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Fetal Treatment 2017: the Evolution of Fetal Therapy Centers:

A joint opinion from the International Fetal Medicine and Surgical Society (IFMSS) and the North American Fetal Therapy Network (NAFTNet)

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Abstract

More than 3 decades ago, a small group of physicians and other practitioners active in what they called “fetal treatment” authored an opinion piece outlining the current status and future challenges anticipated in the field. Many advances in maternal, neonatal, and perinatal care and diagnostic and therapeutic modalities have been made in the intervening years, yet a thoughtful re-assessment of the basic tenets put forth in 1982 has not been published. The present effort will aim to provide a framework for contemporary redefinition of the field of fetal treatment, with brief discussion of the necessary minimum expertise and systems-base for provision of different types of interventions on both a mother and fetus. Our goal will be to present an opinion that encourages the advancement of thoughtful practice, ensuring that current and future patients have realistic access to centers with a range of fetal therapies with appropriate expertise, experience, subspecialty and institutional support while remaining focused on excellence in care, collaborative scientific discovery, and maternal autonomy and safety.

In 1982, practitioners from a dozen institutions in five countries gathered to discuss the emerging field of “fetal therapy”—a new approach to prenatally diagnosed congenital anomalies potentially amenable to intervention before birth— with the goal of changing the natural history of diseases including hydrocephalus, obstructive uropathy, and pulmonary hypoplasia secondary to a congenital diaphragmatic hernia (CDH). Their consensus regarding the state of the art, basic tenets and challenges regarding the science and ethics of interventions which involved two patients in order to benefit the unborn child were published as a short letter in the *New England Journal of Medicine* later that year.[1] Over the last three decades, the field has progressed rapidly[2–4]. Fetal Therapy Centers (FTCs) have developed world-wide as a consequence of advances in prenatal diagnosis, fetal imaging, instrumentation, interventional techniques and expertise. Our understanding of maternal-fetal pathophysiology in a broad range of conditions has also expanded greatly. Examples include ultrasound-guided procedures such as fetal blood sampling or intrauterine transfusion, vesico- or thoraco-amniotic shunt placement[5], cardiac balloon valvuloplasty and stent placement[6], vascular occlusion procedures (bipolar electrocautery, radiofrequency ablation, interstitial laser ablation or thrombogenic coil injection) for complex monochorionic twin pregnancies, hydropic lung lesions or sacrococcygeal teratomas (SCTs), and prenatal stem cell transplantation[7]. Fetoscopic techniques have been developed for laser treatment of twin-twin transfusion syndrome (TTTS)[8] and tracheal balloon occlusion for congenital diaphragmatic hernia (CDH)[9], ultrasound-guided fetal delivery of mesenchymal stem cells[7], and open fetal surgical techniques

predominantly for myelomeningocele[10] and also for some congenital pulmonary airway malformations (CPAMs) or SCTs have been refined. Finally, ex-utero intrapartum treatment (EXIT) has been developed for the delivery of neonates with major obstructive airway anomalies.[11–13]

Despite these advances, the basic tenets (Table 1) applied to fetal treatment have not been re-evaluated in a scientific forum, although some, e.g. placental laser ablation for monochorionic twin pregnancies with TTTS, have departed from the original dictum that “only singletons should be considered as candidates for fetal therapy”. As both diagnostic and surgical techniques have evolved, we have begun to reconsider the role of fetal therapy in conditions that were hitherto under a moratorium e.g. fetal aqueductal stenosis. As the focus of fetal therapy has shifted from not just enabling the survival of a neonate with an otherwise lethal condition to improving its quality of life (e.g. fetal myelomeningocele repair), concerns have arisen regarding the practice of *fetal* medicine in the context of a *maternal* intervention. In 2011, a joint statement of the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics[14, 15] discussed many issues in this emerging field, emphasizing the principles of maternal autonomy, careful assessment of the risk-benefit relationship, advocacy for both mother and fetus in the context of research and innovation, avoidance of unintentional coercion,[16] and the need for collaborative models and centers of excellence. In essence, fetal therapy presents challenges to observing the ethical principles of justice, non-maleficence, and beneficence. As the inherent duality of the maternal-fetal dyad potentially puts optimizing fetal outcome in conflict with what is best for maternal health, Fetal Therapy Centers (FTCs) have an ethical obligation to carefully consider both maternal and fetal wellbeing when *any* form of *in-utero* intervention is being contemplated. Thus, 34 years after the basic tenets of fetal treatment were first published, it is evident that a new approach should be defined that takes into account the numerous advances in the field, the shift in the ethical paradigm of fetal intervention to include the reduction not only of mortality but also of significant morbidity, and the clear obligations that all health care providers have in caring for both the mother and her fetus.[1] In response, members of both the North American Fetal Therapy Network (NAFTNet) and the International fetal Medicine and Surgical Society (IFMSS) have convened to produce the present statement.

Setting Expectations in the Current Era

With all technologies there are two distinct evolutionary phases. First a “development,” phase in which a small number of investigators – usually but not necessarily at academic medical centers -pioneers a new approach, evaluates complications and refines techniques, tests, possibly patents, and publishes their findings. Over time, the technology is recognized, and clinical demand increases beyond the capability of the originators to reasonably perform all cases or tests. At that point, there is a “diffusion” phase as the technology expands to multiple locations to give increasing numbers of patients the benefits of new approach. During this phase utilization rapidly expands, but is often paralleled by a corresponding increase in procedure-related complications. Eventually, experience expands and performance improves across the board. There is a complicated balance between the pioneers’ interests in ensuring the success of new approaches and the potential benefits to

patients, while at the same time not being overly protective or exclusionary in controlling “trade” in an open market.

Several fetal interventions that were once innovative (including those for TTTS, myelomeningocele and CDH) have been evaluated in randomized clinical trials,[8–10, 17] whereas others (balloon valvuloplasty for fetal critical aortic stenosis, intrauterine stem cell therapy for osteogenesis imperfecta) are currently either undergoing trials or are being included in registries. These successes make it probable that as technology advances, the field of fetal therapy may evolve at a pace that outstrips our ability to anticipate or initiate regulation in the field. As practitioners, we must take the initiative to set standards of care for the performance of all fetal procedures in order to achieve the most favorable outcomes, ensure maternal and fetal safety, minimize complications, and provide appropriate resources for their management if complications occur. In addition to proposing a modification to the original philosophical and systems principles (Table 1), we maintain that there should be expectations for the resources, expertise, credentialing, and infrastructure for an organization, medical staff, and personnel who work in a FTC (Table 2). Additionally, since many fetal diseases represent medically and ethically complex situations, we strongly advocate the development of multidisciplinary therapy teams as appropriate.

Scope and Definitions Pertaining to Fetal Treatment

Our proposed modification assumes that all prenatal interventions should be in compliance with the basic principles of fetal therapy (Table 1). Within this scope, fetal therapy can be divided into medical or surgical approaches that aim to achieve a complete prenatal cure, alleviate severe pediatric developmental or functional deficiencies, or optimize the fetal transition to extrauterine life. Fetal interventions are classified broadly to include the following: 1) ultrasound-guided needle procedures (e.g., fetal blood sampling, intrauterine transfusion, shunts, balloon valvuloplasty, radiofrequency ablation or interstitial laser coagulation); 2) fetoscopic procedures (placental laser ablation for TTTS, umbilical cord occlusion, tracheal balloon occlusion, amniotic band release, laser ablation for lower urinary tract obstruction, myelomeningocele repair); 3) open fetal surgery (myelomeningocele repair or resection of some lung masses or teratomas), and 4) EXIT procedures for management of anomalies compromising the newborn’s airway. Though some overlap may exist in the procedures that are offered for a given condition, in our proposed modification, “open” fetal surgery refers to any procedure requiring a hysterotomy in contrast to those involving only the insertion of a fetoscope.

A FTC is more difficult to define, but it should at a minimum be able to provide advanced imaging services, a variety of established fetal therapies and innovative approaches to fetal disease, and possibly conduct, facilitate or participate in research if appropriate to the setting within its particular healthcare delivery system. A FTC may be either a freestanding self-contained center or may draw on expertise and resources from physically separate facilities to provide consultation or therapy and to manage any fetal or maternal complications (including pregnancy termination if this is an option) that may result from the fetal condition or the therapy. It may be more logical to consider the necessary components in the context of

diseases that are treated and services that are provided (Table 2), with a pragmatic approach to inclusion of components suggested in the context of services provided at any given center.

Research trials, registries, regionalization, and planning for the future

Fetal interventions should be subjected to scientific scrutiny by inclusion in institutional, national, regional, or international trials and registries. Initially, the pioneers in this area recognized the need for transparency in reporting outcomes (Table 1). To some extent this has been realized, albeit sporadically, though efforts have largely focused on disease-specific clinical trials or registries. To date, randomized controlled trials for laser therapy for TTTS, open repair of fetal myelomeningocele, early treatment for acardiac twins and tracheal occlusion for fetal CDH have been completed or are underway, and registries exist for fetal cardiac interventions[6], post-trial myelomeningocele repair[18] and fetal monochorionic twin complications and interventions. However, many fetal procedures are not being evaluated rigorously and none of the registries are public or funded beyond their initial startup costs. One attempt to address this need is being made within the North American Fetal Therapy Network (NAFTNet), a consortium of over 30 medical centers in the United States and Canada, which collaborate on research in fetal diseases. Reporting a center's clinical experience is a prerequisite for membership and funding is through institutional membership dues.

To assure both access to care for patients and an adequate patient volume to maintain expertise for practitioners and teams, more attention needs to be focused on resource planning, publication, dissemination and quality benchmarking of outcomes and complications, public reporting, and the larger context of facilitating patient access to appropriate care. There is evidence to support the regionalization of subspecialty care in other areas of medicine,[19–22]. In certain types of fetal therapy (e.g. laser for TTTS and intrauterine transfusion for red blood cell alloimmunization), the benefits of regionalization of care and concentration of volume have been clearly demonstrated[13, 23–25] but in others, support comes from expert opinion only.[26] In fact, it is equally clear that mere volume and/or individual experience does not guarantee excellence in clinical outcomes when center-based medicine is examined (e.g. the “Bristol experience” in which imposed regionalization of congenital cardiac care actually led to worse outcomes for children in the UK).[27] Nevertheless, it seems reasonable to assume that regionalization of care for rare conditions and procedures would allow centers not only to maintain adequate volume and expertise for the fetal interventions *per se*, but also to develop crucial supportive components of care, such as evaluation, counseling, and education. Eventually formalized training and credentialing programs—similar to those regarding nuchal translucency screening or cervical length screening, for instance—might be a reasonable goal. Although often politically daunting, task forces to develop formal recommendations regarding the number and geographic distribution of fetal therapy centers should be formed to address these issues as well as the overarching issue of patient access to care.

We must also plan to train the next generation of fetal therapists. There is currently no formal international program for training in fetal therapy. Several centers in the United States, Canada, UK and Europe offer non-accredited fetal intervention “fellowships” that

can be entered after completion of formal training in either Pediatric Surgery or Maternal Fetal Medicine. Many physicians then enter into an even less well-defined “apprenticeship” model in which junior faculty are gradually allowed to develop the requisite skill set to operate independently. Systems should be developed that allow for more formalized training in fetal intervention, and minimum standards for proficiency—which will vary with provider role and type of procedure—should be discussed in an open forum with practitioners, training program administrators, and Graduate Medical Education or the equivalent officials. These efforts should begin formally as soon as reasonably feasible. The best framework for this effort and the appropriate participants have not been determined, but a formal dialog among major centers in the Americas, Europe and Asia has already begun.

Importance of Oversight

Centers that perform invasive fetal procedures should report their maternal, fetal and newborn outcomes as transparently as possible, for example under the auspices of clinical trials or in registries. For certain procedures (particularly those still considered as innovative or under research), a non-partisan, objective, multidisciplinary institutional oversight committee is important. Such committees should include individuals not directly involved in clinical care of the patients and could consist of Maternal-Fetal Medicine specialist(s), hospital ethicist, pediatric surgeon(s), neonatologist(s), medical staff office chief of staff, and other members as necessary, including patients themselves. These committees may sometimes also serve as reviewing bodies for the purposes of institutional or ethical review board pre-submission review for research proposals or clinical trials.

Summary of Recommendations

Rapid evolution in the field of fetal therapy has led to the need to revise the initial guiding principles set forth by Harrison *et al.* more than three decades ago. Fetal Therapy Centers are ethically obliged to consider both maternal and fetal wellbeing and complications when *any* fetal intervention is being considered. Centers are also obliged to ensure that appropriate training, credentialing, infrastructure, institutional support and oversight are in place. A core organizational structure and expertise level will be essential for all fetal therapeutic procedures and for maternal care. Additional infrastructure and subspecialty availability will be necessary for others. Rather than hindering innovation, appropriate and thoughtful preparation and requirements for infrastructural support and commitment should encourage advancement of the field in the decades to come. In all settings, mechanisms for the provision of training, regulation and oversight should be developed. Multidisciplinary, collaborative, and multi-institutional experience sharing in the form of registries and collaborative multicenter prospective research are essential to continue moving this field forward. As the field matures the development of robust and sustainable training programs will be essential for continual development of fetal therapy. The most appropriate and reasonable balance between safe innovation, development of new high-quality centers, acquisition and maintenance of skills, and realistic patient access to care within or even outside of highly specialized centers must be carefully considered.

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Condensation

A conceptual framework is presented for re-defining the field of fetal treatment, including necessary expertise and systems-base for provision of interventions involving mother and fetus.

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Table 1

Criteria for the Advancement of Fetal Therapy: 1982* versus the present era

Topic	Historical viewpoint	Current era considerations
Nature of the Disorder	The disorder must be of a significant nature and should be a simple structural defect that interferes with organ development, whose alleviation might allow fetal development to proceed normally.	As the spectrum of conditions for which fetal therapy is offered and the goals of therapy have evolved, goals of fetal treatment may begin to alter (e.g. MMC, OI, cardiac procedures) or to cure (TTTS). In some cases there may be benefit one fetus with no benefit to the other (e.g. RFA or laser in complicated MC twin or triplet pregnancies)
Reporting Requirements	All case material should be reported, regardless of outcome, to a fetal-treatment registry or in the medical literature (or both).	Several self-imposed registry efforts are underway but mandatory reporting is not in effect; clinical trials are suffering geographic and regulatory barriers. Infrastructure for reporting largely lacks funding and resources except on a voluntary basis.
Appropriateness criteria	The fetus should be a singleton without concomitant anomalies according to advanced ultrasonographic examination and amniocentesis for karyotype, alpha-feto protein (AFP) and cultures.	Effective therapies for multiple pregnancies with or without an “innocent bystander” (e.g., TTTS, selective reduction of an anomalous twin) may be considered if therapy will prolong and/or improve outcome of that pregnancy. Prenatal genetic screening and diagnosis have evolved exponentially. Current options include diagnostic chromosomal microarray analysis (CMA) and screening via non-invasive prenatal testing (NIPT) for common aneuploidies. The significance of abnormal testing in this context is unclear. The introduction of whole exome sequencing (WES) into clinical practice will undoubtedly further complicate this issue. There may also be genetic conditions such as osteogenesis imperfecta (OI) and some hemoglobinopathies that would benefit from novel stem cell therapies.
Candidate diseases	Selection for treatment must be based on careful clinical evaluation and sound knowledge of the natural history of the fetal disease; intervention can be ethically justified only if there is a reasonable probability of benefit.	Improvements in prenatal diagnosis have improved our ability to diagnose fetal conditions. Our understanding of fetal physiology and pathophysiology has advanced considerably. Predictive measures of morbidity and mortality are being developed to help providers weigh the risks and benefits for the mother and her fetus. These have guided the types of fetal therapy presently offered. Long-term follow-up studies are lacking for most fetal therapies. Animal models do not adequately reflect the human fetal phenotype for many diseases, and extrapolation from animal models must be done with caution.
Center infrastructure	There should be access to a Level III high-risk obstetric unit, and bioethical and psychosocial counseling.	Levels of care for the newborn and for the pregnant woman have been refined and redefined,[26] and the need for a more complex, structured support system has been specifically stated.[14, 15]
Checks and balances	A multidisciplinary team, including a perinatal obstetrician experienced in fetal diagnosis and intrauterine transfusion, an ultrasonographer experienced in the diagnosis of fetal anomalies, and a pediatric surgeon and neonatologist who will manage the infant after birth, should concur on the plan for innovative treatment and obtain approval of an institutional review board.	Multidisciplinary teams should be tailored to the defect(s) being treated, and will usually include a variety of disciplines. These are likely to include some or all of: qualified maternal-fetal medicine specialist(s), geneticists, pediatric surgical specialists, obstetric anesthesiologists, and diagnostic and nursing/midwifery services. An appropriate mechanism for informed consent and oversight with a formal process for reporting and review must be in place. Educational and quality improvement infrastructure is preferable. Ethical oversight, participation in registries and transparent counseling and reporting are crucial for centers proposing experimental or innovative procedures that pose <i>any</i> risk to the mother. Parents must be counseled regarding any alternative therapies and the options of pregnancy termination and neonatal palliative care where appropriate
Goals of treatment	The family should be fully counseled about risks and benefits and should agree to treatment, including long-term follow-up to determine efficacy.	There is increasing focus on short- and long- term effects of fetal therapy on maternal reproductive health. Issues are becoming increasingly complex as the goals of fetal treatment move from primarily achieving survival, to decreasing morbidity and improving the functional and neurodevelopmental outcome of the child.
Maternal safety and autonomy	<i>Implied but not stated:</i> Maternal risks should be minor and acceptable to mother and family.	Maternal expectations have evolved. In contrast to 30 years ago, pregnant women now expect fetal abnormalities to be diagnosed prenatally, and they also expect that for some abnormalities the option for fetal treatment (where available and evidence-based) will be available. As fetal therapy has become more available, uptake has become greater. In addition, some are willing to incur greater personal risk in an effort to improve the prognosis for their fetus. Care must be taken to avoid the pitfalls in perception —just because a procedure is

Topic	Historical viewpoint	Current era considerations
		offered within or outside a research protocol does not imply proven efficacy.

* (Harrison MR, et.al. Fetal Treatment, N Engl J Med 1982;307:1651-2)

abbreviations: AFP, alpha fetoprotein; MMC, myelomeningocele; OI, osteogenesis imperfecta; TTTS, twin-twin transfusion syndrome; RFA, radiofrequency ablation

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Table 2

Necessary Components for the Provision of Fetal Care in the Current Era

Component	Function	Facility where services are rendered
Prenatal diagnostic and management services, including fetal ultrasound and magnetic resonance imaging (MRI) and MFM expertise	Accurate diagnosis of fetal condition Prenatal interventions Co-ordination of prenatal care path	Prenatal imaging center (Fetal Therapy center or contracted)
Obstetric services including Nursing/Midwifery	Management of maternal and obstetric conditions including pregnancy termination	Operating Room Inpatient & Outpatient Services Labor & Delivery
Nurse Coordinators	Care Coordination, Resource (for patients and providers), Education	Inpatient & Outpatient
Obstetric Anesthesia	Maternal management during obstetric or fetal interventions	Operating Room Labor & Delivery
Genetics	Accurate diagnosis of fetal condition Incorporation of additional testing Counseling regarding long-term implications of genetic disease	Inpatient & Outpatient Services, institutional or under contract
Neonatology, including Nursing	Prenatal consultation Peri-partum and post-delivery care ECMO services	Intensive Care Nursery
Pediatric Surgery	Prenatal consultation, prenatal interventional and Post-delivery management	Operating Room, Inpatient & Outpatient Services
Pediatric Anesthesia	Fetal / Neonatal management during surgical interventions	Operating Room
Pediatric Cardiology (invasive and non-invasive imaging)	Prenatal diagnosis, post-partum management fetal hemodynamic monitoring during complex procedures	Inpatient & Outpatient Services
Pediatrics, including Subspecialists and Nursing	Prenatal consultation Post-delivery management Long term developmental follow-up	Inpatient & Outpatient Services
Adult Medicine and Critical Care	Consultation, Assumption of maternal care for select complications of pregnancy or treatment	Fetal Therapy center in close proximity (if the center is in a Children's Hospital)
Social Work and Spiritual Support	Coordination of social services Patient advocacy Perinatal loss support and support for pregnancy termination	Inpatient & Outpatient Services, available to patient and family/support persons
Interpreter and cultural diversity specialist	Consultation, consent, follow-up services especially when multiple therapeutic options are being entertained	Inpatient & Outpatient Services, available to patient and family/support persons
Palliative Care	Palliative post-delivery care, perinatal hospice services	Various settings including hospital and home
Medical Ethicist	Consultation and oversight as needed, for research and clinical arenas	Institutional or centralized
Institutional Review Board	Oversight of experimental and research related interventions	Institutional or centralized
GMP facility	Production of GMP-grade stem cells for fetal intravenous infusion	Prenatal imaging center (Fetal Therapy center or contracted)
Database and Information Technology Support services	Reporting, data collection and sharing, research and quality improvement arenas	Institutional

Abbreviations: ECMO, extracorporeal membrane oxygenation; GMP, Good Manufacturing Practices