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Hanmin Lee

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**Drugs of Choice for Sedation and Analgesia in the Neonatal ICU** **215**

R. Whit Hall and Rolla M. Shbarou

Painful procedures in the neonatal ICU are common, undertreated, and lead to adverse consequences. The drugs most commonly used to treat neonatal pain include the opiates, benzodiazepines, barbiturates, ketamine, propofol, acetaminophen, and local and topical anesthetics. This article discusses the indications for and advantages and disadvantages of the commonly used analgesic drugs. Guidance and references for drugs and dosing for specific neonatal procedures are provided.

## Fetal Surgery

### Overview

**A History of Fetal Surgery** **227**

Tim Jancelewicz and Michael R. Harrison

Over the past 3 decades, fetal surgery for congenital disease has evolved from merely a fanciful concept to a medical field in its own right. Techniques for open hysterotomy, minimal-access hysteroscopy, and image-guided percutaneous fetal access have become well established, first in animal models and subsequently in humans. At the same time, major advances in fetal imaging and diagnosis, anesthesia, and tocolysis have allowed fetal intervention to become a vital tool for subsets of patients who would otherwise endure significant morbidity and mortality. This article offers a concise overview of the history of fetal surgery, from its tumultuous early days to its current status as an important means for the early treatment of potentially devastating congenital anomalies.

**Ethics of Fetal Surgery** **237**

Frank A. Chervenak and Laurence B. McCullough

This article provides a comprehensive approach to the ethics of clinical investigation of fetal surgery. Investigators should address the initiation and assessment of clinical trials to determine whether they establish a standard of care and use an appropriate informed consent process to recruit and enroll subjects, consider whether selection criteria should include the abortion preferences of the pregnant woman, and consider whether

physicians have an obligation to offer referral to such investigation. This approach is comprehensive because it takes account of the physician's obligations to the fetal patient, the pregnant woman, and future fetal and pregnant patients. The comprehensive approach to the ethics of fetal surgery is applied to the example of in utero surgical management of spina bifida.

### **The Maternal Side of Maternal–Fetal Surgery**

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Danny Wu and Robert H. Ball

The term fetal surgery is used widely for fetal intervention during pregnancy; maternal–fetal surgery may be more appropriate, because all these invasive procedures also affect the mother. Although there is no direct benefit to the mother from these procedures, the risk to her is for a purely altruistic purpose. It is therefore important to understand the potential complications of maternal–fetal surgery, so the physician can provide accurate counseling to the patient.

## ***Imaging***

### **The Use of Ultrasound in Fetal Surgery**

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Linda M. Hopkins and Vickie A. Feldstein

Obstetric ultrasound (US) is an integral part of fetal surgery for open and minimally invasive techniques. With advances in US imaging, the ability to refine diagnosis, predict prognosis, and contribute to fetal treatment continues to grow. Current research in fetal diagnosis and treatment includes identifying the most reliable sonographic features for determining prognosis before and after surgery.

### **MRI of the Fetal Central Nervous System and Body**

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Orit A. Glenn and Fergus V. Coakley

MRI is being increasingly used to assess for fetal abnormalities. Although significant progress in the field of fetal MRI has occurred during the past 20 years, continued technical advances will likely contribute to significant growth of the field. Moreover, with continued hardware and software improvements, additional MRI sequences will likely become available. Prenatal MRI complements ultrasound because of larger field-of-view, superior soft tissue contrast, easier and more precise volumetric measurement, and greater accuracy in the demonstration of intracranial and spinal abnormalities. While ultrasound remains the primary modality for fetal imaging, these advantages of MRI make it a valuable adjunct to fetal surgery. Because fetal MRI involves many disciplines, the future of fetal MR will best be achieved through collaborative efforts.

**The Role of Fetal Echocardiography in Fetal Intervention: A Symbiotic Relationship** 301

Priya Sekar and Lisa K. Hornberger

In this review, the authors explore the role of noninvasive and invasive fetal interventions in fetal cardiovascular disease guided by observations at fetal echocardiography. They first review fetal cardiac lesions that may be ameliorated by fetal intervention and then review noncardiac fetal pathologic findings for which fetal echocardiography can provide important insight into the pathophysiology and aid in patient selection for and timing of intervention and postintervention surveillance.

***Specific Diseases***

**Changing Perspectives on the Perinatal Management of Isolated Congenital Diaphragmatic Hernia in Europe** 329

Jan A. Deprest, Eduardo Gratacos, Kypros Nicolaides, Elise Done, Tim Van Mieghem, Leonardo Gucciardo, Filip Claus, Anne Debeer, Karel Allegaert, Irwin Reiss, and Dick Tibboel

Congenital diaphragmatic hernia (CDH) should be diagnosed in the prenatal period and prompt referral to a tertiary referral center for imaging, genetic testing, and multidisciplinary counseling. Individual prediction of prognosis is based on the absence of additional anomalies, lung size, and liver herniation. In severe cases, a prenatal endotracheal balloon procedure is currently being offered at specialized centers. Fetal intervention is now also offered to milder cases within a trial, hypothesizing that this may reduce the occurrence of bronchopulmonary dysplasia in survivors. Postnatal management has been standardized by European high-volume centers for the purpose of this and other trials.

**Tracheal Occlusion for Fetal Congenital Diaphragmatic Hernia: The US Experience** 349

Eric Jelin and Hanmin Lee

Congenital diaphragmatic hernia (CDH) is characterized by a defect in the diaphragm that permits abdominal viscera to herniate into the chest. These herniated viscera are thought to compress the growing lung and cause lung parenchymal and vascular hypoplasia. The genetic defects that cause the diaphragmatic defect may also contribute primarily to lung hypoplasia. Postnatal reduction of the herniated abdominal viscera and correction of the diaphragmatic defect are easily achievable, but the lung hypoplasia persists, often leading to persistent fetal circulation and respiratory failure. This article reviews the experimental basis of fetal therapy for CDH and the US clinical experience with tracheal occlusion.

**Management of Fetal Lung Lesions**

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N. Scott Adzick

Prenatal diagnosis provides insight into the in utero evolution of fetal thoracic lesions such as congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS), congenital lobar emphysema, and mediastinal teratoma. Serial sonographic study of fetuses with thoracic lesions has helped define the natural history of these lesions, determine the pathophysiologic features that affect clinical outcome, and formulate management based on prognosis.

**Fetal Lower Urinary Tract Obstruction**

377

Serena Wu and Mark Paul Johnson

The authors present an overview of the prenatal diagnosis, evaluation, contemporary intervention, and antenatal management of lower urinary tract obstruction. They review early experimental models that confirmed the relation between urinary tract obstruction and renal fibrocystic dysplasia and that early in utero relief of the obstruction could prevent irreversible renal injury. Subsequent studies of the electrolyte and protein concentrations in fetal urine from human cases established prognostic threshold values and helped to develop an algorithm to select candidates for antenatal therapy. Although shunting has improved survival, long-term morbidities remain a significant challenge.

**Twin-to-Twin Transfusion Syndrome: A Comprehensive Update**

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Mounira Habli, Foong Yen Lim, and Timothy Crombleholme

Twin-to-twin transfusion syndrome (TTTS) is a serious complication in about 10% to 20% of monozygous twin gestations with an incidence of 4% to 35% in the United States. Severe TTTS is reported to occur in 5.5% to 17.5% of cases. TTTS is a progressive disease in which sudden deteriorations in clinical status can occur, leading to death of a co-twin. Up to 30% of survivors may have abnormal neurodevelopment as a result of the combination of profound antenatal insult and the complications of severe prematurity. This article presents an overview of what is known about the pathophysiology and the diagnosis of TTTS, the role of echocardiography in TTTS, treatment options available for TTTS, complications of treatment for TTTS, and short- and long-term outcomes of TTTS.

**Complicated Monochorionic Twin Pregnancies: Updates in Fetal Diagnosis and Treatment**

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Larry Rand and Hanmin Lee

Monochorionic (MC) twin pregnancies may develop significant complications, and twin-to-twin transfusion syndrome (TTTS) has become among the best known to obstetricians and patients alike. A significant percentage

of patients referred for suspected TTTS have a different underlying pathologic condition, however, and differentiating the subcategories of MC pathophysiologic conditions may change treatment course and outcome. The key to understanding complicated MC pregnancies lies in the placental angioarchitecture and intertwin vascular communications between the fetuses.

**Fetal Surgery for Myelomeningocele** 431

Shinjiro Hirose and Diana L. Farmer

Fetal intervention for myelomeningocele (MMC) may improve hydrocephalus and hindbrain herniation associated with the Arnold-Chiari II malformation and may reduce the need for ventriculoperitoneal shunting. As of now, there is little evidence that prenatal repair of MMC improves neurologic function. MMC is the first nonlethal disease under consideration and study for fetal surgery. As a result, potential improvements in outcome must be balanced with maternal safety and well-being, in addition to that of the unborn patient.

**Cardiac Anomalies in the Fetus** 439

Christopher G.B. Turner, Wayne Tworetzky, Louise E. Wilkins-Haug, and Russell W. Jennings

Congenital heart disease (CHD) is an attractive target for fetal therapy. With the development of successful neonatal repair for many types of CHD over the last 20 years, fetal therapy has become the next frontier. Concurrent advances in interventional catheterization and fetal imaging provided a foundation for the novel field of fetal cardiac intervention. This article focuses on the current status of in utero catheter interventions for CHD with particular interest in therapy for defects characterized by progressive stenosis or atresia of the semilunar valves, the aortic and pulmonary, with development of subsequent ventricular hypoplasia.

***Research/Future Directions***

**Prenatal Stem Cell Transplantation and Gene Therapy** 451

Matthew T. Santore, Jessica L. Roybal, and Alan W. Flake

At the present time, the most likely and eminent application of stem cell therapy to the fetus is in utero hematopoietic stem cell transplantation (IUHCT), and this stem cell type will be discussed as a paradigm for all prenatal stem cell therapy. The authors feel that the most likely initial application of IUHCT will use adult HSC derived from bone marrow (BM) or peripheral blood (PB), and will focus this article on this specific approach. The article also reviews the experimental data that support the capacity of IUHCT to induce donor-specific tolerance.

**Fetal Tissue Engineering****473**

Christopher G.B. Turner and Dario O. Fauza

Attempts at harnessing the prospective benefits of the therapeutic use of fetal cells or tissues date many decades before the modern era of transplantation. The first reported transplantation of human fetal tissue took place in 1922. Fetal cells or tissues also have been used as helpful investigational tools since the 1930s. Still, it was only in the last three decades that fetal tissue transplantation in people has started to lead to favorable outcomes, yet by and large anecdotally. This article offers an outlook on a relatively new dimension in fetal cell-based therapies, namely the engineering of tissues in the laboratory, along with its prospective applications.

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