The National Institutes of Health Workshop on Fetal Treatment
Needs Assessment and Future Directions

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The National Institute of Child Health and Human Development and Office of Rare Diseases convened a multidisciplinary group of experts on August 16–17, 2004, for a workshop entitled “Fetal Treatment: Needs Assessment and Future Directions.” The purpose of the workshop was to develop a plan for the surgical, obstetric, neonatal, and maternal–fetal fields for the evaluation and dissemination of maternal–fetal surgical innovations and to further the scientific evaluation of maternal–fetal surgery. This article highlights the discussions and outlines recommendations for the future. An overarching recommendation was for the formation of a cooperative group of investigators and clinicians to help set a national agenda for research and clinical progress, as well as emphasize ethical issues.

Prenatal diagnosis of fetal conditions creates increasing hope that effective treatment options are or will be available. At a rapid pace over the past 25 years, prenatal interventions have been developed, investigated experimentally, and offered with increasing frequency to pregnant women. The field of prenatal intervention will grow not only because of increased demand by patients, but also owing to advances in biotechnology resulting in improved diagnostic procedures, safer and more precise surgical instruments, and better methods of drug delivery. Ten years ago, many of the interventions that are generally accepted now—such as open hysterotomy and minimally invasive surgical ap-

ROLE OF ANIMAL STUDIES BEFORE HUMAN INTERVENTION

The history of fetal therapy is deeply rooted in animal experimentation, including evaluating natural history, instrumentation, and hypothesis testing for various diseases, before the original interventions in humans (see box: “Goals for Preclinical Animal Experimentation”). While acknowledging the importance of the compassionate treatment of animals,
GOALS FOR PRECLINICAL ANIMAL EXPERIMENTATION

- Study animal models of fetal pathophysiology and natural history of the untreated condition to evaluate correlates in the human fetus
- Establish the feasibility of proposed fetal intervention
- Define optimal technique and treatment parameters
- Evaluate safety for mother and fetus
- Determine efficacy of proposed treatment
- Study and improve techniques and instrumentation
- Assess long-term outcomes
- Trouble shoot unexpected and adverse clinical outcomes
- Enable multidisciplinary teams the opportunity to work together on innovative procedures

The role of an animal laboratory for clinical fetal treatment centers was less clear. If the technical skills needed for the treatment offered are not routinely acquired during the course of routine practice and are not possessed by an otherwise skilled clinician, it is reasonable to practice first in the animal model. For example, if a clinician is skilled at cordocentesis for diagnostic purposes, it is probably not necessary for her or him to practice the technique of intrauterine intravascular transfusion in the animal. On the other hand, even though it is also a needle placement procedure, it would be recommended for someone to practice intracardiac balloon dilation of stenotic valves in an animal before first human application. Thus, only a fetal treatment center that is developing novel therapies that require new skills or techniques not normally possessed by practitioners or that use treatments not used ex utero would need an animal laboratory.

CLINICAL TRIALS: LESSONS LEARNED

Lessons learned from fetal therapy clinical trials include optimization of protocol development and standardization, problems with recruitment of patients into the trials, fiscal considerations, evolution of the techniques, and the definition of a successful intervention (see box: “Maternal–Fetal Therapy Trials: Key Design Elements”).

The relative paucity of eligible patients for fetal therapy mandates centralization of care to provide the critical expertise in management. Surgical randomized trials are difficult, not only because of some characteristics of surgeons that mitigate against conformity, but also because each patient’s anatomy, physiology, and intraoperative course is unique. Evaluation of a novel therapy requires cooperation of these sites with standardized protocols. It is critical that the surgical, perioperative, and postnatal management be standardized as much as possible. Furthermore, it is ideal if the intervention is not offered outside the trial, which can confuse patients as to what is effective therapy and which removes a selection bias of patients. In the ongoing Management of Myelomeningocele Study trial (MOMS), there is a self-imposed moratorium on performance of in utero repair outside the trial, at the MOMS and at all other American centers. This has been beneficial given the pretrial enthusiasm for the in utero repair by some patients, obstetricians, and fetal therapists without demonstrable benefit, and the issue of nonrandomization for families who wish to have the fetal therapy has been avoided. Other key design elements recommended are shown in the box “Maternal–Fetal Therapy Trials: Key Design Elements”.

Perhaps owing to the rarity of these patients, a common problem with trials is slow enrollment. This can be further compounded when the therapy is offered outside the trial.

Referral of patients into a fetal therapy trial requires that the fetal disorder be diagnosed and that the patient’s doctor be aware of ongoing studies. The front-line medical practitioners (obstetricians, midwives, family practitioners) who are seeing these patients need continual reminders of the trials and require easy referral access.

Studies and trials of fetal intervention are expensive owing to a number of factors. To standardize as many components of the trial and obtain high quality data, it is ideal for patients to be treated and delivered at the same site that incurs the cost of travel and housing. The need for central treatment results in travel for many patients and results in issues with third-party payers over “out of network” co-pay rates and refusal to pay for “routine” care in the course of a research study. Furthermore, if federally funded, it is important that the participants be inclusive of all potentially eligible subjects, regardless of insurance status. Because of the multidisciplinary nature of fetal therapy, costs are shared among many departments. To participate in
a fetal therapy trial, all potentially at-risk departments must agree to bear any noncovered costs.

The field of fetal therapy is continually evolving, and ongoing trials face the problem of evolving techniques and instrumentation while trying to maintain and follow a standard protocol. The congenital diaphragmatic hernia trial illustrates well the issues with technology development. Originally conceived as a tracheal clipping study, it became possible to achieve tracheal occlusion by transesophageal balloon placement after the study had started. Alterations in the technique often result in interruption in enrollment, need for retraining, and determination of how to compare outcomes from the 2 different methods.

Determination of what defines a successful procedure is often difficult in maternal–fetal interventions and may be different for the mother and the fetus. Fetal treatment protocols are designed to improve the health of the fetus and, in the majority of cases, that of the mother as well. Whether one considers maternal outcomes in terms of procedural risk or success may be semantic, but it is critical that maternal health outcomes after maternal–fetal therapy be studied. Is success for the fetus simply survival, discharge from the nursery for a child with an otherwise lethal disorder, or an intact survivor? For instance, subtle neurologic damage can produce deficits in executive function that may not be demonstrable until a child is at least 9 years of age and certainly constitute a significant outcome.
FETAL THERAPY STUDY DESIGN AND RESEARCH PRIORITIES

- What is the best way to obtain safe access to the fetus?
- How will treatments of the future be delivered?
- What is the best way to prevent complications involving the fetal membranes and to treat them when they do occur?
- What are the effects on the fetus of maternal drug therapy used in the perioperative period, such as anesthetics, tocolytics, and antibiotics?
- What is the nature and the extent of the placental/fetal blood/fetal brain barrier and how can that be used to protect the fetus or conversely overcome to allow for in utero treatment of fetal brain disorders?
- What is the best way to prevent premature birth?
- What is the natural history of targeted fetal diseases?
- What are the societal implications of fetal therapy, especially with respect to the continuum of prevention of fetal disease through to the issue of eugenics?
- How should maternal and paternal consent best be obtained before undertaking fetal treatment?
- What is the impact of fetal treatment on maternal physical, reproductive, and mental health and how can the risk of negative health consequences be managed?
- What is the best way to achieve and maintain optimal fetal positioning during in utero surgery?
- How long should pediatric patients be followed after fetal intervention? What type of neonatal/pediatric outcome data should be collected? Who (ie, what type of specialists) should be involved in assessment of pediatric outcome?
- What are the effects of resuscitative efforts on the fetus, including the use of maternally or fetally administered vasopressors and fluids and chest compression?

CORE MISSIONS OF THE COOPERATIVE FETAL THERAPY GROUP

- Protect the pregnant woman in clinical and research projects
- Advocate for the fetus in clinical and research projects
- Emphasize the ethical issues in maternal–fetal therapy
- Help set a national research agenda by addressing the following:
  a. When is there sufficient preliminary evidence to support a trial for a particular fetal problem and intervention?
  b. What would be appropriate outcome measures of the trial?
  c. Who should be involved in planning and executing the trial?
  d. When is the research evidence strong enough to support clinical use of a technology or approach?
  e. What are the high priority areas for research in fetal therapy?
- Provide a level of infrastructure for maternal–fetal medicine efforts in the areas of:
  a. Data collection
  b. Education and training for study coordinators
  c. Development and promulgation of guidelines for what constitutes convincing evidence for maternal–fetal therapy
- Provide a level of protection to the centers as research and clinical components would be vetted by group experts

PUBLIC HEALTH IMPLICATIONS AND ETHICAL CHALLENGES OF FETAL THERAPY

The public health implications of fetal treatment research include an ethical obligation for robust support for fetal treatment research so that demand and practice do not surpass scientific data about the benefits and risks of the procedures. Ethical and public health arguments that call for skepticism and restraint regarding fetal treatment research include these: that few patients benefit from the treatments studied because the conditions rarely occur in the general population, fetal research is expensive and risky in view of the limited number of potential beneficiaries, and the inherent inequality between the mother and the fetus in determining the risk-benefit ratio.
Prevent equipoise. Fetal therapy research raises additional important questions including whether treatment is transforming a lethal condition into a chronic, debilitating condition; the impact that fetal therapy has on social concepts and attitudes toward disability; and whether a pregnant woman would be pressured to undergo fetal treatment if the intervention was cost-effective and part of parental duty by the public at large.

The robust support for fetal research stems from the potential impact on the prevention of fetal death and neonatal death and disability; the value placed by society on children and on physical autonomy and intellectual adequacy; the potential to ameliorate fetal disease and decrease morbidity from nonlethal and serious disorders; and the drive to add to knowledge and to understand more basic mechanisms of human development and health. The consequences of not doing research in fetal treatment are enormous and reflect an all-too-common occurrence in the history of innovations in medicine: the lack of adequate evaluation of new interventions before widespread implementation.

INFORMED CONSENT AND HUMAN SUBJECTS PROTECTION

Consent for maternal–fetal surgery and trials requires careful attention to the potential risks and benefits to both the mother and fetus, and federal law requires that researchers obtain the consent of the father of the pregnancy if at all possible. Given the fetal condition with its incipient emotional implications, the consent process is further complicated. This complicated issue is the backbone of research studies and would benefit from research and monitoring of the consent process for maternal–fetal treatment research.

Prospective patients often have gathered information about the condition from a variety of sources, including the World Wide Web, where there is no control over the content. For instance, a Google search on “in utero surgery” resulted in 44,900 hits in October 2004. Importantly, the Web could provide some solutions. For instance, an established Web site with pertinent information could not only assist with standardizing the information about a research trial or a potential treatment, but also be an avenue for disseminating information to doctors, health care plans, hospitals, and counselors to assist with recruitment.

RECOMMENDATIONS

Recommendations for study design and research needs (see box: “Fetal Therapy Study Design and Research Priorities”), covering numerous fetal conditions and diseases that are currently being evaluated or have the potential for intervention, were explored. An overarching recommendation was for the formation of a cooperative group of investigators and clinicians to help set a national agenda for research and clinical progress and emphasize ethical issues. This group would have several core missions (see box: “Core Missions of the Cooperative Fetal Therapy Group”). It was recognized that creation of such a cooperative group would be a challenge given the innovative and entrepreneurial nature of current fetal therapists, but this step is crucial for the benefit of the field. Several models of national cooperative groups exist that might provide a basis for developing the cooperative fetal treatment group. These include the Gynecologic Oncology Group, Children’s Oncology Group, General Clinical Research Centers, Mental Retardation Research Centers, and the Society for Assisted Reproductive Technology. The ability of this group to work with third-party payers to provide coverage for the procedures and to enforce standards it developed for centers would be important features. The role of this group in clinical and/or research trials and the benefits of belonging or the consequences of not belonging to this group would need to be defined. The participants agreed that the protection of maternal health is paramount and that such risks are poorly known. As a result, an initial project of the cooperative group might be to develop a registry of maternal outcomes following in utero treatments.

APPENDIX

Fetal Treatment Workshop Participants

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