



Preface
Maternal-Fetal Surgery



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Guest Editor

Maternal-fetal surgery is, by design, inherently innovative. When those whose work has been integral to the development of this budding subspecialty are questioned about their motivation, the reply is invariably the same: at a critical point in their career, they observed a progressively worsening malformation that, if discovered in a newborn, would be readily treatable. Because the anomaly was diagnosed in a fetus remote from term, however, their hands were tied. All they could do was watch helplessly as the malformation worsened with agonizing certainty until the mother finally delivered a baby far too injured to rehabilitate successfully. The anguished frustration resulting from such a traumatic experience often leads to the determined declaration, “This is treatable!”

At this crucial point, however, the newly energized clinician confronts the awful realization that the early, easily recognizable, predictably progressive malformation is not treatable. Not now. Not yet. There are no reliable techniques to approach the problem. Even if the concepts were clear, there are no tools for accomplishing the goal. This is the moment of truth when the idealistic clinician must be transformed into a focused researcher.

Years of work follow. Ideas evolve, with scenarios deconstructed and reconstructed among equally dedicated colleagues. The literature is scoured for any piece of information that might fit into the growing riddle. Inspiration often comes at unexpected times and from seemingly unrelated sources—a presentation at a routine conference, a little-noticed journal article. Suddenly, the solution appears. Animal models are developed, hypotheses are strengthened, and all the experimental work is fruitful. Everything is falling into place.

Eventually, the limits of laboratory and animal models must be admitted. At some point, the only way forward is a human experiment. The carefully designed

and meticulously tested procedure must be performed in a human pregnancy, on a living human fetus. In the transition from a laboratory enterprise to a clinical therapy, new systems must be developed. Social workers, ethicists, ministers, nurses, and administrators must be drawn into the preparation to deal with real human conditions, to relieve real human suffering. The successful research collaboration must be transformed into a coherent, supportive clinical team.

Some of the carefully developed procedures yield immediate success, but many more do not. Unanticipated complications occur, and the limitations of the laboratory and animal models become stunningly obvious, as patients experience preterm labor (the “Achilles’ heel” of maternal-fetal surgery), amniorrhexis, bleeding, uterine scar dehiscence, and unforeseen neonatal morbidity resulting from the incompletely understood sequelae of prenatal intervention. Institutional tensions mar relationships and foster misunderstanding, collegiality vaporizes, and clinical teams not sufficiently mature to weather the maelstrom of accusations and fingerpointing may succumb to smothering layers of institutional oversight and regulation. Such is the history of maternal-fetal surgery.

Yet some programs survive, some procedures show early promise, and with perseverance, insight, and the ability to improve with every setback, some interventions evolve to the point that a clinical trial becomes mandatory. In the history of maternal-fetal surgery, the 1960s and 1970s comprised the age of discovery. During this time, brilliant and visionary individuals laid the foundation for future researchers. The 1980s and 1990s comprised the age of innovation, when scientifically and socially responsible collaborative interdisciplinary teams developed ever more sophisticated procedures to treat congenital malformations, at the same time reducing maternal morbidity and improving neonatal outcomes. Now, we are in the midst of the time of trials.

Congenital diaphragmatic hernia, the undisputed queen of attempted maternal-fetal interventions, from which have grown the bulk of our current arsenal of fetal intraoperative physiology, operative techniques, and equipment, is still under investigation. After two human trials using historical controls, Michael Harrison and the Fetal Therapy group at the University of California–San Francisco embarked on the first prospective randomized trial in the history of maternal-fetal surgery. While that trial has been temporarily suspended for interim review, a European consortium led by Kypros Nicolaides in London and Jan Deprest in Belgium has embarked on a pilot study based largely on the lessons learned from the American experience of almost 25 years. A similar randomized trial, under the auspices of Eurofetus, is widely expected in the near future. Dr. Harrison summarizes our current state of knowledge of this disorder in this issue.

Lower urinary tract obstruction, the very first congenital anomaly successfully treated prenatally, is attracting greater attention as a result of disappointing long-term outcomes. This condition is detailed by Nick Fisk and his colleagues at Queen Charlotte’s Hospital, London, in this issue. The National Institutes of Health in the United States is calling for new research into the etiology and treatment of this anomaly, especially the disappointing bladder function often associated with prenatal therapy.

More than 250 cases of intrauterine repair of spina bifida have now been performed at eight centers worldwide, almost all in the United States. Promising short-term outcomes, especially an apparent reduction in the need for neonatal shunting for hydrocephalus, substantial risks associated with almost universal preterm delivery after prenatal therapy, and the lack of long-term outcome data have prompted the first multi-institutional prospective randomized trial of open uterine maternal-fetal surgery in the United States. Scott Adzick of Children's Hospital of Philadelphia, Michael Harrison of the University of California–San Francisco, and I, coordinated by the data monitoring center at George Washington University in Washington, DC, and led by the renowned statistician Elizabeth Thom, are collaborating in the Management of Myelomeningocele Study (MOMS) Trial, which is funded by the National Institute of Child Health and Human Development. Further information is available from the excellent website www.spinabifidamoms.com, or from the study patient coordinator, Dr. Catherine Shaer, at 1-866-ASK-MOMS. Noel Tulipan, Pediatric Neurosurgeon at Vanderbilt, discusses the current status of this therapy in this issue.

Fetal valvuloplasty, attempted mainly in Europe for the past 15 years with limited success, achieved a breakthrough in the past year with a promising handful of successful cases at Boston Children's Hospital and several other centers in the United Kingdom. Wayne Tworetzky of Harvard Medical School reveals the rationale for prenatal intervention in a variety of restrictive fetal cardiac lesions, as well as insights gained through recent experience, in his brilliant article. A multicenter trial is widely anticipated as experience at a growing number of centers increases.

Fetal gastroschisis is rarely lethal but is commonly morbid for affected newborns. Dominique Luton in Paris has almost singlehandedly transformed the prenatal conceptual approach to this common congenital anomaly. His findings are detailed, for the first time, in this issue. A multinational prospective randomized trial of his proposed therapy, amniotic fluid exchange in the third trimester, is currently underway. Interested collaborators can obtain more information by accessing the Fetal Diagnosis & Therapy Web site at Vanderbilt University: www.fetalsurgeons.com.

Few complications of multiple gestation have been more controversial than the twin–twin transfusion syndrome (TTTS). During the 1990s, therapeutic camps allied with amnioreduction, based largely on the work of John Elliott in Phoenix, and laser photocoagulation of communicating placental vessels, pioneered by Julian DeLia, currently in Milwaukee, became so polarized that publication of pertinent research was problematic because of hostile reviewers. In the midst of this gridlock, the Eurofetus consortium, led by Yves Ville in Paris and Jan Deprest in Leuven, Belgium, courageously launched a prospective randomized trial of amnioreduction versus laser photocoagulation of communicating placental vessels for TTTS. Within just the past few months, the Eurofetus trial was halted by the principal investigators after an interim analysis demonstrated survival rates roughly double in the laser therapy group, and morbidity among survivors about half that of those treated with amnioreduction. In the United States, two trials are currently

underway. Ruben Quintero in Tampa, who revolutionized our current concepts of TTTS by means of a clinical staging system that can be used to more accurately compare treatment and outcomes of TTTS, is spearheading an international study of advanced cases (stages III and IV) using a novel statistical tool known as quasirandomization. His provocative and timely analysis of the current status of the diagnosis and treatment of TTTS is presented in this issue. Further information about his study can be obtained by contacting the Florida Institute for Fetal Diagnosis and Therapy at www.fetalmd.com or by calling 1-888-FETAL-77. A second prospective randomized trial of amnioreduction versus endoscopic laser therapy, the TTTS Trial, is funded by the National Institute of Child Health and Human Development. Participating laser centers are Children's Hospital of Philadelphia (CHOP), led by Tim Crombleholme, and the University of California–San Francisco, headed by the sagacious Michael Harrison. Additional information is available at www.chop.edu or 1-800-IN-UTERO.

Maternal-fetal surgery for treatment of progressive congenital anomalies has evolved dramatically since the pioneering fetal transfusions performed by Liley and Adamsons. Today, the number of anomalies potentially treatable prenatally is growing annually. Initially limited to intervention for only severe life-threatening complications, fetal treatment is now most commonly performed to improve the quality of life for fetuses with nonlethal malformations. The field has now matured to the point that we are privileged to witness an equally dynamic era, with a growing number of trials designed to compare prenatal therapy with conventional, usually postnatal treatment. This is truly the time of trials for maternal-fetal surgery. But what of the future?

For those with sufficient vision, the future of maternal-fetal surgery lies in the development of a new subspecialty of Fetal Diagnosis and Therapy, incorporating researchers and clinicians from the fields of genetics, ultrasound, radiology, perinatology, neonatology, pediatric surgery, pediatric neurosurgery, pediatric urology, pediatric cardiology, anesthesia, and gynecologic endoscopy in a bold enterprise to carry prenatal therapy into the next age of a well-defined discipline of dedicated fetal surgeons devoted to improving the lives of fetuses with congenital malformations.

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