerable time and effort to reconcile. The requirements of translation and back translation of the consent forms used at the foreign sites were labor intensive, and special care had to be taken to ensure that consent forms at different sites were comparable.

Other challenges A number of other issues posed study challenges, among them child care, confidentiality, and cultural differences in fears of medical procedures and of participation in research.

Child care was clearly an issue for patients coming for testing, and often, study staff had to come up with ways to amuse children while mothers were undergoing testing. There were, of course, confidentiality issues in approaching subjects. Study staff were fortunate to be able to review the charts first and decide who needed to be approached for participation; in a clinic, it was not always easy to find a space where staff could confidentially talk to a patient.

In Asia and Australia, in particular, there was a fear of needles that had to be overcome, because of the requirement of blood drawing. In many places, there was a fear of research. There were patients who did not want to fast overnight.

... in the U.S., those sites where the 75-gram test had been adopted, which was the same as the study test, had higher recruitment rates than those sites where the study test required additional justification.

Patient Drop Out Thirty two thousand patients consented to the protocol, but only 23,000 were eligible for analysis. Why did patients drop out? Some simply failed to keep the glucose tolerance test appointment after agreeing to be in the study. Some started the glucose tolerance test but did not complete it. Some were eliminated from the sample, because they tripped the exclusion criteria, and a few delivered their babies elsewhere, although it was certainly a study goal to only recruit people who were going to deliver at the centers.

Conclusions

For a number of reasons, such as those mentioned above, it took longer to do the study than had been originally anticipated, but, ultimately, the results clearly established maternal and neonatal risks for maternal glucose levels lower than those used to diagnose overt diabetes. The study provided evidence of the clinical utility of a 75-gram test in detecting risk. No single diagnostic cut point clearly emerged from study results. However, based on a review of the HAPO study, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recently identified criteria for pregnancies with increased risk of adverse perinatal outcomes. It was recommended that a diagnosis of GDM be made when any of the following thresholds are met or exceeded: fasting plasma glucose: 0.92 g/L, 1 hour: 1.80 g/L, or 2 hours: 1.53 g/L after the 75 g oral glucose test. Professional organizations around the world are currently considering adopting these criteria into clinical practice guidelines.

References

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Opioid Dependence

Hendree E. Jones, Ph.D.
Professor, Department of Psychiatry and Behavioral Sciences
Department of Obstetrics and Gynecology
Johns Hopkins School of Medicine

This presentation describes the MOTHER study, a controlled trial of the impact of methadone versus buprenorphine treatment during pregnancy on maternal outcomes and on the occurrence of neonatal abstinence syndrome. Ethical issues and lessons learned are also discussed.

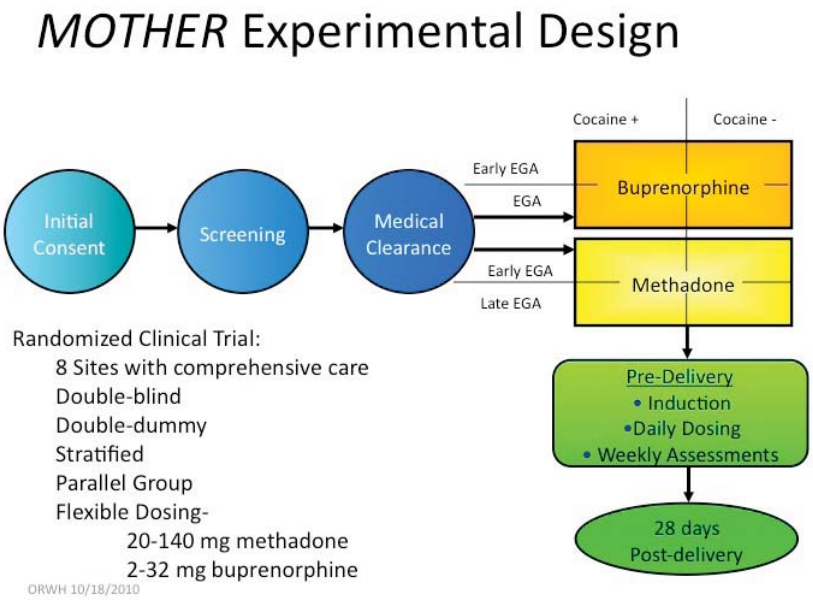
The Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study

Background and Aims Methadone, a full mu-opioid agonist, is the recommended treatment for opioid dependence during pregnancy. However, prenatal exposure to methadone is associated with a neonatal abstinence syndrome (NAS) characterized by central nervous system hyperirritability and autonomic nervous system dysfunction, which often requires medication and extended hospitalization. Buprenorphine, a partial mu-opioid agonist, is an alternative treatment for opioid dependence but has not been extensively studied in pregnancy. This study is a multi-site double-blind comparison of methadone and buprenorphine treatment to evaluate the possible impact of buprenorphine versus methadone given to opioid-dependent pregnant women during pregnancy on maternal and neonatal outcomes.

Design The design was a multi-site study involving eight sites, all of which had experience with clinical trials, an infrastructure for treating drug-dependent pregnant women, and the capability of providing comprehensive care, including obstetrics, postnatal care, pediatric care, and psychiatric care. Six of the sites were in the U.S., and two were foreign, one in Canada and the other in Austria.

After initial consenting, women went through an intensive initial screening and were cleared for participation by a medically responsible investigator who reviewed all of their information. Their information was reviewed by an obstetrician, an internist, and a psychiatrist to make sure that they were otherwise healthy enough to participate in the study. The design details are shown in Figure 1.

FIGURE 1



Source: Slide presented at *Issues in Clinical Research: Enrolling Pregnant Women* Meeting, October 2010, National Institutes of Health, Bethesda, Maryland

The sample of 175 women was stratified on estimated gestational age, and then on cocaine use; they were randomized to buprenorphine or methadone. Following an induction procedure, women had to come in to the participating centers every day for dosing, and they were assessed weekly for adverse events. Dosing was flexible since, as pregnancy progressed, there was a need to increase the dose of medication. Blind unit increases were followed, so every patient had the same opportunity to receive the same number of increases or decreases in their medication. Average doses at delivery were well within the therapeutic window.

Neonates were followed for at least for 10 days for NAS, unless they required longer treatment, in which case they were followed until they were released from the hospital. All of the babies and mothers were followed for 28 days post-delivery.

Results The mothers in both arms had very similar opioid dependence outcomes, as well similar rates of other illicit drug use. There were very low rates of concomitant drug use during that study. Their general health was excellent.

There were no significant differences in overall rates of NAS among infants exposed to buprenorphine and those exposed to methadone, but there was a benefit of buprenorphine in reducing the severity of NAS among neonates with this complication. These results must be considered in light of the markedly different rates of attrition, which were largely due to greater patient dissatisfaction with buprenorphine than with methadone.

Findings from the study suggest that buprenorphine should be considered a first-line treatment option in pregnancy. In selecting a course of treatment, however, clinicians should also take into account the possibility of reduced adherence and the ceiling effect of this medication as compared with methadone. The findings hold the promise to change national guidelines. Several countries have expressed interest in the data, and they are considering incorporating study findings into clinical practice.

Ethical Considerations

A 2010 review of laws governing substance use disorders in pregnancy noted that a number of misconceptions, which impede treatment, exist about them. The disorders often occur in the context of multiple vulnerabilities and stressors. It is important to recognize that the disorders usually start before pregnancy and can be severe illnesses. Like other illnesses for which there are no cures, they require ongoing therapy and support.

Punishment of pregnant women for drug use has been repeatedly shown to be ineffective for reducing the extent of the problem.

Punishment of pregnant women for drug use has been repeatedly shown to be ineffective for reducing the extent of the problem. It is important to rely on the best available research and principles of evidence-based treatment to avoid flawed assumptions about drug use by pregnant women and its effects on the fetus and neonate.

In the MOTHER study, investigators and study staff were sensitive to the need for compassion and respect for the patient. Stigma was an ever present issue, in particular, in the neonatal intensive care units, where the women were often not well-treated. If they wanted to breastfeed, they were often undermined in their breastfeeding abilities. One of the most powerful ways to help overcome that stigma was to have in-services with the nursing staff or other health care providers, where women who had been successful came in and told their own stories, good and bad, about what had happened to them in their hospital experiences.

Lessons Learned

Careful site selection is extremely important. All potential sites were carefully screened before they included in the study. The screening was important in order to determine firsthand what type of experience the site had with opioid dependent pregnant women and what type of comprehensive care environment existed.

Despite this screening, one site in the MOTHER study ended up not recruiting. The country in which the site was located would allow buprenorphine to be used for clinical purposes, but would not allow it to be used in clinical trials with pregnant women. Thus, that site could not randomize patients.

Different approaches to screening were used at different sites. The foreign sites only wanted to screen face to face. At the Center for Addiction and Pregnancy, patients were screened by reviewing medical charts before an approach was made to the woman. If a woman was approached without that screening and was told that she may qualify for a study but later told she was disqualified, this could be a very distressing experience. It is important to approach only those patients who in fact have a high probability of being able to participate in the protocol.

Eight RO1s were used to fund this study and that gave site investigators a fair amount of autonomy. However, when one site was struggling with recruitment, this also made it difficult to move the funding to another site to help increase recruitment elsewhere.

In conclusion, pregnant women deserve to benefit from medical advances. Treatment advances for pregnant women need to be made within a thoughtful and ethical framework that synthesizes the risks and benefits for the fetus and mother.

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3. McCullough L.B., Coverdale, J.H. and Chervenak, F.A. (2005). A comprehensive ethical framework for responsibly designing and conducting pharmacological research that involves pregnant women. *American Journal of Obstetrics and Gynecology, 193*(3 Pt 2), 901-907.

Discussion

Panel: Dr. Elyse Cardonick, Dr. Robert Coustan, Dr. Kimberly Yonkers, and Dr. Hendree Jones

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, it 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: *Experiences with registries.* Do women enrolled in the pregnancy cancer registry have an option to give permission to allow contact if someone wants to reach them?

Panel comments: Patients in the cancer registry have the option of giving permission to be contacted. There is also a "Pregnant with Cancer" Network (www.pregnantwithcancer.org) that patients can find on the web. This was started by three women who were diagnosed with cancer while they were pregnant. Women who are in their network are willing to talk to other women.

Audience comment: *Differences among IRBs.* There appears to be substantial differences among IRBs in how they assessed risk in the prospective cohort study of perinatal depression. The MOTHER study was higher risk study. Was IRB variability an issue?

Panel Comments: The MOTHER study, which included a sample of opioid dependent pregnant women, was relatively high risk, but the review process by the IRBs was not unusually difficult. The prospective depression study by comparison was low risk, and yet, there were more questions raised about the protocol and more IRB variability among sites. What accounts for the difference? Part of the difference may be that, in the MOTHER study, two randomized trials that had an almost identical protocol to the one proposed had already been done, and the consent form that had been used was available.

Afternoon Wrap-up

Catherine Y. Spong, M.D.
Chief, Pregnancy and Perinatology Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

This research forum was held to address the ethical, IRB, and recruitment issues that investigators face in the conceptualization, initiation, and conduct of clinical research studies enrolling pregnant women. A number of panels addressed these issues, and it is my privilege to highlight some overall themes, issues, and future directions from the wealth of information that has been presented this afternoon.

The panels we have heard from today include Ethical Principles of Research on Effective Treatments During Pregnancy, Regulatory Requirements and Global Health Issues, Clinical Research Experiences in Enrolling Pregnant Women in Studies of Infectious Diseases and Maternal-Fetal Medicine, and Clinical Research Experiences in Enrolling Pregnant Women in studies of Chronic Diseases.

Earlier today we heard a summary from Dr. Grady of the morning presentations. These presentations established a foundation for the moral imperative of moving forward with pregnancy research. A number of key issues were identified, among them:

Key Issues

- Pregnant women as a complex population
- The need to develop a research agenda
- The need to ask the correct (sophisticated) questions
- The importance of changing a presumption of exclusion to one of inclusion of pregnant women in research
- Funding issues
- The need to develop a transparent and explicit framework to consider tradeoffs between maternal and fetal interests in pregnancy research
- The need for regulatory clarity / reform, and guidance on how to interpret existing regulations
- The need for more data on IRB interpretations of regulations concerning pregnant women in research
- The need to confront legal liability challenges that lead to reticence to include pregnant women in research

My purpose here is not to restate these excellent points, but to elaborate instead on some of issues of complexity of pregnancy research based on what we heard this afternoon concerning regulatory requirements, as well as from researchers involved in specific studies of pregnant women with infectious diseases, maternal fetal medicine, and chronic health conditions.

Complex Implications of Complexity

The traditional identification of pregnant women as a "vulnerable" population for purposes of conducting research has been a disservice. In the past, children, women in general, minorities, and pregnant women, in particular, have been identified as "vulnerable." For the first two groups, substantial strides have been made toward inclusion in research, but for the last two, progress is not what it should be, and pregnant women are the most underrepresented group in research today. To achieve the goals of the second wave of women's health research and to expand the benefits of research to pregnant women, we need to provide ongoing education to many communities, including health care workers, researchers, IRB members, and pregnant women themselves.

One change that must result from today's forum is recognition that pregnant women are better considered as "complex," rather than "vulnerable." "Complex" means that there are special considerations to take into account in studying them; not that they should be protected from inclusion in research. Some implications of this complexity are discussed below.

When undertaking research involving pregnant women, one must always bear in mind the complexity of the maternal-fetal unit. Even though the interests of the mother and the fetus are conceptually separable, in practice, clinical researchers must consider the effects of an intervention on the maternal-fetal unit. If a woman is enrolled in a trial with therapeutic benefit potential for her, especially if she is affected by a serious debilitating or life-threatening disease, her therapeutic benefit can also be seen as a benefit to the fetus, and, later on, to the child. Having a healthy living mother is of great benefit to a child. That benefit, and any direct maternal therapeutic benefit, need to be weighed against any possible risks to the fetus of maternal treatment.

In considering medication studies for the mother in pregnancy, the potential risks are often more heavily weighed than the potential benefits. This can lead to misapplication of the precautionary principle. It is a seeming paradox that pregnant women are usually excluded from drug trials, yet clinically, they are often prescribed the same drugs that were not considered safe for testing on them during the drug approval process. Today, we have heard that, if a drug is to be widely used in women of childbearing age, including women who could become pregnant while on the drug or pregnant women who will have clinical need of the drug, it is imperative that safety and efficacy data be gathered on its use in that population, earlier, rather than later, in the process.

Presenters have pointed out how contradictory it is to consider a medication off label for a pregnant woman, when, in fact, she has been using the medication prior to pregnancy. Pregnancy itself should not change the medication use to off-label. These are all issues that we need to address.

Pharmacokinetics issues are another example of the complexities of research in pregnancy. Not only is the pregnant state physiologically different than the non-pregnant state, but physiology also changes over the course of the pregnancy; it is not static. When blood volume doubles in pregnancy, the effects on drug metabolism are significant. Furthermore, in trying to use the lowest dose of medication in order to not harm the fetus, there is a risk that the pregnant woman may be undertreated, while the fetus is still exposed to risk from the medication.

Consent procedures raise complex issues that are relatively unique to pregnancy studies. Studies that target the fetus, and not the mother, may still require the consent of the father. In some cases, such as HIV, which the mother may transmit the infection to the fetus, she may have gotten it from her partner. Consent procedures currently in place can complicate studies of sexually transmitted diseases.

The timing of consent in pregnancy also adds layers of complexity to consent procedures. Consent is very different if one is obtaining it before the pregnancy begins or in early pregnancy versus at times of acute stress, such as when a woman in labor or active preterm labor. Consent issues are different postpartum than they are during pregnancy, and consent issues differ depending on the mental health of the patient.

Asking the Right Sophisticated Questions in Pregnancy and Beyond

We have also heard today how important it is to ask the right questions in a sophisticated manner. Pregnancy research can be valuable, not only for the health of pregnant women and her fetus, but also for the woman's longer term health outcomes. Currently, the majority of pregnancy-related research confines itself to issues of the pregnancy and perhaps the immediate postpartum period. There needs to be more emphasis on the life course impact of treatment or non-treatment of medical conditions during pregnancy. For instance, an NHLBI conference held in September 2010 focused on the long-term implications on cardiovascular health of preeclampsia in pregnancy. Pregnancy itself can impact long-term maternal health.

Despite many impediments and barriers to pregnancy research, we have heard today of the successes of networks and recent trials, both nationally and internationally, using rigorous long-term outcomes. This demonstrates that pregnancy research that asks the right sophisticated questions can be done, but it is still not done often enough. In the future, it will be critical to identify the "low hanging fruit" in terms of research that can be done relatively quickly and using existing resources, while at the same time identifying and prioritizing long-term key projects, not only for pregnancy-specific conditions, but for the long term health of the mother.

MEETING SUMMARY AND FUTURE DIRECTIONS

Janine A. Clayton, M.D.
Acting Director, Office of Research on Women's Health
National Institutes of Health

Closing Remarks

In today's forum we have heard about the ethical complexities and IRB and regulatory challenges investigators face when attempting to conduct clinical trials in pregnant women. The speakers in the first two panels provided a wealth of perspectives related to risk perception, risk reasoning and the ethics of balancing risks and benefits in pregnancy research. We know that the first Federal regulations governing pregnancy researches were rooted in historic events such as the thalidomide and DES tragedy. Developed to prevent similar future events, the regulations reflected a presumption of exclusion of pregnant women from research of investigational agents of more than minimal risk, without consideration of the potential benefits of therapy or the potential risks associated with the lack of treatment. A 2001 revision modified the regulations in a way that calls for the inclusion of pregnant women in research if a number of conditions are also met. The revised regulations also increase the autonomy of the pregnant woman to make informed decisions about her participation in research. However, the effects of past decades of conservative and "protectionist" regulations remain and continue to influence the behavior of scientists, regulatory bodies and IRBs, perhaps because of legal concerns.

We have also heard how the regulatory categorization of pregnant women needs to change from a "vulnerable" population to a "complex" population. Among the complexities that need to be taken into account are the effect of interventions on the maternal-fetal unit when considering the inclusion of pregnant women as participants in clinical research and the potential follow-up and monitoring that should occur should a pregnancy occur while on a study intervention. This perspective would enhance pregnant women's health by beginning a dialogue that is currently thwarted by focusing on protecting them from inclusion or excluding them from enrollment in clinical studies. This approach would change the scientific conversation from a presumption of exclusion to a consideration of appropriate inclusion of pregnant women in research, along with attention to pregnancy-related scientific and ethical issues. The role of legal liability concerns combined with regulatory issues in contributing to a persistent apparent reluctance to include pregnant women on the part of IRBs that affects the clinical research that can be approved when pregnant women are proposed as subjects was also discussed. There are no quick fixes or easy remedies for science-regulatory stances that have become embedded in institutional cultures. But these issues need to be addressed as part of a comprehensive effort to make progress in this area of research.

Along with challenges and barriers, we've also heard today of progress. The presumption of exclusion is giving way to a growing recognition that "pregnant women get sick, and sick women get pregnant." The *Second Wave Initiative* is in the forefront of ethically-based and scientifically-justified advocacy for the responsible inclusion of pregnant women in clinical research. We have heard that the FDA is aware of the need to remedy the lack of dosing and safety information on pharmaceuticals used in pregnancy and is increasingly open to considering evidence other than that from the gold standard, randomized, controlled clinical trial to inform pregnancy labeling.

In two afternoon panels, we heard from eight researchers who have conducted research on the health needs of pregnant women with conditions ranging from cancer and HIV/AIDs to depression and opioid dependence. These presentations provided specific examples of successful research approaches and specific strategies for overcoming barriers encountered. The researchers used designs ranging from randomized trials to registries. Their pioneering studies have provided data that has informed treatment and changed clinical practice.

Despite many lingering barriers, we do have evidence of progress underway. Moving into the future, what needs to be done to advance the research agenda?

Moving into the Future

This forum takes place one month after the 20th Anniversary of the founding of ORWH and the launching of a new NIH research agenda on women's health. That agenda presents a vision for 2020. As one of our first activities following the anniversary, ORWH convened this forum along with our collaborating partners. Given the history of the office, this topic seems especially fitting. ORWH was established to address inequities in the inclusion of women in NIH clinical research. At present, the percentage of female and male enrollment in NIH-funded non-sex specific clinical research are roughly equivalent. This forum reminds us that in 2010 pregnant women continue to be excluded from the vast majority of clinical studies.

As I listened to today's presentations panels and wrap up summaries, I was impressed with the excellence and dedication of the scientists who work in this area. I took notes on many action-oriented suggestions. What are some things that ORWH in collaboration with other NIH institutes, centers and offices and the FDA can consider to move this aspect of the research enterprise forward? I have selected five activities here that seem to be high priority and cut across many specific issues.

1. There has been a call today for the establishment of a research agenda to address the health needs of pregnant women. Speakers today have talked of the importance of plucking the "low hanging fruit" as a first priority by mining existing studies and resources. A step to accomplish this would be to convene a working group of interested researchers, in consultation with ethicists and other appropriate stakeholders, to identify and prioritize specific studies that may be readily explored or adapted to address questions of importance to pregnant women and their health concerns.

2. We have also heard today of the need for a research agenda not only for the projects which could be mined for additional value but also for new pregnancy specific and/or longer term projects. In a world of competing scientific priorities and diminishing resources, we need to consider ways to create an agenda that states our priority research and realities of funding.

3. Readily accessible information resources are essential. Many of today's talks referred to information resources that can inform various aspects of pregnancy research. It is worthwhile to create an internet resource that provides a gateway to information such as ongoing projects and pregnancy registries, regulatory guidance and IRB documents specifically addressing pregnant women; and other publications and resources addressing ethical and scientific information. Such a tool could facilitate innovative approaches to address the research needs for the inclusion and recruitment of pregnant women in clinical research.

4. We have heard today about the complexities involved in IRB deliberations in the context of Federal regulations and prevailing ethical concerns that limit pregnancy research. New contraceptive requirements that IRBs are considering for women of child-bearing potential may significantly affect information to be gained from research. Addressing such issues requires a concerted, collaborative approach. We need to consider ways for stakeholders and the relevant communities of researchers, health care providers, academic institutions, ethicists, IRB representatives, attorneys and professional societies, to collaborate and resolve institutional and societal barriers and challenges related to the conduct of research that can inform the health care of pregnant women.

5. Our meeting today has included dedicated scientists, clinicians, ethicists and others who are active in the field of pregnancy research or ethics. Their contributions have been invaluable. To move the agenda forward and improve the health of pregnant women, we will need to increase the pool of interested researchers. We also need to reach out to those in the biomedical research community who do not normally consider this issue, but conduct the majority of biomedical research and who may not be aware of the value of appropriate inclusion of pregnant women in research. We need to devise ways to communicate broadly with key audiences to expand the appreciation of the need for the responsible inclusion of pregnant women in clinical research.

You may recall a company slogan, "We Try Harder." Today, as we listened to all the presentations, comments, ideas and strategies, there was thoughtful consideration of the current regulatory requirements related to research on pregnancy as well as the constraints in resources facing the scientific community today. I am convinced that not only do we have to "try harder"; we also have to "try smarter."

Finally I would like to thank Angela Bates and Mary Foulkes for organizing the meeting and Dr. Vivian Pinn and ORWH for providing the support necessary to convene this meeting. Of course, I thank all of you who participated today. We will be in communication with you, and we look forward to working together on new steps and approaches related to the enrollment of pregnant women in clinical research.

APPENDICES

Appendix 1: Research Forum Agenda

Appendix 2: Biographical Sketches of Speakers, Moderators, and Presenters

Appendix 3: Ancillary Materials

Appendix 1: Research Forum Agenda

ENROLLING PREGNANT WOMEN:
ISSUES IN CLINICAL RESEARCH
An ORWH Research Forum

AGENDA

8:00 am – 8:30 am
REGISTRATION

8:30 am – 8:45 am
WELCOME AND INTRODUCTIONS

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health, and Director
Office of Research on Women's Health

Alan E. Guttmacher, M.D.
Director, *Eunice Kennedy Shriver* National Institute
of Child Health and Human Development

8:45 am – 11:50 am
ETHICAL PRINCIPLES OF RESEARCH ON EFFECTIVE TREATMENTS DURING PREGNANCY

8:45 am – 8:55 am
Moderator: Celia J. Maxwell, M.D.
Associate Professor of Medicine, Vice President Health Sciences
Howard University Hospital

8:55 am – 9:15 am
Direct Benefit to Pregnant Women
Anne Drapkin Lyerly, M.D.
Trent Center for Bioethics, Humanities and History of Medicine
Assistant Professor of Obstetrics and Gynecology, Duke University

9:15 am – 9:35 am
Justice in Health Research: Beyond Protection from Risks
Ruth R. Faden, Ph.D., M.P.H.
Director, Berman Institute of Ethics, Johns Hopkins University

9:35 am – 9:55 am

Treating Important Medical Conditions During Pregnancy

Margaret Olivia Little, Ph.D., Director

Kennedy Institute of Ethics and Department of Philosophy
Georgetown University

9:55 am – 10:05 am

DISCUSSION

10:05 am – 10:20 am

BREAK

10:20 am – 10:30 am

Moderator: Tim Johnson, M.D.

Bates Professor of the Diseases of Women and Children
Chair of Obstetrics and Gynecology, University of Michigan

10:30 am – 10:50 am

Treatment During Pregnancy: Are We Asking the Right Questions?

Katherine L. Wisner, M.D., M.S.

Professor of Psychiatry, Obstetrics, Gynecology and Reproductive Sciences
University of Pittsburgh School of Medicine

10:50 am – 11:20 am

IRB Perspective on Inclusion of Pregnant Women in Clinical Research

Robert J. Levine, M.D.

Professor of Medicine and Lecturer in Pharmacology
Senior Fellow in Bioethics, Yale University

11:20 am – 11:50 am

DISCUSSION

11:50 am – 12:00 pm

MORNING WRAP-UP

Christine Grady, M.S.N, Ph.D.

Deputy and Acting Chief, Department of Bioethics
Warren G. Magnuson Clinical Center, National Institutes of Health

12:00 pm – 1:15 pm

LUNCH (*ON YOUR OWN*)

1:15 pm – 2:00 pm

REGULATORY REQUIREMENTS AND GLOBAL HEALTH ISSUES

1:15 pm – 1:20 pm

Moderator: Castilla McNamara, Ph.D., M.P.A.
National Institute on Deafness and other Communication Disorders
National Institutes of Health

1:20 pm – 1:35 pm

Pregnant Women in Clinical Trials: Scientific and Ethical Considerations

Sara F. Goldkind, M.D., M.A.
Senior Bioethicist, Office of Good Clinical Practice
Office of the Commissioner, Food and Drug Administration

Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff,
Office of New Drugs, Center for Drug Evaluation and Research
Food and Drug Administration

1:35 pm – 1:50 pm

Global Health issues and US Regulation 45 CFR46, Subpart B

Duane Alexander, M.D.
Senior Scientific Adviser for Global Maternal and Child Health Research
Fogarty International Center, National Institutes of Health

1:50 pm – 2:00 pm

DISCUSSION

2:00 pm – 2:50 pm

CLINICAL RESEARCH EXPERIENCE IN ENROLLING PREGNANT WOMEN – INFECTIOUS DISEASES AND MATERNAL FETAL MEDICINE

Moderator: Christopher E. Taylor, Sc.D.
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases

Panel I:

- ***The H1N1 trial*** – Richard L. Gorman, M.D., NIAID
- ***MFMU Network and H1N1 registry*** – Catherine Y. Spong, M.D., NICHD
- ***Malaria-HIV Co-Infections*** – Myaing M. Nyunt, M.D. Ph.D., Johns Hopkins University
- ***Antiretrovirals*** – D. Heather Watts, M.D., NICHD

2:50 pm – 3:00 pm
DISCUSSION

3:00 pm – 3:20 pm
BREAK

3:20 pm – 4:20 pm
CLINICAL RESEARCH EXPERIENCE IN IN ENROLLING PREGNANT WOMEN – CHRONIC DISEASES

Moderator: Cora Lee Wetherington, Ph.D.
Women & Sex/Gender Differences Research Coordinator
National Institute on Drug Abuse, National Institutes of Health

Panel II:

- ***Cancer*** – Elyce H. Cardonick, M.D., Cooper University Hospital
- ***Depression*** – Kimberly A. Yonkers, M.D., Yale University
- ***Hyperglycemia and Adverse Pregnancy Outcomes*** – Donald R. Coustan, M.D. Women and Infants Hospital of Rhode Island
- ***Opioid Dependence*** – Hendrée E. Jones, Ph.D., Johns Hopkins University

4:20 pm – 4:30 pm
DISCUSSION

4:30 pm – 4:45 pm
WRAP-UP AND FUTURE DIRECTIONS FOR RESEARCH

Catherine Y. Spong, M.D.
Chief, Pregnancy and Perinatology Branch
National Institute for Child Health and Human Development
National Institutes of Health

4:45 pm – 5:00 pm
SUMMARY AND FINAL REMARKS

Janine Austin Clayton, M.D.
Acting Director
Office of Research on Women's Health

5:00 pm
ADJOURN

Appendix 2: Biographies of Speakers, Moderators and Presenters

(Listed in Alphabetical Order)

Duane Alexander, M.D.

Dr. Alexander was named Director of the *Eunice Shriver Kennedy* National Institute of Child Health and Human Development (NICHD) on February 5, 1986, after serving as Acting Director. Dr. Alexander also served a four-year term as the Institute's Deputy Director and was the Assistant to the Director, beginning in 1978. After 23 years as NICHD Director, in 2009 he moved to the NIH Fogarty International Center as Senior Scientific Advisor for Maternal and Child Health to the Center Director.

Much of his career has been with the NICHD. After receiving his undergraduate degree from Pennsylvania State University in 1962, Dr. Alexander earned his medical degree from Johns Hopkins University School of Medicine in 1966. Following his internship and residency at the Department of Pediatrics at Johns Hopkins Hospital, Dr. Alexander joined NICHD in 1968, as a clinical associate in the Children's Diagnostic and Study Branch. Following his tenure with the Branch, he returned to Johns Hopkins as a fellow in pediatrics (developmental disabilities) at the John F. Kennedy Institute for Habilitation of the Mentally and Physically Handicapped Child.

Dr. Alexander returned to the NICHD in 1971, when he became Assistant to the Scientific Director and directed the NICHD National Amniocentesis Study. The study established the safety and accuracy of prenatal diagnosis using amniocentesis, now widely used to detect numerous genetic disorders and inborn errors of metabolism. From 1974 to 1978, Dr. Alexander served as medical officer in the Office of the Assistant Secretary for Health, in what is now the Department of Health and Human Services (DHHS). During that time, he was also the physician on the staff of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, whose recommendations form the basis of current DHHS regulations that protect human subjects in research.

Dr. Alexander is a diplomate of the American Board of Pediatrics, a member of the American Academy of Pediatrics (AAP), and the American Pediatric Society. For many years, he served as the United States' Observer on the Steering Committee on Bioethics for the Council of Europe. As an officer in the Public Health Service (PHS), Dr. Alexander received numerous PHS awards, including the Commendation Medal in 1970, the Meritorious Service Medal in 1985, the Surgeon General's Exemplary Service Medal in 1990 and the Surgeon General's Medallion in 1993 and 2002.

In 2002, Dr. Alexander received the Arnold J. Capute Award from the AAP for his contributions to the health and well-being of children with disabilities, and in 2009 he received the AAP William Bartholome Award for Excellence in Bioethics. In 2004, the American Medical Association awarded him the

Dr. Nathan Davis Award for Outstanding Government Service. He has also received outstanding public service awards from numerous organizations, including the American College of Obstetricians and Gynecologists, American Psychological Association, American Academy of Physical Medicine and Rehabilitation, American Academy of Pediatrics, Society for Research in Child Development, Association of Academic Physiatrists, the American Society for Reproductive Medicine, and the Population Association of America.

Elyce H. Cardonick, M.D.

Dr. Cardonick is an Associate Professor, Department of Obstetrics and Gynecology and the Division of Maternal Fetal Medicine at the Robert Wood Johnson Medical School. She is board-certified in Obstetrics and Gynecology and subspecialty trained and boarded in Maternal-Fetal Medicine. She received her medical degree from the Medical College of Pennsylvania and completed her post-graduate training at Albert Einstein College of Medicine in Bronx, NY. She completed her fellowship training in Maternal-Fetal Medicine from Thomas Jefferson University Hospital in Philadelphia. During her Fellowship at Jefferson, she became involved in the care of women who were pregnant and diagnosed with cancer. Most of the cases she has worked with involve women diagnosed during pregnancy with breast cancer, Hodgkin's disease, or melanoma. She has been studying these cases since 1996 and has developed a registry of patients who have cancer and are pregnant; and another registry for patients who are cancer survivors and get pregnant after treatment. She has over 200 patients who have different types of cancer, not limited to those listed above, in these registries. The registry continues to expand, helping to give research data and information to patients and physicians who are handling cases similar to the ones in the registry. Dr. Cardonick also facilitates the interaction of women in the registries so they can support one another if desired. Dr. Cardonick is also the medical advisor to the Pregnant Cancer Support Group sponsored by the American Cancer Society (www.pregnantwithcancer.org).

Janine Austin Clayton, M.D.

Janine A. Clayton, MD is the Deputy Director of the Office of Research on Women's Health, in the Office of the Director at the National Institutes of Health in Bethesda, Maryland, USA. She is the author of over 70 scientific publications, journal articles and book chapters. Prior to joining the Office of Research on Women's Health, she was the Deputy Clinical Director of the National Eye Institute, NIH. A board certified ophthalmologist, Dr. Clayton's research interests include immune-mediated diseases of the cornea and conjunctiva, women's eye health and the standardization of outcome measures for diseases of the anterior segment, and the role of sex and gender in ocular health and disease. Dr. Clayton has a particular interest in ocular surface disease and discovered a novel form of disease associated with premature ovarian insufficiency which affects young women.

Dr. Clayton is a native Washingtonian and received her undergraduate degree with Honors from the Johns Hopkins University and her M.D. from Howard University College of Medicine. She completed a residency in ophthalmology at the Medical College of Virginia and fellowship training in Cornea and External Disease at the Wilmer Eye Institute at Johns Hopkins Hospital and in Uveitis and Ocular Immunology at the National Eye Institute. Dr. Clayton has been an attending physician and clinical investigator in cornea and uveitis at the NEI since 1996, conducting research on inflammatory diseases of the anterior segment and providing medical and surgical uveitis fellowship training. Her clinical research has ranged from randomized controlled trials of novel therapies for immune mediated ocular diseases to studies on the development of digital imaging techniques for the anterior segment.

Dr. Clayton has received several awards from NIH and has been recognized as a leader by her peers. She received the Senior Achievement Award in from the Board of Trustees of the American Academy of Ophthalmology (AAO) in 2008, and was selected as a 2010 Silver Fellow by the Association for Research in Vision and Ophthalmology (ARVO) in recognition of "…accomplishments, leadership and contributions to the Association… to help further ARVO's mission to facilitate the advancement of vision research and the prevention and cure of disorders of the visual system worldwide." Dr. Clayton has served on critical committees at the NIH Clinical Center, and currently serves on the FDA Advisory Panel for Ophthalmic Devices, the executive committee of the Women's Eye Health.Org, the medical and scientific advisory board of Tissue Banks International, and the editorial boards of The Ocular Surface and Oral Diseases.

Dr. Clayton was named Deputy Director, Office of Research on Women's Health, Office of the Director at the National Institutes of Health in June, 2008. In September 2011, Dr. Clayton was appointed Acting Director of the Office on Research on Women's Health and serves as co-chair of the NIH Working Group on Women in Biomedical Careers.

Donald R. Coustan, M.D.

Dr. Coustan is Professor of Obstetrics and Gynecology at the Alpert Medical School, Brown University. He is the immediate past Obstetrician & Gynecologist-in-Chief, Women & Infants Hospital of Rhode Island and Chace/Joukowsky Professor and past Chairman, Department of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University. He is currently Professor of Obstetrics and Gynecology and attending physician in Maternal-Fetal Medicine at the above institutions. He graduated from Yale Medical School in 1968, and did his internship in Internal Medicine and residency in Obstetrics and Gynecology at Yale-New Haven Medical Center. After two years in the Navy, he returned to Yale in 1975. He moved to Brown and Women & Infants Hospital in 1982. In 1991 became Chair of the Department of Obstetrics and Gynecology at Brown. He stepped down from the chair in 2008.

Dr. Coustan has published widely in the areas of diabetes and pregnancy and gestational diabetes. He is Regional Director for North America of the HAPO study. Dr. Coustan has served as President of the Rhode Island Medical Society, and of the Society for Maternal-Fetal Medicine. He has served on the Board of Directors of the American Diabetes Association, and on the National Advisory Committee of the Robert Wood Johnson Clinical Scholars Program.

Ruth R. Faden, Ph.D., M.P.H.

Dr. Faden is the Philip Franklin Wagley Professor of Biomedical Ethics and Executive Director of Johns Hopkins Berman Institute of Bioethics. She is also a Senior Research Scholar at the Kennedy Institute of Ethics, Georgetown University. Dr. Faden is the author and editor of numerous books and articles on biomedical ethics and health policy including A History and Theory of Informed Consent (with Tom L. Beauchamp), AIDS, Women and the Next Generation (Ruth Faden, Gail Geller and Madison Powers, eds.), and HIV, AIDS and Childbearing: Public Policy, Private Lives (Ruth Faden and Nancy Kass, eds.). Dr. Faden is a member of the Institute of Medicine and a Fellow of the Hastings Center and the American Psychological Association. She has served on several national advisory committees and commissions, including the President's Advisory Committee on Human Radiation Experiments, which she chaired. Current research interests include bioethics and public policy; ethics and cellular engineering; ethics and neuroscience; ethics and bioterrorism; ethics, genetics and public policy; research ethics; and justice.

Karen B. Feibus, M.D.

Dr. Feibus is the clinical team leader for the Maternal Health Team, part of the Pediatric and Maternal Health Staff in the Office of New Drugs at FDA's Center for Drug Evaluation and Research. Prior to taking this position four years ago, Dr. Feibus was a medical officer and acting team leader in the Division of Nonprescription Clinical Evaluation. Dr. Feibus received her undergraduate degree from Cornell University and her Doctorate of Medicine from the Georgetown University School of Medicine. She completed her obstetrics and gynecology residency training at Rush Presbyterian St. Luke's Medical Center in Chicago, Illinois and the University of Maryland Medical System in Baltimore, Maryland. In 2008, she completed a Certificate in Public Health through FDA and the Georgetown University School of Continuing Education and is currently working on a Masters in Public Health through the University of North Carolina, Chapel Hill.

Sara F. Goldkind, M.D. M.A.

Dr. Goldkind is the Senior Bioethicist at The Food and Drug Administration in the Office of Good Clinical Practice located within the Office of the Commissioner. She did her internship and residency at Boston City Hospital, and is a board- certified internist. Dr. Goldkind completed a fellowship in clinical medical ethics at the University Of South Florida School Of Medicine, where she was on the faculty within the Department of Medicine. She also obtained a Master's Degree in religious studies focusing on comparative religious ethics and public policy.

Richard L. Gorman, M.D.

Since 2008, Dr. Gorman has served as the Associate Director for Clinical Research at the Division of Microbiology and Infectious Disease at the National Institute of Allergy and Infectious Diseases, (NIAID). Before that, Dr. Gorman practiced pediatric primary care in suburban Baltimore for 20 years. He graduated with a B.A. in physics from the Catholic University of America. He graduated with a M.D. from the State University of New York's Down State Medical Center. He did his pediatric residency at Children's Hospital National Medical Center in Washington, D.C. He completed a General Pediatric Academic Development fellowship at Johns Hopkins. Dr. Gorman has been the Director of the Pediatric Emergency Room at the University of Maryland Hospital, Chair of the Pharmacy and Therapeutics Committee of University of Maryland Hospital and the Medical Director of the Maryland Poison Center.

Dr. Gorman has served as a member and Chair of the AAP Committee on Drugs and as Chair of the AAP's Section on Clinical Pharmacology and Therapeutics. From 1999 to 2006, he has served on the Pediatric Advisory Committee of the FDA. In 2005, Dr. Gorman received a Special Achievement Award from the Maryland Chapter of the AAP for his advocacy work on behalf of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.

Christine Grady, M.S.N., Ph.D.

Dr. Grady is the Deputy and Acting Chief of the Department of Bioethics at the Warren G. Magnuson Clinical Center, NIH. She is also Head of the Department's Section on Human Subjects Research. Her current research interests include research subject recruitment, incentives, vulnerability, and international research ethics. She has served on Institutional Review Boards for the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Dr. Grady is a Senior Research Fellow at the Kennedy Institute of Ethics, and was elected as a Fellow of the American Academy of Nursing and a Fellow of the Hastings Center. She is the author of over 40 published papers in bioethics, HIV disease, and nursing that have appeared in books and scholarly journals. She has participated in numerous intergovernmental task forces and is the recipient of several awards, including the NIH Director's award twice (1997 and 1999) and the Assistant Secretary of Health Award (1988). She currently serves on three editorial boards of professional journals in bioethics and nursing, and she has lectured widely at national and international conferences, professional societies, universities, and health care institutions on ethical issues in clinical research and clinical care.

Alan E. Guttmacher, M.D.

Dr. Guttmacher became the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development in August 2010. Previously, he served as Acting Director of the Institute, beginning in December 2009. A pediatrician and medical geneticist, Dr. Guttmacher came to NIH in 1999 to work at the National Human Genome Research Institute, where he served in a number of roles, including seven years as the Deputy Director and, from August 2008 to December 2009, as the Acting Director. In those roles, he oversaw the Institute's efforts to advance genome research, integrate that research into health care, and explore the ethical, legal, and social implications of human genomics. Dr. Guttmacher came to NIH from the University of Vermont, where he directed the Vermont Regional Genetics Center and Pregnancy Risk Information Service, the Vermont Newborn Screening Program, and the Vermont Cancer Center's Familial Cancer Program, founded Vermont's only pediatric intensive care unit, and was the principal investigator for an NIH-supported initiative that was the nation's first statewide effort to involve the general public in discussion of the Human Genome Project's ethical, legal, and social implications. He also conducted research, taught, and had a busy practice in clinical genetics. A graduate of Harvard College and of Harvard Medical School, Dr. Guttmacher completed an internship and residency in pediatrics and a fellowship in medical genetics at Harvard and Children's Hospital of Boston. He is a member of the Institute of Medicine and a Fellow of the American Academy of Pediatrics

Timothy Johnson, M.D.

Dr. Johnson is Bates Professor of the Diseases of Women and Children and Chair of Obstetrics and Gynecology at the University of Michigan Medical School. He is also Arthur F. Thurnau Professor, Professor of Women's Studies, Research Professor in the Center for Human Growth and Development, and Interim Director of GLOBAL REACH at the University of Michigan. His education and training have been at the University of Michigan, University of Virginia and Johns Hopkins University. He is a Fellow of the American College of Obstetricians and Gynecologists (ACOG) and a Fellow of the American Institute of Ultrasound in Medicine. After service in the U.S. Air Force, he rejoined the Johns Hopkins faculty, eventually to become Director of the Division of Maternal Fetal Medicine. Since 1993, he has been Chair of the Department of Obstetrics and Gynecology at the University of Michigan and has seen its national rankings reach into the "top ten" by NIH and USNWR metrics. He has received research and training grants from NIH, DHHS, Carnegie Corporation and others. He is active in international teaching and training especially in Ghana, Africa and is an honorary fellow of the West African College of Surgeons, honorary fellow of the Ghana College of Physicians and Surgeons, and Fellow *ad eundem* of the Royal College of Obstetricians and Gynaecologists (London). He is author of over 250 articles, chapters and books. He has served on numerous editorial boards, study sections, professional committees, societies and boards and is an elected member of the Institute of Medicine of the National Academy of Science. In 2005, Dr. Johnson was awarded the Distinguished Service Award, the highest honor of ACOG. He is Past President of the Association of Professors of Gynecology and Obstetrics and Editor of the *International Journal of Gynecology and Obstetrics.*

Hendrée E. Jones, Ph.D.

Dr. Jones is Associate Professor, Psychiatric and Behavioral Sciences and Director of Research for the Center for Addiction and Pregnancy (CAP), a community-based treatment center at The Johns Hopkins Bayview Medical Center. Since its inception in 1991, CAP has been committed to generating evidence-based research and applying these findings to improve the treatment provided. Given the various disciplines involved in the program (obstetrics, pediatrics and psychiatry), this is an ideal setting for patients to receive comprehensive care. Research projects conducted at CAP have examined a wide variety of questions including optimal medication and counseling services for pregnant women with substance use disorders, the role of partners in the treatment process for women at the program, the cost and benefit of the services provided, and novel behavioral treatments for pregnant women with active substance use disorders.

Dr. Jones recently joined the Substance Abuse Treatment Evaluations and Interventions (SATEI) Research program at RTI International, where she is focusing on developing comprehensive drug abuse treatment for vulnerable women in North Carolina and internationally. She has three main areas of research interest. First, she is a leading expert in the examination of pharmacotherapies to treat drug dependence during pregnancy and the impact of prenatal exposure to these medications and drugs of abuse. Second, she has been creating and testing novel behavioral interventions to help prevent relapse to drug use in pregnant women. Third, she specializes in researching issues of differences in drug addiction. Dr. Jones holds a doctorate in Psychology from Virginia Commonwealth University/Medical College of Virginia, and is a licensed Psychologist.

Robert J. Levine, M.D.

Dr. Levine, at Yale University, is Professor of Medicine and Lecturer in Pharmacology, Director of the Law, Policy and Ethics Core of the Center for Interdisciplinary Research on AIDS and Senior Fellow of the Interdisciplinary Center for Bioethics. He is a Fellow of The Hastings Center and the American College of Physicians; a member of the American Society for Clinical Investigation, past President of the American Society of Law, Medicine & Ethics (two terms), past Chairman of the Connecticut Humanities Council and Director of PRIM&R (Public Responsibility in Medicine and Research). In the past he was also Chair of the Institutional Review Board at Yale-New Haven Medical Center (1969 - 2000), Founding Co-Director of Yale University's Interdisciplinary Bioethics Center, Chief of the Section of Clinical Pharmacology at Yale, Chair of the Section on Medico-Legal Matters and R&D Administration of the American Society for Clinical Pharmacology and Therapeutics, Associate Editor of *Biochemical Pharmacology* and Editor of *Clinical Research*. Dr. Levine is the founding Editor of *IRB: A Review of Human Subjects Research* (Editor 1979 – 2000 and currently Chair of the Editorial Board) and has served several federal and international agencies involved in the development of policy for the protection of human subjects.

He is the author of numerous publications including the book, *Ethics and Regulation of Clinical Research* (2 editions). In the last 35 years, most of Dr. Levine's research, teaching and publications have been in the field of medical ethics with particular concentration on the ethics of research involving human subjects.

Dr. Levine has been awarded the Outstanding Achievement Medal from the Office for Human Research Protection, U.S. Department of Health and Human Services, in 2004 for his role in the development of the *Belmont Report*; the Lifetime Award for Excellence in Human Research Protection from the Health Improvement Institute in 2004, the Lifetime Achievement Award for Excellence in Research Ethics from PRIM&R in 2005, the Distinguished Alumni Scholar Award from The George Washington University in 2008 and the Academy of Pharmaceutical Physicians and Investigators Special Recognition Award in 2009.

Margaret Olivia Little, Ph.D.

Dr. Little is Director of Georgetown's Kennedy Institute of Ethics and an Associate Professor in the Department of Philosophy at Georgetown University. She completed graduate training at Oxford, Princeton, and the University of California at Berkeley. She has served as visiting faculty at the Department of Bioethics at NIH and at Johns Hopkins University. Dr. Little's research interests are bioethics, including law and public policy issues. She brings to bear two perspectives that are often thought to be in deep conflict— analytic philosophy and feminist theory.

Anne Drapkin Lyerly, M.D. M.A.

Dr. Lyerly is the Associate Director of the Center for Bioethics and Associate Professor of Social Medicine, Obstetrics and Gynecology and Maternal and Child Health at the University of North Carolina, Chapel Hill. A practicing obstetrician/gynecologist and bioethicist, she undertakes ethical and empirical inquiry into morally complex issues in women's reproductive health. Her research has been funded by NIH and the Greenwall Foundation including an award from the Faculty Scholars Program. She co-founded, with Maggie Little and Ruth Faden, the *Second Wave Initiative*, aimed at making progress toward responsible inclusion of pregnant women in research and toward evidence-based therapeutics during pregnancy. She and Professor Little also co-founded the Obstetrics and Gynecology Risk Research Group, an interdisciplinary group that examines the assessment, communication and management of risk during pregnancy. Her work has been published in a breadth of journals, including *Science*, the *American Journal of Public Health*, and the *Hastings Center Report*, and the *New York Times*. She was the 2007-2009 Chair of the American College of Obstetricians and Gynecologists Committee on Ethics and Co-Chair of the 2009 Program Committee for the American Society of Bioethics and Humanities. Dr. Lyerly was the first graduate of the Duke/NCCU BIRCWH which is the ORWH Building Interdisciplinary Research Careers in Women's Health program.

Celia J. Maxwell, M.D.

Dr. Maxwell is Associate Professor of Medicine and Vice President for Health Sciences at Howard University Hospital. She is and has been the Principal Investigator of several prestigious projects including The Center for Infectious Disease Management and Research, and the Centers for Disease Control and Prevention-Comprehensive AIDS Training Initiative. She is board-certified in Internal Medicine and Infectious diseases, and is a Fellow of the American College of Physicians, as well as a member of several boards and scientific associations. Dr. Maxwell gives numerous talks to professional and lay audiences and is a frequent guest on radio and television. She also lectures to diverse groups, including physicians, educators, students, national service organizations, and she has several publications in the areas of sexually transmitted diseases and parasitology. In 2008, Dr. Maxwell was recognized as one of America's leading doctors by Black Enterprise Magazine.

Castilla F. McNamara, Ph.D. M.P.A.

Dr. McNamara is the Population Tracking Officer at the National Institute on Deafness and Other Communication Disorders (NIDCD). She implements the NIH Inclusion and Tracking policy. As a certified IRB professional, Dr. McNamara offers advice on resolving issues concerning human research protections. Her research experience includes maternal and neonatal epidemiological studies with the University of Illinois Perinatal Network and sexually transmitted diseases studies at Howard Brown Health Center in Chicago. She was a chair of the Community Advisory Board at AIDS Research Alliance Chicago and served as a member on the Community Constituency Group, Research Implementation Committee, Quality Improvement Committee, and Performance Oversight Committee for the Community Programs for Clinical Research on AIDS. She has clinical experience in mental health, particularly in substance abuse and death and dying at long term care facilities.

Myaing Myaing Nyunt, M.D., Ph.D.

Dr. Nyunt is an Assistant Professor of Clinical Pharmacology and International Health at the Johns Hopkins Bloomberg School of Public Health. She received her B.A. in Natural Sciences from Simon's Rock College of Bard, an M.D. from George Washington University Medical School, and an M.P.H. in International Health from Johns Hopkins University School of Public Health. She trained as a resident in General Medicine in Johns Hopkins Bayview Medical Center and completed a fellowship in Clinical Pharmacology at Johns Hopkins School of Medicine and a Ph.D. in Clinical Investigation at the Johns Hopkins University School of Public Health.

Dr. Nyunt's research combines clinical and laboratory-based approaches to understand antimalarial and antiretroviral drugs with an emphasis on the pregnant population. She has led a multi-center clinical trial to evaluate antimalarial drug pharmacokinetics in pregnant women of Mali and Zambia, as well as a Phase I clinical trial of drug interaction between antimalarial and antiretroviral drugs in healthy volunteers and

a Phase I/II clinical study to evaluate causal prophylactic activity of an investigational antimalarial compound in healthy volunteers challenged with *Plasmodium falciparum* malaria. Her research was supported by NIH, Johns Hopkins Malaria Research Institute, Center for Global Health and PhRMA Foundation. Currently she is leading a clinical trial to evaluate the efficacy, safety and pharmacokinetics of antimalarial drugs in pregnant women living with HIV in Mali.

Her academic career focuses on the clinical application of pharmacology in pregnant women, and her long term vision is to build a clinical research program to systematically evaluate drug therapy, with a major emphasis on antimalarial and antiretroviral drugs, to optimize treatment outcomes; to broaden the understanding and meaningful clinical application of clinical pharmacology to optimize public health interventions in the developing world; and to train young scientists in developing countries to become independent clinical investigators.

Vivian W. Pinn, M.D.

Dr. Vivian W. Pinn is the first full-time Director of the Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH), an appointment she has held since 1991and as NIH Associate Director for Research on Women's Health since 1994. Dr. Pinn came to NIH from Howard University College of Medicine in Washington, D.C., where she had been Professor and Chair of the Department of Pathology since 1982, and has previously held appointments at Tufts University and Harvard Medical School. She has been invited to present the ORWH's mandate, programs and initiatives to many national and international individuals and organizations with an interest in improving women's health and the health of minorities. The ORWH was established by Congress to ensure the inclusion of women (and minorities) in clinical research funded by the NIH, and Dr. Pinn has led NIH efforts to implement and monitor the inclusion policies. One of her recent areas of focus has been to raise the perception of the scientific community about the importance of sex differences research across the spectrum from cellular to translational research and implementation into health care. Dr. Pinn is currently co-chair, along with the Director of NIH, of The NIH Working Group on Women in Biomedical Careers which is developing and implementing programs and policies to improve the advancement of women in biomedical careers.

Dr. Pinn recently completed a national initiative to reexamine priorities for the women's health research agenda for the 21st Century, involving more than 1500 advocates, scientists, policy makers, educators and health care providers in a series of scientific meetings and public hearings across the country to determine progress as well as continuing, or emerging areas in need of research. This new strategic plan for the coming decade, *Moving into the Future with New Dimensions and Strategies: a Vision for 2020 for Women's Health Research*, was presented publicly at the September 2010 scientific symposium and celebration of the 20th anniversary of the ORWH.

Dr. Pinn, a native of Lynchburg, Virginia, earned her B.A. from Wellesley College in Massachusetts, and received her M.D. from the University Of Virginia School Of Medicine in 1967, where she was the only woman and minority in her class. She completed her postgraduate training in Pathology at the Massachusetts General Hospital, during which time she also served as Teaching Fellow at the Harvard Medical School. She was Associate Professor of Pathology and Assistant Dean of Student Affairs at Tufts before leaving to join the faculty at Howard. She is a member of long standing in many professional and scientific organizations, in which she has held many positions of leadership, including being the 2nd woman President of the National Medical Association in 1989 after serving in many other capacities including Speaker of the House of Delegates and Trustee.

Dr. Pinn has received numerous honors, awards, and recognitions, and has been granted 11 Honorary Degrees of Laws and Science since 1992. She is a fellow of the American Academy of Arts and Sciences and was elected to the Institute of Medicine in 1995. Among her honors are the Alumni Achievement Award from Wellesley College in 1993, and she served on the Wellesley College Board of Trustees. She also received the second annual Distinguished Alumna Award from the University of Virginia, was honored by the UVA medical school as one of their Alumni Luminaries and was invited to serve as the 2005 speaker for the University of Virginia Commencement, the first African American woman to be so honored. The UVA School of Medicine established the "Vivian W. Pinn Distinguished Lecture in Health Disparities," and further honored her in the fall of 2010 by naming one of its 4 advisory colleges for medical students in her name, the "Vivian Pinn College of UVA". Most recently, The Foundation for Gender Specific Medicine honored Dr. Pinn in May of 2011 with the renowned "Athena Award" for her work in the Office of Research on Women's Health. She was also presented in May 2011, with the distinguished "Tufts University School of Medicine Dean's Medal" conferred only rarely to individuals whose service to the school and career in medicine have enhanced the University's national standing. Tufts University also established the "Vivian W. Pinn Office of Student Affairs" in her honor at the time her former students and the Medical School also honored her with the establishment of a scholarship fund named for her to assist disadvantaged students to attend.

Catherine Y. Spong, M.D.

Dr. Spong is Chief of the Pregnancy and Perinatology Branch at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) where she oversees grants and contracts in the areas of maternal fetal medicine, pregnancy and neonatology. She is board-certified in maternal fetal medicine and obstetrics and gynecology. Dr. Spong is also the Associate Editor of *Obstetrics & Gynecology* and an Editor of *William's Obstetrics, Management of High Risk Pregnancy* and *Protocols of High Risk Pregnancy*. She is a Fellow of the American College of Obstetricians and Gynecologists and a member of the Society for Maternal Fetal Medicine, Society for Gynecologic Investigation, Society for Neuroscience,

and Perinatal Research Society. Her research interests focus on maternal and child health, emphasizing prematurity and fetal growth restriction, and she is the Program Scientist for the NICHD Maternal Fetal Medicine Units Network, a network of 14 sites in the US that performs clinical trials in high risk pregnancies. In addition, Dr. Spong is interested in the developing fetus and neuroprotective agents to prevent fetal injury for which she is the holder of several patents. She has received numerous awards, is in Who's Who in America, received the Achievement Award from the Society for Maternal Fetal Medicine and the NIH Director's Award. She has published over 140 peer-reviewed papers and organized numerous national and international conferences. Dr. Spong has also been on *The Early Show*, the *Diane Rehm Show* and *NPR's All Things Considered* discussing women's health and pregnancy topics.

Christopher E. Taylor, Sc.D.

Dr Taylor is currently the Bacterial Diseases Program Officer, in the Respiratory Diseases Branch, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID). Previously he served as Assistant Professor in the Department of Microbiology and Immunology, The Medical College of Pennsylvania (currently Drexel University), and earlier was a Senior Staff Fellow in the Laboratory of Immunogenetics, NIAID. He has received several awards including the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) "Young Investigator Award", in 1992, he served as Chair, The Immunology Division, ASM and in 2009 Embassy Science Fellow, Freetown Sierra Leone.

D. Heather Watts, M.D.

Dr. Watts is a Medical Officer, Pediatric Adolescent and Maternal AIDS Branch at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). She is board-certified in obstetrics and gynecology and maternal-fetal medicine. She has been conducting clinical research in pregnant women since 1985. After completing medical school at Jefferson Medical College and residency at Thomas Jefferson University Hospital, she completed a fellowship in Maternal Fetal Medicine and Infectious Diseases at the University of Washington. She was on the faculty at the University of Washington School of Medicine for 13 years until coming to NICHD in 1998. At the University of Washington, she designed studies and enrolled pregnant women in many clinical trials evaluating treatment of conditions during pregnancy, including preterm labor, herpes, and HIV infection. She was the site principal investigator for several trials of the Pediatric AIDS Clinical Trials Group (now the International Maternal, Pediatric, and Adolescent AIDS Clinical Trials Group) for pregnant women, including the landmark ACTG076 study of zidovudine for prevention of maternal to child transmission of HIV. At NIH, she continues her work with IMPAACT along with several other research networks including the Microbicide Trials Network.

Cora Lee Wetherington, Ph.D.

Dr. Cora Lee Wetherington joined the National Institute on Drug Abuse (NIDA) in 1987. Since 1995, she has served as NIDA's Women and Sex/Gender Differences Research Coordinator. In that role, she serves as Chair of NIDA's Women and Sex/Gender Differences Research Group and as NIDA's representative to the National Institutes of Health (NIH) Coordinating Committee of the Office of Research on Women's Health. In these various roles, her activities are aimed at advancing and integrating the study of women and sex/gender differences into all areas of drug abuse research. Dr. Wetherington also serves as a Program Officer in NIDA's Behavioral Sciences Research Branch within the Division of Basic Neuroscience and Behavioral Research, where she oversees a program of extramural preclinical research that includes the study of sex differences, vulnerability to drug abuse, and the behavioral and neurobiological effects of exposure to drugs during lifespan development. Dr. Wetherington received her Ph.D. in experimental psychology from the University of North Carolina at Greensboro in 1976. Prior to joining NIDA in 1987, Dr. Wetherington was a psychology professor at the University of North Carolina at Charlotte, where for 12 years she conducted research in the field of animal learning and behavior. Her research was funded in part by grants from NIH and the National Science Foundation.

Dr. Wetherington is a Fellow of two Divisions of the American Psychological Association—Division 25: Behavior Analysis, and Division 50: Psychopharmacology and Substance Abuse. In 2005, she was awarded the Meritorious Research Service Commendation by the American Psychological Association Board of Scientific Affairs for her leadership in promoting research on women, sex/gender differences, and drug abuse. In 2010 she received the J. Michael Morrison Award from the College on Problems of Drug Dependence. She serves on the board of editors of *Clinical & Experimental Psychopharmacology*. She has served on the board of editors of *The Journal of the Experimental Analysis of Behavior* and *The Behavior Analyst*, and has conducted guest reviews for various other journals. She also serves on the editorial board of NIDA Notes, a position she has held since 1988. She is coeditor of three books, including *Drug Addiction Research and the Health of Women*.

Katherine L. Wisner, M.D. M.S.

Dr. Wisner is Professor of Psychiatry, Obstetrics/Gynecology and Reproductive Sciences, Epidemiology and Women's Studies at the University of Pittsburgh School of Medicine, and Director of the Women's Behavioral HealthCARE program at the Western Psychiatric Institute and Clinic (WPIC) of the University of Pittsburgh Medical Center. She also serves as an investigator at the Magee-Women's Research Institute and as an adjunct faculty member of RAND Corporation, Pittsburgh. Dr. Wisner is board certified in general and child and adolescent psychiatry. She has chaired the Human Subject Committee of

the American College of Neuropsychopharmacology, and is the past President of the Marcé International Society for the Study of Childbearing-Related Psychiatric Illness. Dr. Wisner is a Distinguished Fellow of the American Psychiatric Association, and she was a consultant for the U.S. Centers for Disease Control and Prevention's Safe Motherhood Initiative, the Agency for Healthcare Research and Quality's report on Perinatal Depression, and the Food and Drug Administration's Pediatric Subcommittee on the effects of maternal SSRI use on newborns. Dr. Wisner completed the prestigious Executive Leadership in Academic Medicine (ELAM) program from Drexel University.

Kimberly A. Yonkers, M.D.

Dr. Yonkers is Professor of Psychiatry, and of Obstetrics, Gynecology and Reproductive Sciences at Yale University School of Medicine. Dr. Yonkers' research focuses on mood and anxiety disorders in women. Her specific interests include sex differences in these conditions and treatment of these conditions during pregnancy. She also investigates the efficacy and effectiveness of pharmacological treatment of perinatal mood disorders and premenstrual dysphoric disorder (PMDD). She collaborates with researchers, community clinics and hospitals in the greater New Haven and Fairfield counties, in an effort to increase understanding of women's psychiatric health issues. She has developed a Substance Use Risk Profile-Pregnancy Scale for screening for prenatal substance use. Dr. Yonkers graduated from Amherst College, and Columbia University Medical School, and did her residency in Psychiatry at McLean Hospital/Harvard Medical School.

Dr. Yonkers is a past president of the North American Society for Psychosocial Obstetrics and Gynecology, and she serves on the editorial boards of the *Archives of Women's Mental Health, Maternal and Child Health Journal,* the *Journal of Women's Health*, and *General Hospital Psychiatry*.

Appendix 3: Ancillary Materials

Papers Distributed at the Meeting

Couzin-Frankel, J. (2010). Drug safety. New network to track drugs and vaccines in pregnancy. *Science 327*(5969),1066-1067.

Goldkind, S.F., Sahin, L., Gallauresi, B. (2010). Enrolling Pregnant Women in Research—Lessons from the H1N1 Influenza Pandemic. *New England Journal of Medicine 326*(24),2241-2243.

Lyerly, A.D., Mitchell, L.M., Armstrong, E.M., Harris, L.H., Kukla, R., Kuppermann, M. and Little, M.O. (2009). Risk and the pregnant body. *Hastings Center Report 39*(6),34-42.

Macklin, R. (2010). Enrolling Pregnant Women in Biomedical Research. *Lancet 375*(9715), 632-633.

McCullough, L.B., Coverdale J.H. and Chervenak, F.A. (2005). A comprehensive ethical framework for responsibly designing and conducting pharmacologic research that involves pregnant women. *American Journal of Obstetrics and Gynecology 193*(3 Part 2), 901-907.

Putting Gender on the Agenda: Editorial (2010) *Nature 465*(7299), 665.

Other Information

Second Wave Initiative
http://secondwaveinitiative.org.
Website includes a Case Statement and many references.

ORWH Summary of Meeting Report

Foulkes, M., Grady C., Spong C.Y., Bates, A. and Clayton, J.A. (2011). Clinical research enrolling pregnant women. A workshop summary *Journal of Women's Health*. August 5 (e-pub ahead of print)

Abstract Clinical research investigates mechanisms of human disease, interventions, or new technologies, but pregnant women are often excluded from clinical studies. Few studies, beyond research on pregnancy, are designed to address questions relevant to pregnant women. A recent National Institutes of Health workshop considered the barriers and opportunities in conducting clinical research studies enrolling pregnant women.

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