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SPECIAL ARTICLE

Research Ethics in Obstetrics and Gynecology

Suthee Panichkul, M.D.,*.

** Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok 10400, Thailand*

ABSTRACT

Women should be presumed eligible to participate in obstetrics and gynecology studies. The potential for pregnancy should not automatically exclude a woman from participating in a study although the use of contraception may be required to participate. A significant concern in moving forward with enrolling pregnant women in research is that an intervention could cause harm to the fetus, and especially that the intervention or medication under study could cause a birth defect or other harms. Researchers and research ethics committees must ensure that potential research participants are adequately informed about the risks to breastfeeding women and their infants, and about the risks to pregnant women (including future fertility), their pregnancies and their fetuses. When evidence concerning risks is unknown or conflicting, this must be disclosed to the pregnant or breastfeeding woman as part of the informed consent process.

Keywords: pregnancy, research ethics, informed consent, fetus

Correspondence to: *Suthee Panichkul, M.D., Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok 10400, Thailand, Email address: sthpanich@hotmail.com*

Research Ethics in Obstetrics and Gynecology

Women must be included in health-related research unless a good scientific reason justifies their exclusion. Women have been excluded from much health-related research because of their child-bearing potential. As women have distinctive physiologies and health needs, they merit special consideration by researchers and research ethics committees. Only the informed consent of the woman herself should be required for her research participation. Since some societies lack respect for women's autonomy, in no case must the permission of another person replace the requirement of individual informed consent by the woman[1].

Guidelines for women who participate in clinical research[2]

1. Participation in clinical trials for women of reproductive age requires the capability of women to make their own choices, free of coercion, about healthcare as well as access to family planning.

2. Women of reproductive age are capable of making decisions about risks of potential teratogenicity as part of the decision-making around whether to participate in a clinical trial, and should be given their

choice. Even in the setting of no access to contraception or abortion, a woman's right to consider the risks of a clinical trial, in terms of teratogenicity and her own reproductive capacity, should belong with the woman.

3. Requirements to "prove" infertility with multiple pregnancy tests or proof through pathologic confirmation of hysterectomy or oophorectomy can raise psychological and practical barriers that discourage and can psychologically harm potential research subjects.

4. Consent to participate must always be the autonomous, informed choice of women of reproductive age.

5. A key benefit of inclusion is identifying potentially harmful side effects in a carefully controlled trial setting rather than after marketing and use where more women stand to be harmed before untoward side effects have been identified. Women have an equal right to the benefits (and harms) of research and to the knowledge gained that will inform better dosing and drug information after market entry.

Vulnerability of women

Despite the current general presumption that favors the inclusion of women in research, in many societies women remain socially vulnerable in the conducting of research. For example, they may suffer negligence or harm because of their submission to authority, their hesitancy or inability to ask questions and a cultural tendency to deny or tolerate pain and suffering[3]. When women in these situations are potential participants in research, researchers, sponsors and ethics committees must take special care in the research design, assessment of risks and benefits as well as the process of informed consent, to ensure that women have the necessary time and appropriate environment to make decisions based on information provided to them[4, 5].

When the research involves household surveys or interviews, researchers must take special care to ensure that the women are interviewed in a private place without the possibility of intrusion by other family members. In such studies, women must be given the option of conducting the interview in a setting of their choosing outside the home. Breach of confidentiality in these types of research could result in serious harms to women, even when the only information disclosed is their participation in the research. In studies involving women who have experienced gender-based violence, participation in interviews may cause emotional distress. Researchers must be prepared with referrals for psychological counselling if the need arises[1, 5].

Research involving pregnant women

Women of child-bearing potential must be informed in advance of the possibility of risks to the fetus should they become pregnant during their research participation. When participation in research might be hazardous to a fetus or a woman when she becomes pregnant, sponsors and researchers must guarantee access to pregnancy tests, effective contraceptive methods before and during the research and to a safe and legal abortion[6].

Research involving pregnant women presents specific scientific, ethical and legal complexities. The physiology of pregnancy changes dramatically across weeks, months and trimesters with complex feedback loops within and among the maternal body, placenta and fetus. Although trade-offs between maternal and fetal risks and benefits can introduce difficult challenges in study design, these are not in themselves a reason to exclude pregnant women. Several factors must be considered before pregnant women are excluded, including whether extrapolated knowledge from trials with pregnant animals and nonpregnant humans is available; whether the study offers the potential for direct benefit to the woman, her fetus or both and whether risks of inclusion already have been clearly established and minimized[6, 7].

A significant concern in moving forward with enrolling pregnant women in research is that an intervention could cause harm to the fetus, and especially that the intervention or medication under study could cause a birth defect or other harms. Although a cognitive bias exists toward considering the risks of intervention, including the risk of inclusion in research, a risk associated with failing to intervene and

exclusion from research also exists. Pursuit of zero risk to the fetus may come at a cost to the woman and the fetus and sets a standard that is not expected from parents enrolling infants and children in research. Maternal and fetal risks are deeply interconnected, and consideration of enrolling pregnant women in research requires balancing the risk of fetal harm with the potential for benefit and the importance of the information to be gained concerning the health of women and fetuses. Women of reproductive age have been directly excluded from research due to the concern of a potential of pregnancy in this age; indirectly by creating high barriers to inclusion with serial pregnancy testing and contraceptive requirements; and by cultural and legal barriers that preclude women of reproductive age from making decisions about their care including participating in clinical trials[6]. The consequences of this are significant as they result in drugs being used in populations where they have not been tested in, increasing the rate of drug reaction or failure as well as preventing access to new drugs that might prove lifesaving[7]. The arguments of fetal protection that exclude women of reproductive age question a woman's ability to make reasoned choices about fertility while on a clinical trial, reducing her rights to make choices about health care, reproduction and participation in clinical trials[7].

The inclusion of pregnant women in clinical research can be justified based on the reasons listed below.

1) The prospect of direct and indirect benefit to fetus

2) The imposition of no more than minimal risk for studies involving no prospect of benefit to fetus

3) A reasonable ratio of maternal benefit to fetal risk Tradeoffs between the fetus and the future child risk should be responsive to potential participants' values.

Although women of child-bearing age must be given the opportunity to participate in research, they must be informed that the research could include risks to the fetus when they become pregnant during the research. Access to a pregnancy test, to effective contraceptive methods and to a safe and legal abortion must be guaranteed before exposure to a potential teratogenic or mutagenic intervention[8-10]. When effective contraception and safe abortion are unavailable and alternative study sites are not feasible, the informed consent discussion must include information about the risk of unintended pregnancy, the legal grounds for abortion and information about reducing harms from unsafe abortion and subsequent complications. Also, when the pregnancy is not terminated, participants must be guaranteed a medical follow-up for their own health and that of the infant and child[10-12].

Regarding women who become pregnant during research, many biomedical protocols call for terminating the participation of women who become pregnant during the research. In cases where a drug or biological product is known to be mutagenic or teratogenic[13, 14], pregnant women must be removed from the study, and followed up and provided care through the duration of their pregnancy and delivery. Access to diagnostic tests must be provided to reveal any fetal anomalies. When anomalies are detected, women who wish may be referred for an abortion. When no evidence is found on the basis of which a potential harm to the fetus can be assumed, women who become pregnant should not automatically be removed from the study, but must be offered the option to continue or end their participation. For instance, in some cases it may be appropriate for a woman to stay in the study for safety monitoring but removed from the study drug. When the woman opts for continued participation, researchers and sponsors must offer adequate monitoring and support[1, 15].

Pregnant and breastfeeding women[1, 16]

Pregnant and breastfeeding women have distinctive physiologies and health needs. Research designed to obtain knowledge relevant to the health needs of the pregnant and breastfeeding woman must be promoted. Research among pregnant women must be initiated only after careful consideration of the best available relevant data.

For research interventions or procedures having

the potential to benefit either pregnant or breastfeeding women or their fetus or infant, risks must be minimized and outweighed by the prospect of potential individual benefit. For research interventions or procedures that have no potential individual benefits for pregnant and breastfeeding women:

1) the risks must be minimized and no more than minimal; and

2) the purpose of the research must be to obtain knowledge relevant to the particular health needs of pregnant or breastfeeding women or their fetuses or infants.

When the social value of the research for pregnant or breastfeeding women or their fetus or infant is compelling, and the research cannot be conducted among nonpregnant or nonbreastfeeding women, a research ethics committee may permit a minor increase above minimal risk[17, 18].

Short term and long term follow-up of the fetus and the child may be required in research involving pregnant and breastfeeding women depending upon the study intervention and its potential risks. As a general rule, health-related research involving pregnant women that has the potential to harm the fetus should be conducted only in settings where women can be guaranteed access to a safe, timely and legal abortion in the event that participation in the research makes the pregnancy unwanted[19].

Informed consent and risks and potential individual benefits

Researchers and research ethics committees must ensure that potential research participants are adequately informed about the risks to breastfeeding women and their infants, and about the risks to pregnant women (including future fertility), their pregnancies, their fetuses and their future offspring. Information must also include steps taken to maximize potential individual benefits and minimize risks[20, 21]. When evidence concerning risks is unknown or conflicting, this must be disclosed to the pregnant or breastfeeding woman as part of the informed consent process. She must be the one to make the final decision about the acceptability of these risks to her and her fetus or infant[22-25]. Women must also be informed the difficulty involved in determining causality in cases of fetal or infant abnormalities. Pregnant women may be recruited for research in which no prospect of potential individual benefit is available to them or the fetus only when the risks of the intervention are minimal. The involvement of pregnant women in research is complicated by the fact that it may present risks and potential individual benefits to the fetus as well as to the woman. Participation of breastfeeding women in biomedical research may similarly pose risks to the nursing infant. Research in pregnant and breastfeeding women must be initiated only after careful consideration of the best available data from preclinical research in pregnant animal models, research in nonpregnant women, retrospective observational studies and pregnancy registries[26-28].

In communities or societies where cultural beliefs accord more importance to the fetus than to the woman's life or health, women may feel constrained to participate or not to participate, in research. Special safeguards must be established to prevent undue inducement to pregnant women to participate in research in which interventions hold out the prospect of potential individual benefit to the fetus but not to the woman herself[26].

Patient perceptions of clinical research in pregnancy

The requirement for paternal consent in research with pregnant women does not mirror the requirement for dual-parent consent for research with children. Although fetal safety most commonly is seen as a reason to exclude pregnant women from research, this experience also speaks to the need to include pregnant women in research. Anything beyond a minimal risk; however, must be weighed carefully against the potential benefits to the woman and fetus when the advisability of participation is considered[28].

Although pregnancy is a time for caution when considering research trials, it also represents the only opportunity to study interventions aimed at treating pregnant women. For example, trials aimed at

determining appropriate tocolysis to prevent preterm birth or interventions to treat gestational diabetes can be conducted only during pregnancy. In addition, research during the process of labor and delivery is vital to improving care for women and their newborns. The fact that a pregnant woman is entering labor or in labor does not preclude her from consenting to participate in research[23]. A pregnant woman in labor may be able to undergo the appropriate informed consent process for research, similar to individuals with conditions that may have parallel connotations to labor, including life-threatening, emotionally distressing or emergency situation, e.g., appendicitis, cancer diagnosis and myocardial infarction[24].

Nonpregnancy-related interventions that may benefit a woman during pregnancy

A significant proportion of pregnant women undergo therapies aimed at managing nonobstetric medical conditions. Studies have estimated that more than 60% of pregnant women use at least one prescription medication during their pregnancies. Most of these medications have not specifically been studied during pregnancy. The unknown risk status of the vast majority of FDA-approved medications puts fetuses at risk[19]. Had these drugs been studied in pregnancy early in their use, data on risk may have provided an opportunity to better balance the risks and benefits of their use. Because pregnancies are increasingly occurring among older women and those with complex medical problems, the use of prescription medications by pregnant women is likewise increasing. Physicians who care for pregnant women with complex medical problems, and the pregnant women themselves, are faced with making health care decisions based on insufficient clinical evidence in an era when evidence-based medicine is standard practice[18, 19].

The challenge of caring for pregnant women on the basis of insufficient evidence is similar to treating children before reforms in responsible pediatric research. In 1994, the NIH publicly recognized a need for increased research in the pediatric population because of a significant gap in knowledge regarding safe and effective treatments[21]. Guidance required the default inclusion of children in clinical, social and behavioral research unless the investigator produced a cogent reason for their exclusion. As a result, current therapeutic information exists for some, though certainly not all, medications with respect to pediatric dosing, safety, and pharmacology[27, 28].

Broad exclusion of pregnant women from research trials actually may place fetuses at risk because of a resulting lack of applicable knowledge regarding how best to treat pregnant women with concomitant medical conditions. However, inclusion of a token number of pregnant women in a study would not provide sufficient meaningful information regarding the maternal and fetal effects of the intervention. Alternatively, requiring inclusion of an adequate number of pregnant women to meet power requirements for the primary outcome (or to exclude uncommon fetal morbidities) could raise prohibitive obstacles to research. Thus, thoughtful, responsible study design aimed at appropriate inclusion of pregnant women in research trials, when possible, while maintaining fetal safety as a key corollary consideration, is an important goal[25, 29].

Conclusion

All women, regardless of race, ethnicity, sexual orientation or socio-economic status, should be presumed eligible to participate in research studies. The potential for pregnancy should not automatically exclude a woman from participating in a study although the use of contraception may be required to participate. Including women in research studies is necessary for valid inferences about health and disease in women. The generalization of results from trials conducted among men may yield erroneous conclusions that fail to account for the biologic differences between men and women. Although many improvements have occurred since the time of systematic exclusion of women from research trials, more work needs to be completed concerning the design of research trials so that they do not inappropriately constrain the reproductive choices of study participants or unnecessarily exclude pregnant women. Importantly, researchers and funding organizations must recognize

the ways in which fertility, in the context of research trials, has been managed historically in a manner that is not evidence-based and is overly burdensome for female participants in research and that they make the necessary changes to remedy this situation.

Potential conflicts of interest

The author declare no conflict of interest.

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