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MOMS, Moms, and Their Babies

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No circumstance presents a greater challenge to the formulation of rules for ethical conduct of research than that posed by the relationship between the mother and fetus. The ethical challenge implicit in this relationship was recognized and addressed by a charge from Congress to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Belmont Committee) to "conduct an investigation and study of the nature and extent of research involving living fetuses, the purpose for which research was undertaken, and alternative means for achieving such purposes."[1] Upon completion of their deliberations, the Commission issued the report "Research on the Fetus" in 1975. Even the choice of title reflects the difficulty in approaching this relationship as the titles for later publications about special populations used the words "Research involving" children or prisoners rather than the words "Research on" as in the 1975 report. The Belmont Report led to formulation of a special category of rules for the conduct of research in this population of potential subjects as defined in the Code of Federal Regulations (CFR) Title 45, Part 46, subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research.

The federal regulations for conducting research in the pregnant woman provide the legally acceptable framework for research in this population, but the actual studies in this population are limited in number and are inadequate to provide much of the information needed to provide informed care. Indeed, most studies exclude pregnant women and require removing subjects who become pregnant from further interventions if enrolled in a research study. Much of the reticence to pursue research in these patients probably stems from previous disasters in medical treatment such as those encountered with fetal thalidomide exposure and the resulting birth defects or fetal exposure to DES (diethylstilbestrol, the first synthetic form of estrogen) and late risks for cancer in female offspring.

Those attempting to follow good clinical practices or teach evidence-based medicine suffer from the challenges faced in conducting research in this special population and there are those who argue that for much of the medical care in this population of patients "our evidence base for current treatments is so weak that standard practice is itself more like experiment than treatment."[2] In a *New England Journal of Medicine* "Perspective" article, Goldkind et al noted the H1N1 influenza pandemic that disproportionately affected pregnant women probably because of underdosing vaccine in the absence of clinical trials in this population as an example of the problems encountered by the lack of research in pregnant women.[3] Citing their work at the US Food and Drug Administration, Goldkind and colleagues discuss several other examples of inadequate or inappropriate medical care resulting from lack of understanding basic pharmacokinetics in pregnant women that point out the seriousness of the problem. Their examples support the importance of including more pregnant women and their fetuses in clinical trials. Such trials must proceed with a clear understanding of the ethical concerns and the ethics of planning clinical trials in pregnant women must be well established.

Recently, Ochsner has embarked on providing innovative fetal therapy based on the results of an unprecedented study of fetal surgery for myelomeningocele. The plan for therapy follows the results of the Management of Myelomeningocele Study (MOMS) trial that reports the results of a cooperative national effort to definitively provide an answer to the question of whether fetal surgery is superior to conventional postnatal surgical intervention for repair of myelomeningocele.[4] This study was planned after a small group of subjects appeared to respond well to fetal intervention. Rather than adopting this procedure before definitive data were available to support the

safety and effectiveness of the intervention, potential providers of fetal intervention met and agreed to refer all potential candidates for intervention to 1 of 3 centers. The study was conducted as a randomized trial with all prenatal and postnatal surgery subjects planned for cesarean section at 37 weeks' gestation at the enrolling institution. Subjects assigned to the postnatal repair arm of the study were repaired by the same team that performed the prenatal repairs. Subsequent decisions for shunts to palliate hydrocephalus (one of the complications of this disease) were made by a core group of neurosurgeons blinded to the prior management. Physical, developmental, and neurological evaluations were performed at 12 and 30 months of age. The study demonstrated superior results in selected primary and secondary endpoints as well as increased risks for some negative outcomes in the fetal surgery arm. In fact, the study was terminated earlier than planned when interim analysis demonstrated the superiority of the prenatal surgical intervention.

The MOMS trial has been cited by many as a model of a well-designed and ethically appropriate study in the pregnant subject that demonstrates superiority utilizing a profoundly different approach to a congenital defect. It is unlikely that the evidence to support or reject this course of treatment would have been demonstrated without exposing a much larger group of subjects to potential risk were a less carefully considered approach adopted. This trial should serve as a focal point for defining the elements of ethically sound clinical trials in this very special population of subjects.

Recognition that pregnant subjects present an ethically challenging population because of the sometimes conflicted interests of the mother and the fetus does not exclude these patients from the expectation of medical management based on the evidence necessary to provide good clinical care. Extending care to provide medical benefit only to the fetus as exemplified by repair of myelomeningocele in the MOMS trial at the risk of harm to the mother exposed many questions that deserve critical evaluation not only for performing the research but also for extending the research to provide sound medical care for these patients. The discourse surrounding this study has focused on defining the moral status of the fetus, the rights of the mother to control her body, the potential obligation of the mother to subject herself to significant risk for potential fetal benefit, and even to exploration of the definition of *benefit* as it pertains to the complex relationship between mother, fetus, and the child that the fetus will become.

The MOMS trial demonstrates the utility of fetal intervention and will hopefully be one of many studies for evaluation of fetal therapy. The argument that the studies be performed in an ethical fashion is at least as important as the argument to provide well-designed studies to answer critical clinical questions. Accessible models to fulfill both of these needs must be developed to encourage ethical care of the pregnant patient and her developing child.

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