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Enrolling Pregnant Women: Issues in Clinical Research

Mary C. Blehar, PhD
Office of Research on Women's Health, NIH

Catherine Spong, MD
Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH

Christine Grady, PhD
Department of Bioethics, Warren G Magnuson Clinical Center, NIH

Sara F. Goldkind, MD, MA
Office of Good Clinical Practice, Office of the Commissioner, FDA

Leyla Sahin, MD
Pediatric and Maternal Health Staff, Maternal Health Team, Office of New Drugs, Center for Drug Evaluation and Research, FDA

Janine A Clayton, MD
Office of Research on Women's Health, NIH

Introduction

The NIH Office of Research on Women's Health (ORWH) was established in 1990 in response to Congressional, scientific and advocacy group concern that a lack of systematic and consistent inclusion of women in NIH-supported clinical research could result in clinical decisions made for women based on findings from studies of men—without evidence that they were applicable to women. The establishment of ORWH also heralded earnest efforts by NIH to develop a research agenda addressing gaps in scientific knowledge about women's health across the lifespan. In 1993, the Office's role in monitoring inclusion of women in NIH clinical research was codified by the NIH Revitalization Act. Over the past 20 years, much progress has been made in inclusion, so that females are currently 49 percent of subjects in NIH funded studies that include both male and female participants.

Over its 22 year history, ORWH has played a major role in coordinating and advancing a women's health research agenda at NIH. Based on a national collaborative effort that involved scientists, advocates, and other stakeholders, ORWH released a report, “Agenda for Research on Women's Health for the 21st Century: A Report of the Task Force on the NIH Women's Health Research Agenda for the 21st Century.” (DHHS, 1999) In 2009, the Office embarked on an update of the 1999 report through a series of scientific regional workshops and public hearings. The product of this effort was “Moving into the Future with New Dimensions and Strategies: A Vision for 2020 for Women's Health Research” released in September 2010 (DHHS, 2010). From the recommendations of 40 topic-focused scientific

Corresponding Author: Mary C. Blehar PhD, Office of Research on Women's Health National Institutes of Health, Department of Health and Human Services 6707 Democracy Blvd. Suite 400, MSC 5484, Bethesda, Maryland 20892-5484 Telephone: 301-402-1770 Fax: 301-402-1798 mary.blehar@nih.gov.

workgroups at five regional meetings, the agenda distilled six cross-cutting and overarching goals to advance women's health and sex/gender research. One goal, to “actualize personalized prevention diagnostics and therapeutics for women and girls”, included specific objectives for research on conditions affecting pregnant women and research on the effects of pregnancy-related conditions on the subsequent health of women and their offspring. In October 2010, ORWH convened a workshop to address ethical, regulatory, and scientific issues raised by the enrollment of pregnant women in clinical research.

Defining the Need

In 1994 an Institute of Medicine report (Mastroianni, Faden & Federman, 1994) on challenges and barriers to the inclusion of women in clinical research recommended that pregnant women be presumed eligible for participation in clinical studies. The majority of members of the report's authorship committee also endorsed a recommendation that investigators and institutional review boards (IRBs) exclude pregnant women from participation only when (1) there was no prospect of medical benefit to the pregnant woman, and (2) a risk of significant harm to the offspring was known or could be plausibly inferred. Despite the report, today pregnant women continue to be excluded from the vast majority of pharmacological therapeutic or preventive trials.

This exclusion is highly consequential. Over 4 million women in the United States give birth annually. Among them are women affected by serious illnesses such as hypertension, diabetes, asthma, mental disorders, autoimmune disorders, cancers and others that require ongoing or urgent treatment during pregnancy. Approximately 64 percent of pregnant women are prescribed one or more medications for chronic illnesses or for conditions that arise during pregnancy (Andrade et al. 2004). Nonetheless, very few drugs are approved for use during pregnancy. In addition, most drug labels have little pregnancy data to inform prescribing decisions. Efforts to address this problem have resulted in a draft FDA rule[1], which will improve the information in labeling after it publishes as a final rule. Although there are significant physiologic changes in pregnancy, including near doubling of maternal blood volume and alterations in binding proteins, the pharmacokinetics and efficacy of drugs in pregnancy are, by and large, unknown. Toxicity and teratology studies of pregnant animals imperfectly or inconsistently predict human effects. As a result, therapeutic decisions for pregnant women are often made without an evidence base. Treatment of the mother may be inadequate, exposing the fetus to therapies at a dose which does not provide a benefit to the mother (Lyerly, Little & Faden, 2008).

As an example, in 2001, in response to concern over the public health consequences of anthrax exposure, the CDC recommended a 60-day course of ciprofloxacin for pregnant women, because the high risk associated with developing anthrax was judged to outweigh possible teratogenic risk of the drug. Based on amoxicillin's superior safety profile in pregnancy, the American College of Obstetrics and Gynecologists recommended that clinicians treating at risk pregnant women exposed to anthrax switch to amoxicillin if the anthrax was found to be penicillin-responsive (ACOG 2002). This strategy may have exposed pregnant women to under-treatment. A 2007 study funded partly by the FDA and NIH, indicated that amoxicillin concentrations adequate to prevent anthrax were most likely unachievable during pregnancy due to increased metabolism of the drug (Andrew et al., 2007).

In 2009, when the H1N1 pandemic occurred and pregnant women were identified as a high risk population, no immunogenicity data were available in pregnant women to inform dosing

[1] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

of the H1N1 vaccine, and no pharmacokinetic data in pregnant women were available to inform dosing of antivirals (Goldkind, Sahin & Gallauresi, 2010). Due to the threat posed by H1N1 during pregnancy, clinical trials in pregnant women are subsequently being conducted.

Pregnancy Research: Historical Background of Exclusion

With such compelling needs, why are pregnant women largely excluded from clinical research? This is an important area for further study because the reasons for exclusion are not well documented. However, reasons include at least fear of harm to the fetus and threat of legal liability; concern about the complicated physiology of pregnant women; uncertainty whether pregnant women would be willing to participate; regulations which classify pregnant women as a "vulnerable" population in need of special protections in research; and vague, ambiguous, and restrictive wording of regulations, which IRBs in turn interpret conservatively for pregnant subjects.

In 1974 Congress asked the newly established National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to make recommendations for the conduct of research involving pregnant women and fetuses. In its work, the Commission was influenced by a number of contemporaneous events such as the 1973 *Roe v. Wade* decision, the subsequent emergence of a notion of a "maternal-fetal conflict" (Markens, Browner & Press, 1997) and the occurrence of serious birth defects as a consequence of pregnancy exposures to thalidomide and diethylstilbestrol. The recommendations of the Commission were codified in Federal Regulations at Subpart B of 45 CFR 46.

Pregnant women, fetuses and neonates are often considered vulnerable and are protected by additional regulations, along with children and prisoners. In 2001, the wording of Subpart B was changed from a prior more proscriptive approach to a more inclusive approach. The new language states that pregnant women or fetuses *may be involved* in research if all of ten conditions are met. The current wording of Subpart B is given in Table 1. Despite these modifications, pregnant women continue to be excluded from clinical trials.

As part of the effort to develop scientifically rigorous and evidence-based treatment options for pregnant women, FDA reviews protocols for clinical research involving this study population, on a case-by-case basis. Based on this experience, FDA has developed guidance to help researchers and IRBs understand the Agency's current thinking in this regard. For example, FDA has issued guidance on pharmacokinetic studies during pregnancy,[2] clinical lactation studies[3] and pregnancy exposure registries[4]. Recognizing the additional ethical and scientific complexities associated with studying pregnant women in the setting of a clinical trial, FDA is developing guidance on this topic[5].

In 2009, the *Second Wave Initiative* was founded at Georgetown University to promote the responsible inclusion of pregnant women in clinical research based on ethical reasons and medical need (Little, Lyerly & Faden, 2011). During the October 2010 ORWH workshop the current status of research involving pregnant women and future needs were discussed in light of the above issues and concerns. A workshop summary report (Foulkes, Grady, Spong, Bates & Clayton, 2011) and a more extensive report of workshop proceedings (ORWH, 2011) provide detail on presentations and topics. Below is a focus on three major

[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072133.pdf
[3] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127505.pdf
[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071639.pdf
[5] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm314767.htm

interrelated scientific and science regulatory issues that emerged as important concerns at that meeting.

Recommendation 1: Define Pregnant Women as a Scientifically "Complex" Population and Change the Presumption of Exclusion

In order to appropriately address health needs, pregnant women should be reclassified from their current status as a "vulnerable" population to that of a medically complex population, necessitating special scientific and ethical considerations. A corollary is the need to change the presumption of exclusion of pregnant women to one of inclusion. These issues are discussed below.

Ethical Issues

Ethical issues in pregnancy research have received extensive consideration elsewhere (McCullough, Coverdale, Chervenak, 2006; Lyerly, Little, Faden, 2008, 2011; Macklin, 2010). Macklin (2010) stated that "the most compelling reason to justify the inclusion of pregnant women in 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."

Groups are considered vulnerable when they have a compromised ability to protect their interests and provide informed consent. In general, pregnant women are capable of protecting their own interests and giving their own informed consent. However, because they are also responsible for protecting the interests of the growing fetus, who cannot consent to research or may have unique susceptibility to risks, there are additional distinctive issues that a pregnant woman needs to consider with regard to the risks and benefits of participation in clinical research, resulting from the interdependence of the maternal-fetal unit. Even though the interests of the mother and the fetus are conceptually separable, in practice, the notion of maternal-fetal conflict poses a false dichotomy. If a pregnant woman affected by a serious debilitating or life-threatening disease is enrolled in a trial with therapeutic benefit potential for her, her health is closely linked to the health of the baby and later to the health of the child who will receive benefit from maternal care. Those benefits and direct maternal therapeutic benefit need to be weighed against any possible risks to the fetus of maternal treatment or non-treatment.

A major impediment in moving forward with enrolling pregnant women in research is a concern that an intervention could cause harm resulting in birth defects. There is a baseline rate of approximately 3 percent for birth defects, although it is difficult to predict which babies will have birth defects. In research that includes pregnant women, the mother's health status coming into the study is known and the assumption is usually that the fetus is healthy. An adverse fetal outcome tends to be attributed to the research intervention despite the baseline rate of birth defects. There is a need to develop special scientific models that address the baseline rate issue and attribution of causation in clinical interventional research in pregnancy.

The Physiology of Pregnancy

Pregnant women are an especially dynamic subset of women, in whom pregnancy related physiological changes occur that can potentially alter a drug's pharmacokinetics and efficacy. Not only is the pregnant state physiologically different than the non-pregnant state, but also physiology changes over the course of the pregnancy. When blood volume doubles in pregnancy, the effects on drug metabolism are significant. Dosing and interval recommendations established for non-pregnant women cannot automatically be extrapolated

to pregnant women (Little 1999; Chambers, Polifka & Friedman, 2008). In 2004, the FDA issued draft guidance on pharmacokinetic studies in pregnancy. The guidance emphasized that treatment of conditions in pregnant women ought to optimize results for the maternal-fetal pair. In order to do that it is important to obtain pharmacokinetic data that reflect changes in drug metabolism and are relevant across pregnancy.

Moving from a Presumption of Exclusion to One of Inclusion

The need to reclassify pregnant women as a complex population was recognized in the 1994 IOM report. This reclassification is an important step toward engaging more scientific and ethical dialogue on pregnancy research. However, reclassification needs to proceed along with a change in the presumption of exclusion of pregnant women to one of inclusion.

Currently researchers must justify the inclusion of pregnant women and specify what special protections are going to be put in place. Interestingly, there is no requirement to justify their exclusion from a protocol. Since the NIH began to require inclusion of women, ethnic minorities, and children in research, pregnant women are the only population for which justification for exclusion does not need to be given.

A 1998 NIH directive on children in clinical research, for example, called for a presumption of inclusion, consistent with subpart D of the human subjects' regulations and a need to justify exclusion. Following that directive and with further impetus from the Pediatric Research Equity Act (Public Law 108–55, 2003), there has been a marked increase in the number of clinical trials and studies that include pediatric subjects. A similar NIH directive for the inclusion of pregnant women would move the field to a more balanced scientific consideration of issues.

Recommendation 2: Clarify Existing Regulations and Focus on IRB Behavior as it Facilitates or Impedes Pregnancy Research

There are several factors leading to reluctance to include pregnant women in clinical research. Researchers are sometimes concerned about the physiologic complexity in pregnancy, and possible legal liability. Existing regulations governing the inclusion of pregnant women in clinical research are somewhat ambiguous, imposing another significant barrier to their implementation. Additionally, IRBs may go beyond regulatory requirements when the proposed subjects are pregnant women. Although not specific to pregnancy research, variation among IRBs in the interpretation of regulations for the same protocol is a further impediment, especially in multisite studies.

Problems have been identified with IRB interpretation of regulations governing clinical research that includes pregnant women as subjects (Levine, 2011). As an example, wording in Subpart B states that pregnant women or fetuses may be involved in research if all of ten enumerated conditions are met. Condition (a) specifies that research may be conducted where scientifically appropriate, preclinical and clinical studies on non-pregnant women provide an adequate basis for assessing potential risks to pregnant women and fetuses. IRBs are left to interpret how much prior research is sufficient and they typically interpret this directive conservatively.

The interpretation of “minimal risk to the fetus” in condition (d) of Subpart B is particularly 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.

Testing of drug therapies in a pediatric population presents an analogous situation to testing of drugs in a pregnant population. Several studies reveal inconsistencies among IRBs in

applying regulations governing clinical research to studies involving children (Whittle et al, 2004; Kimberly et al., 2006). A survey (Shah et al., 2004) asked IRB chairs to evaluate the degree of risk for various kinds of research on children. For a study in children testing a drug already found safe in adults, only five percent of IRB chairs said that the study presented minimal risk and 72 percent felt that this 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.

Although IRB inconsistency is likely due in large part to differences in interpreting regulatory requirements and ethical standards, it might also stem from some IRB members' lack of necessary expertise regarding research ethics and regulations for research with special populations of children or pregnant women. Specialized committees as well as training of IRB members in the specific requirements of regulations for such populations may be helpful.

A July 2011 Federal Register Announcement sought input on possible changes to the Common Rule and to Federal Regulations 21 CFR Parts 50 and 56 Human Subjects in order to enhance protections for research subjects and reduce burden, delay, and ambiguity for investigators. The announcement noted that regulations have not kept pace with the evolving human research enterprise, the proliferation of multi-site clinical trials and observational studies, the expansion of health services research, research in the social and behavioral sciences, and research involving databases, the Internet, and biological specimens in repositories, and the use of advanced technologies, such as genomics.

Proposed revisions included those to reduce impediments to IRB approval for multisite protocols. Although the changes discussed did not specifically address regulatory-defined “vulnerable” populations such as pregnant women, it was noted that regulations for these populations will likely be affected by changes and will need to be harmonized, as appropriate, with any changes made to the Common Rule.

In summary, there is wide agreement about the need to clarify regulations governing the inclusion of pregnant women and fetuses in clinical research and to increase consistency among IRBs in decision making procedures. More transparency in IRB decision processes concerning pregnancy research is needed. In this regard, surveys of IRBs similar to those conducted for pediatric research would be useful. The NIH should consider the value of adopting a policy of inclusion and a need to justify exclusion for pregnant women similar to the policy adopted for pediatric research.

Recommendation 3: Develop a Pregnancy Research Agenda

A research agenda on pregnancy should address both areas of high clinical need as well as scientific opportunities while at the same time capitalizing on existing resources. Among major elements to be included in such an agenda are: (1) research to promote evidence-based clinical practice; (2) identification of questions that can be addressed with existing data and through ongoing studies; (3) identification of new studies in high scientific impact areas.

Promote Evidence-Based Clinical Practice

Studies of the effects of interventions in pregnancy are clearly a priority to move forward to inform evidence-based clinical practice. It is important to consider including pregnant women in certain ongoing clinical trials addressing interventions for conditions that are not related to pregnancy but that pregnant women suffer from, such as hypertension and asthma.

However, inclusion of pregnant women in such trials has to be planned for reasons of safety and interpretation of expected differences. FDA and NIH encourage researchers to engage in early discussions with appropriate FDA and NIH staff when a trial enrolling pregnant women is considered. The physiologic changes occurring in pregnancy may require greater numbers across gestational ages to clearly identify and define optimal treatment regimens. In addition, there is a need for more trials specific to pregnancy. Although in these trials, exclusion is not a relevant concern, as all participants are pregnant, the size, number, and type of these trials need to be augmented.

Capitalize on Existing Studies and Resources

Opportunistic study designs such as pharmacokinetic studies and pregnancy registries, which collect data on dosing and pregnancy outcome, respectively, are encouraged when appropriate. In these types of studies, enrolling pregnant women who are already using the medication of interest, that is, have already been prescribed the drug for therapeutic purposes by their physician, obviates the need to begin a medication in the research setting. (Healthcare providers and patients can access a list of available pregnancy registries at the FDA's Office of Women's Health website[6].) Furthermore, with little or no additional risk to the pregnant woman or her fetus and without changes to the regulatory environment, a wealth of data may also be available from ongoing studies that include cohorts of pregnant women. Input from clinical and health services researchers, ethicists and policymakers is needed to identify and prioritize existing studies that may be readily mined or adapted to address questions of importance to pregnant women and their health concerns.

Pregnancy Research: New Opportunities

Currently, the majority of research on pregnancy confines itself to issues of the pregnancy and extends to early neurodevelopmental outcomes of the child. Although these areas continue to be highly important, a new paradigm is emerging that views pregnancy in terms of its implications for later health and seeks to understand the longer term effects of treatment or non-treatment of illness during pregnancy on later maternal and child health and even the health of offspring as adults.

Pregnancy may unmask chronic disease; pregnancy outcomes may predict future disease; and pregnancy may provide an opportunity to identify health risks and disease. Normal changes in pregnancy present a picture of a “metabolic syndrome”, with insulin resistance, hyperlipidemia, increased coagulation factors, upregulation of the inflammatory cascade and increased white blood cells. Most women tolerate these changes with no problems but others develop diseases such as gestational diabetes and thromboembolisms.

Severe preeclampsia leading to preterm birth is a major cause of maternal and fetal morbidity and mortality. Recent epidemiological findings have challenged a long-held view that preeclampsia is inconsequential for later health (Ray, Vermeulen, Schull, Redelmeier, 2005). Rather it is now recognized as an early indicator of a woman's risk for later vascular disease --hypertension, myocardial infarction, stroke, and renal disease. Pregnancy is a metabolic and vascular `stress test' for women and those who `fail' are at increased risk of long-term cardiovascular complications. The risk is highest among women who develop both maternal (e.g., hypertension and proteinuria) and fetal (e.g., intrauterine growth restriction) manifestations of abnormal placentation, especially with preterm delivery. Translational research should continue to increase fundamental understanding of the mechanisms linking pathological syndromes of pregnancy to later disease and to provide new therapeutic and preventive targets.

[6] http://www.fda.gov/scienceresearch/specialtopics/womenshealthresearch/ucm134848.htm

Furthermore, it is hypothesized that, in response to intrauterine stresses, the fetus makes adaptations that persist into postnatal life. These changes include epigenetic modifications of gene expression. Prenatal programming of the epigenome is viewed as a critical determinant of offspring outcome and stands at the interface between environment and genetics. Maternal experiences such as stress and obesity are associated with a host of neurodevelopmental and metabolic diseases, some of which have been characterized into the second and third generations. The mechanism through which determinants such as maternal diet or stress contribute to disease development in the child likely involves a complex interaction between the maternal environment, placental changes, and epigenetic programming of the embryo. Changes in epigenetic programming provide the developmental link between prenatal risk exposure and later outcomes (De Boo & Harding, 2006). A small number of studies have identified heritable epigenetic effects of environmental perturbations on offspring that may provide a mechanism for explaining trans-generational influences (Anway et al., 2005; Crews et al., 2007).

Moving into the Future with Pregnancy Research

A 2011 review of the policy implications of the NIH Agenda for Women's Health research noted that women's health research is at a scientific turning point for the 21st Century with the incorporation of new scientific approaches and technologies into the agenda. However, women's health research must also address important clinical care and public health issues (Wood, Blehar & Mauery, 2011).

Despite substantial progress over the past two decades in increasing the inclusion of minorities and children in clinical research, pregnant women remain highly under-served in this regard. Due to the complexity of issues raised by efforts to increase their inclusion, a multidisciplinary collaborative approach is required, consisting of scientists, ethicists, clinician researchers, clinicians and pregnant women themselves as advocates for their health interests.

There is a clear and compelling rationale for increased pregnancy research in order to address the pressing therapeutic needs of pregnant women. Additionally, there is accumulating evidence that pregnancy provides a unique window into understanding fundamental mechanisms underlying observed links between a pregnant woman's health and her later health and the health of her children. While pregnancy research raises myriad complex issues and challenges, its clinical value and its potential for generating new scientific knowledge about lifespan and intergenerational development demand that the challenges be met.

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Table 1

The Current Wording of §46.204 Subpart B

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 resulted 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.