Friday, March 8, 2002

8:30 - 11:00 am

PHARMACO - POLITICS

Moderator: Peter J. Davis, MD

Clinical Trials: Are Clinicians Getting the Information They Want?

Mark S. Schreiner, MD

How Have Pediatric Clinical Trials Influenced Practice: Past & Future

Christopher Milne, DVM, MPH, JD

Post-Marketing Drug Safety: Does FDA Approval Provide Guarantees?

Jerrold Lerman, MD

Generic Drugs: Availability and Viability

Clair M. Callan, MD

Questions & Discussion

How Have Pediatric Clinical Trials Influenced Practice: Past & Future

Christopher-Paul Milne, DVM, MPH, JD

Despite the fact that many of the improvements in drug regulation resulted from overhauls prompted by notable drug disasters occurring mainly in children, by the 1960s children had essentially become therapeutic orphans. At that time, drug manufacturers were required to either study drugs in children or put disclaimers on the label that discouraged their use in children. The circumstances militating against the conduct of pediatric clinical trials were considerable: little incentive for drug sponsors; ethical, product liability and medical malpractice concerns; the hardship of enrolling pediatric patients; and the difficulties with drug administration and patient compliance. Little change occurred until the 1990s when a new push spearheaded by advocates for pediatric drug testing incorporated the Better Pharmaceuticals For Children Act as the pediatric studies provision of the FDA Modernization Act (FDAMA). In November of 1997, FDAMA was signed into law, ushering in a whole new era for pediatric clinical trials. The FDAMA pediatric studies incentive program grants drug companies an additional 6-month period of market exclusivity (i.e., a patent extension or similar form of protection from competition) for all new or marketed drugs with the same active ingredient in exchange for conducting pediatric studies on the drug named in the written request issued by FDA. Within 4 years of its passage, a pediatric research infrastructure has been built that now encompasses 50,000 pediatric participants and 5,000 researchers and conducts 3 times the number of pediatric clinical trials as were conducted before the FDAMA era.

The impacts for pediatric patient care, both during clinical trials and in the general population are manifold. Safety information is available early on in the development of pediatric indications for drugs as extrapolation from adult data and juvenile animal toxicity testing are more uniformly employed. In addition, more information will become available after marketing of the drug begins as long-term follow-up becomes part of the approval process through post-marketing commitments. Some written requests call for long-term follow-up for as long as 10 years for a host of effects covering hormonal, psycho-social, physical and endocrinologic maturation. Pediatric studies are also contributing to better evidence-based medicine, not only because over 70 diseases and conditions are being studied for causal (i.e., pharmacokinetic/pharmacodynamic studies) or confirmatory (adequate and well-controlled clinical trials) evidence, but also because new evaluative tools are being developed to assess outcomes with greater accuracy and objectivity. Survey data collected by Tufts University's Center for the Study of Drug Development (Tufts CSDD) indicated that 20% of sponsors had developed new clinical assessment tools. Also, therapeutic areas with a sparse evidence base are being explored. A review by Tufts CSDD of all new drug applications approved from 1991-1996 for which pediatric trials had been conducted showed that 45% were anti-infectives, while only 16% were CNS and cardiovascular drugs. Now one-quarter of the written requests issued by FDA have been in those latter therapeutic areas. There have been notable successes in other therapeutic categories as well – such as anesthesiology and analgesia –

of the 40 or so drugs listed by FDA as priority drugs for pediatric studies in these therapeutic areas, 25% have already been the subject of written requests by FDA. Tufts CSDD survey data also shows that 20% of pediatric studies have involved the development of new child-friendly formulations. Thus, dozens of new formulations will become available to pediatric practitioners over the next few years, helping to mitigate the challenge of therapy compliance. Lastly, pediatric practitioners are often denied the benefit of prescribing information on drugs available for a number of common diseases, as 28 of the top 50 prescribed medicines have been issued written requests because they lack pediatric studies. As better information and formulations become available, preventable medical errors resulting from two common sources - inappropriate dosing and improper extemporaneous compounding – should decrease for pediatric patients.

Will the nascent pediatric research infrastructure be made of sand or stone? Will pediatric clinical trials become a routine part of drug development? The pediatric studies incentive program is scheduled to sunset in 5 years. While the FDA's mandatory rule for pediatric assessments of new drugs may provides one impetus for maintaining the pediatric research infrastructure, new economic incentives will be necessary. Market factors may help! Underserved markets for pediatric drugs are beginning to garner attention. One reason is that many previously underdiagnosed or undertreated pediatric diseases and conditions – such as SAR, type II diabetes, pain, psychiatric and behavioral disorders, and hypercholesterolemia – are now being addressed. Reimbursement trends also favor the development of a pediatric drug market as MCOs often prefer drugs (especially ones labeled for pediatric use) to other treatment options for pediatric illness, government programs are expanding insurance coverage for children, and disease management programs for chronic juvenile diseases are emerging. However, there are countervailing forces at work – controversy concerning the overmedication of children and concern that the rising cost of drugs is particularly affecting pediatric drugs, for example. Designing ethical but effective pediatric drug trials will continue to be challenging, especially as trials must increasingly move overseas to find sufficient patients in certain therapeutic areas. Circumstances overseas will impact the future of the pediatric research infrastructure in the U.S. in other ways as drug development becomes increasingly international and the market adapts to the needs of a world where nearly half the inhabitants are children.

Suggestions for Further Reading

Institute of Medicine. Report of a workshop: Drug Development and the Pediatric Population. National Academy Press, Washington, DC; 1991

Milne C-P. Pediatric research: coming of age in the new millennium. Am. J. of Therapeutics 1999; 6(5):263-282. (Reprints available from author)

FDA Pediatric web site (including transcripts of ethics subcommittee meetings and link to AAP web site) located at: http://www.fda.gov/cder/pediatric/

Post-Marketing Drug Safety: Does FDA Approval Provide Guarantees?

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Nothing in life is guaranteed with the exception of taxes and death. The FDA is no exception to this truism. When a new drug is identified, extensive tissue and animal studies are undertaken to test the properties of the compound before the drug is administered to humans. Any evidence of a serous untoward response is likely to arrest development of that drug. However, the responses in animals and tissues may not predict the responses to the drug in humans. The most common example of this effect in anaesthesia is perhaps the species differences in upper airway responses to inhalational agents. Although ether anesthetic agents are well-tolerated by animals during inhalational inductions, they are not in humans. Suffice it to say, animals and in vitro tissue testing are not substitutes for research in humans.

Drug development proceeds through Phases 1, II and III until the drug is approved. Several years ago, the FDA and other federal regulatory authorities stipulated that research must be conducted in pediatric, obstetric and geriatric patients if a new drug is to reach the market. This has resulted in a substantial increase in pre-release research in these age groups, thereby providing some evidence of dose requirements, responses and efficacy. However, the numbers of patients in these subspecialty groups that must be enrolled for the drug to be approved may not be large. This holds particularly true if a pediatric indication is not being sought. As a result, 20, 30 or 40 children may be sufficient for approval depending upon the circumstances.

How safe are the drugs that are approved for use in humans? For the most part, these drugs are quite safe. The drugs must be examined for organ toxicity and teratogenicity before proceeding with studies in humans. In fact, drugs that are approved are well tolerated by the majority of patients. And yet, we have witnessed several drugs in the past few years that caused fatal or near-fatal responses in humans. In the case of anesthesia, the most recent example was the introduction of rapacuronium. This agent, which was a rapid onset and offset aminosteroidal compound, resulted in several near-fatal episodes of bronchospasm in infants and children. Using the Pediatric Anaesthesia Conference discussion group as a forum to solicit opinion, George Meakin and I requested that clinicians who have used rapacuronium, convey their experiences with the drug in children. What we received was an avalanche of 19 episodes of severe bronchospastic reactions to rapacuronium. These cases may very well never have been compiled into such a compelling indictment of this drug had it not been for the Internet and the willingness of our colleagues to bring attention to these adverse responses. As a

result of the publication of our series of children and two other case reports, rapacuronium was withdrawn from clinical use last year. This represents the first time an anesthetic agent was withdrawn post-release based on clinical experience presented by clinicians.

Are all drugs safe? NO, they are not. Every drug represents a risk/benefit ratio where we, the clinicians, must weight the risks and benefits when deciding to use a medication. The complication that your patient experienced may not be the sole complication, even though it is not reported in the PDR. It remains our professional responsibility to closely observe our patients and report any adverse event that may be attributed to a drug. Voicing that complication on the internet such as PAC discussion group where a broad range of responses can help direct future action against this drug is key. As well, there are several sites that collect adverse reactions including MedWatch (http://www.fda.gov/medwatch/) that should identify or red-flag adverse events with drugs. This doesn't always happen in a timely manner. But, this remains one subject that clinicians have and now know they can change effectively and efficiently, reshaping the contour of paediatric anesthesia and the care we provide children.

1. MEAKIN GH, PRONSKE EH, **LERMAN J**, ORR R., JOFFE D, SAVAREE AM, LYNN AM. Bronchospasm after rapacuronium in infants and children. Anesthesiology 2001:94(5);926-7
(accompanying editorial)

Pharmaco-Politics
Generic Drugs: Availability and Viability

Clair M. Callan MD, MBA

The objectives of this presentation are to;

- Describe the various considerations that may have an impact on the availability as a drug moves off patent;
- Evaluate whether generic drug shortages are increasing in frequency and any factors that might contribute to that; and to
- Propose a model that would enhance the commercial viability and availability of generic drugs.

A generic drug is one that is identical or bioequivalent (+/- 20%) to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. That sounds pretty clear but there are nuances that result in some differences between a generic and brand name drug that may not always be evident to the prescriber or the dispenser. Generic drugs must be approved by the FDA for marketing. To obtain this approval the following conditions must be met;

The generic must contain the same active ingredient(s) as the brand name although inactive ingredients may vary,

The generic must be identical in strength, dosage form, and route of administration

It must be bioequivalent to the brand name product, although the range of equivalence is relatively broad (+/- 20%) and the test relatively limited.

The generic must meet the same batch requirements for identity, strength, purity and quality and it must be manufactured under the same standards of GMP regulations required for brand name drugs.

All of these criteria are designed to minimize differences between a generic and a brand name product and to guarantee to the clinician that if a lower cost generic is prescribed over a brand name product the clinical outcome will be the same without risk or harm to the patient. However, this is not always the case and there are reports of problems with the use of generics, including lack of efficacy or an increase in side effects when a generic is used. As an example, an evaluation study of outcomes was conducted in which cost containment was practiced by 6HMOs via formulary limitation (12000 patients). The results were interesting. Patients receiving generic drugs had significantly more ER visits and admissions. There was also an increase in total cost of administered drugs (Horn,AJMC)

An important difference between generic drugs and brand name drugs is that generic drugs are never tested for safety/efficacy. This is presumed to exist because they are generic. The most significant testing for the anticipated effect of the drug is for bioequivalence. However, bioequivalence need only be demonstrated within+/-20%; and it is not tested on the final form used to administer the drug. Generics do not have to under go studies of multiple administration or absorption. Several studies have shown

substantial absorption differences between different versions of the same drug (up to 50%. A business decision to alter a formulation to cut costs may have an impact on absorption. But unless there is a major change in the formulation the FDA does not have to be notified until the regular update on the drug is due to the agency.

Manufacturers will develop aggressive strategies to protect their brand name drug, particularly if it generates a lot of income for them as it approaches the limit of its patent life. Generic drugs, although they mean more affordable prescriptions, or lower drug costs for individual departments, are perceived as an economic threat. It is attractive for department chairs or others with budget responsibilities to recommend use of a generic over a brand name drug. On the other hand, drug innovators work hard to try to maintain patent protection for their products. There are several ways of doing this, including dealing directly with a generic manufacturer to prevent market availability. If the first generic manufacturer does not market the drug, no one else can market it for 180 days. Patent lawsuits can tie up a drug's availability for several years. Other options include making some adjustment to the basic drug in an attempt to extend the patent life. When a drug has a large market position manufacturers will strategically plan for patent extensions even before the original drug is approved by the FDA. Other approaches include doing clinical studies to support a new indication for the drug

Drug Shortages occur for a variety of reasons. Short-term back orders can occur either because of a manufacturing glitch, difficulty in getting supplies from vendors or even an increased use of the drug greater than that anticipated by the company. Likewise, long term unavailability can be a result of all of the above causes with little option for a quick resolution. A marketing/business decision by a company can be a factor in long-term unavailability.

Drugs, diagnostics and vaccines have all been involved in recent shortages. Product delays and shortages have increased in frequency and severity in recent years according to both FDA and ASHP. But why is this occurring? Is there a real reason, or is this the result of the industry trying to manipulate the use of certain products for a greater financial return?

A shortage occurs when the supply of an approved product does not meet the current demand. There are several reasons that this can occur.

1. FDA enforcement decisions, such as noncompliance with GMP, may result in the drug being removed from the market. This usually occurs if the FDA is concerned about the safety of the product, or if the company has a history of difficulty with compliance and the FDA is unwilling to put them on probation.
2. Shortages or disruptions in availability of raw or bulk materials to manufacturers of the final product. Some sources come from unusual sites, such as trees in the Amazon. Vendors of raw and bulk materials also have to comply with FDA regulations and may be shut down by the agency for non-compliance. This is a particular problem with single-source suppliers.
3. Individual lot problems. There may be a problem with potency, or stability or even the packaging that can result in product being withdrawn from the market.

If the drug involved is one that has a challenging manufacturing process this could result in long-term unavailability. Labeling issues have caused several drugs to be taken off the market until it can be relabeled.

4. Reallocation of resources by the manufacturer can result in drug shortages. An acquisition of a new company, or a decision to close a plant for any number of reasons, or even a change in management may lead to a shortage of a product.
5. A decision to discontinue marketing for business reasons. Normally adequate notice must be given to the FDA and customers before this decision is implemented. By law manufacturers should notify FDA at least 6 months prior to discontinuing a drug but some circumstances, such as economic hardship, reduces this time requirement and this requirement is not strictly enforced.
6. Pharmaceutical industry consolidation may result in discontinuation of some products.
7. Shifts in the market; e.g. large quantities purchased unexpectedly by one organization such as the military. This can result in unavailability of a drug in other areas.
8. Unexpected increases in demand such as a new off-label use that gets a lot of publicity, or a disease outbreak, even a bioterrorism event.
9. "Just-in-time" inventory management. This method was introduced some years ago as a way of controlling costs. It requires good cooperation between the customer and the supplier to make sure that a shortage does not occur. Winter months can wreak havoc with otherwise well planned inventory management.

Impact of shortages

Significant public health consequences can result if there is a shortage of a drug, not the least of which is compromised patient care. There are increased costs to the health care system as a result of shortages, either because a more costly product has to be used, or a patient doesn't get the drug and becomes increasingly ill. As anesthesiologists you are very aware of the impact drug shortages have had on your ability to provide good quality anesthesia care. Some examples of drug shortages in anesthesia include; Succinylcholine chloride, naloxone, phenobarbital injection and fentanyl. Other recent drug shortages include; Dexamethasone injection, bleomycin/ganciclovir, influenza vaccine, pneumococcal conjugate vaccine and DPT.

Role of Federal Government in drug and Vaccine shortages.

Who is responsible when a drug shortage occurs, or even for preventing a shortage from occurring? The primary responsibility lies with the manufacturer. But the government also has responsibility in this area. The FDA is the primary authority for assisting with shortages. Their goal is to prevent or alleviate shortages of medically necessary drug products. Medically necessary drug products are those that are used to treat/prevent serious disease or medical condition **and** no other alternative is available. Patient inconvenience is an insufficient basis to classify a product as medically necessary. The FDA cannot force a manufacturer to make or market a product and cannot take one manufacturers drug and give it to another.

The CDC also has a role in product shortages. They are primarily involved with vaccine supplies. Their job is to monitor available supplies and coordinate a response to a shortage if one occurs. A good example of this was the flu vaccine shortage that occurred last year. The CDC works with the advisory committee on Immunization Practices. This committee can change recommendations for vaccine use in response to shortages. Last year they changed the recommended dates for administering vaccine to December from October and also recommended patients at risk and health care workers be vaccinated first. All was going well with this plan until Sept. 11th.

Although the Federal Government has responsibilities in responding to shortages or delays in drug availability there are some limitations. The main problem for the agencies seems to be resources. It is a concern that several of the agencies including FDA do not yet have a director since the change in administration. The agency should take a leadership role in addressing the problem of drug, vaccine and diagnostic agent shortages.

The issue of drug shortages was discussed during the Interim meeting of the AMA House of Delegates in December 2001. As a result of House action, the AMA has sent a letter to Secretary Thomson stating that the AMA recommends that DHHS establish a departmental task force to explore the causes of drug, diagnostic agent, and vaccine shortages and maldistribution. This task force should also identify appropriate solutions to such issues as those of liability, reimbursement and availability of products to most vulnerable populations. The task force should include representation from FDA, CDC and AHRQ, and it should get input from the pharmaceutical industry, wholesalers/distributors, physician and pharmacy organizations and consumers. The AMA is also recommending that Secretary Thomson commission studies to identify and recommend solutions for any underlying breakdown in the system that leads to shortages.

What else can be done to prevent/reduce drug shortages? Physicians and other clinicians should realize that they have a role in identifying shortages. Earlier notification of a shortage to the FDA should result in faster action. They can be contacted on line at http://www.fda.gov/cder/drug/shortages. However, adequate resources must be made available to the FDA to address shortages when they occur. These resources should be available on a regular basis and not be "borrowed " when needed. That will only result in a delay in another area. FDA has informed AMA that available resources to address drug and vaccine shortages are limited. Lack of resources will be exacerbated if product shortages increase in frequency and severity.

Expansion of the definition of a "medically necessary" product, to include those that have a significant impact on a physicians' ability to provide quality and timely care should be considered. FDAs decision on "medically necessary" is made primarily to define the internal process by which it will handle the shortage. Physicians can take a proactive role to educate the Agency about the need for other drugs, such as Fentanyl and muscle relaxants. FDA could redefine "medically necessary" so that patients who are suffering (but not in danger of dying) be prioritized and the drug become available. However, expanding this definition will increase the work of the FDA, already short of resources.

Manufacturers, their representatives and the FDA should improve communications about shortages to physicians. Physicians need to know the reason for the shortage, when the product will become available, any alternate sources of the product and or alternative therapies and recommendations for their use. It is the responsibility of the FDA to initiate and coordinate messages about drug shortages.

Possible financial incentives to manufacturers could be considered in some cases to encourage them to market a medically necessary, but unprofitable drug. Some of these incentives already exist. The Orphan Drug and pharmacy associations Act allows manufacturers to get a product approved for a special population with fewer clinical trials. The recent introduction of pediatric studies to extend exclusivity for those manufacturers who conduct clinical trials in the pediatric population. Other incentives need to be considered to stop discontinuation of 'essential' drugs and vaccines that are not profitable.

The AMA members have taken steps to try to address this problem. Specialty societies such as ASA can join in this effort with the hope that the more noise that is made about the issue the greater there is a chance for some improvement. It is unclear if this will contribute to the commercial viability and availability of generic drugs. Adequate, proactive communication from manufacturers to both clinicians and the agencies should help defray some of the annoyance and inconvenience that occurs when a drug is unavailable. Manufacturers need to develop a greater sensitivity to the needs of their customers- clinicians, patients and hospitals.

12:30 - 2:30 pm

FETAL SURGERY

Moderator: Francis X. McGowan, Jr., MD

Evolution and Spectrum of Fetal Interventions
N. Scott Adzick, MD

Anesthesia for Fetal Surgery
Jeffrey L. Galinkin, MD

Designing a Clinical Trial of Fetal Surgery: The Myelomeningocele Saga
Leslie N. Sutton, MD

Questions & Discussion

Antenatal Diagnosis and Fetal Surgery

N. Scott Adzick, M.D.

Most congenital defects of interest to pediatric surgeons can be detected before birth by sonography, and new techniques such as color doppler ultrasound and ultrafast fetal magnetic resonance imaging have enhanced the accuracy of prenatal evaluation.[1] Frequently diagnosed anomalies include an abdominal wall defect (omphalocele, gastroschisis), bowel obstruction, diaphragmatic hernia, lung lesion, obstructive uropathy, neural tube defect, neck mass, sacrococcygeal teratoma and adrenal neuroblastoma. The prenatal detection and serial sonographic study of fetuses with anatomic malformations has permitted delineation of the natural history of these lesions, definition of the pathophysiologic features that affect clinical outcome, and formulation of management based on prognosis. Pediatric surgeons familiar with the management of the lesions before and after birth are involved in management decisions and family counseling along with obstetricians, neonatologists, geneticists, anesthesiologists and other specialists. Most correctable fetal anomalies are best managed by appropriate medical and surgical therapy after planned delivery at term. Prenatal diagnosis may also influence the timing or mode of delivery (cesarian section or vaginal delivery) and, in some cases, may lead to elective termination of the pregnancy. In some life-threatening cases, fetal surgery is available. Fetal surgery required the development of surgical, anesthetic, and tocolytic techniques, demonstration that fetal intervention was safe for the mother and her future reproductive potential, and resolution of ethical issues.[2,3] Fetal surgery is currently offered at a very limited number of highly specialized centers around the world. The indications for fetal intervention as well as long-term follow-up of these interventions are evolving.

The most severely affected fetuses with congenital diaphragmatic hernia have herniation of the liver into the fetal chest as well as sonographic signs of severe pulmonary hypoplasia. The original approach of complete in utero congenital diaphragmatic hernia repair was unsuccessful because acute reduction of the liver from the fetal chest into the abdomen led to compromised umbilical venous flow, resulting in fetal bradycardia and death.[4] More recently, temporary in utero tracheal occlusion (performed open or fetoscopically) can prevent the normal outflow of fetal lung fluid which in turn enhances fetal lung growth.[5,6] Early results suggest a salutary effect on survival, and a randomized clinical trial to test this therapy is planned.

As an outgrowth of the fetal intervention efforts, the concept of ex utero intrapartum therapy was devised to treat fetal airway obstruction due to giant fetal neck masses or intrinsic airway problems.[7] This approach utilizes a planned cesarean section with preservation of the maternal-fetal placental circulation for oxygenation of the fetus. This maneuver provides time for procedures such as direct laryngoscopy, bronchoscopy, endotracheal intubation or tracheostomy to secure the fetal airway, thereby converting an emergent airway crisis into a controlled situation during birth. Once the airway is established, the umbilical cord is divided and the fetus delivered.

Myelomeningocele occurs in about one in every 2,000 live births and can result in severe lifelong physical disabilities including paraplegia, hydrocephalus, incontinence, sexual dysfunction, skeletal deformations, and mental impairment.[8] Myelomeningocele represents the first non-lethal anomaly which has been treated by fetal surgery. Compelling experimental evidence shows that the neurological deficit associated with myelomeningocele is not entirely caused by the primary defect of neurulation, but rather is due to chronic mechanical injury and amniotic-fluid induced chemical trauma that progressively damages the exposed unprotected fetal neural tissue during gestation.[9] Early results indicate that fetal myelomeningocele repair before 25 weeks gestation can salvage neurologic function, reverse the hindbrain herniation of the Arnold-Chiari II malformation, and diminish the need for postnatal ventriculoperitoneal shunt placement.[10-12] Experience is limited and long-term follow-up will be required to assess the durability of the benefits. An NIH-sponsored randomized clinical trial comparing fetal myelomeningocele repair with postnatal myelomeningocele repair is planned involving the teams at the Children's Hospital of Philadelphia, Vanderbilt University, and the University of California, San Francisco.

Some other simple anatomic problems are amenable to repair before birth. Congenital cystic adenomatoid malformation is a benign cystic lung mass. A large fetal lung mass can cause mediastinal shift, hypoplasia of normal lung tissue, polyhydramnios, and cardiovascular compromise leading to fetal hydrops and death. These lesions can be resected in utero if they are predominantly solid or multicystic.[13] Percutaneous thoracoamniotic shunting is effective in the setting of a single large cyst. Sacrococcygeal teratoma is the most common neonatal tumor with an incidence of 1 in 35,000 live births. Some fetuses with large teratomas develop high-output cardiac failure, hydrops and die in utero – a sequence that can be reversed by removing the tumor before birth.[14,15] Fetal urethral obstruction interferes with the development of the fetal kidneys and lungs. The natural history of fetal urinary tract obstruction has been well documented by the sonographic follow-up of untreated cases, and selection criteria for fetal treatment have been developed based on the ability to predict fetal renal function using fetal urine electrolyte levels and the sonographic appearance of the fetal kidney.[16] Although most fetuses do not require fetal intervention, a fetus with bilateral hydronephrosis due to urethral obstruction in whom oligohydramnios develops may benefit from in utero decompression by a catheter shunt placed percutaneously under sonographic guidance.[17]

Minimally invasive or fetoscopic approaches will have an increasing therapeutic role in the future as indications, instrumentation, and techniques are refined.[18] Abnormalities of monochorionic twin pregnancies that may require fetoscopic treatment occur when abnormal placental chorionic vessels connect the circulations of the twins leading to an imbalance of blood flow with consequent changes in amniotic fluid volume, growth retardation and hydrops. For acardiac twin pregnancies, the normal twin has been salvaged by occlusion of the umbilical circulation of the abnormal twin using fetoscopic bipolar coagulation. For twin-twin transfusion syndrome, a fetoscopically directed laser can be used to divide the vessels.[19] An NIH-sponsored multinstitutional randomized clinical trial comparing fetoscopic laser therapy to amnioreduction will begin in 2002.

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Anesthesia for Fetal Surgery

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Fetal surgery is a rapidly growing and evolving area. EXIT procedures, fetoscopic procedures, and midgestation fetal procedures for meningomyelocele and congenital cystic adenomatous malformations of the lung are being done more frequently at more sites today. To parallel the advances in fetal surgery, it is important to advance and disseminate anesthetic management for these procedures.

Fetal surgery is based on years of animal and clinical research. In contrast, anesthesia for fetal surgery is based mainly from clinical experience. The studies that do exist were performed in pregnant sheep with volatile anesthetic agents.[1;2] Current anesthetic techniques for fetal surgery are based on case reports and translation of the pregnant sheep anesthetic responses.[1-5]

Maternal Anesthetic Considerations

Fetal surgery involves the simultaneous treatment of two patients. It is therefore incumbent on the anesthesiologist to monitor and treat both the fetus and the mother. The physiology of the parturient contributes to increased anesthetic risk for both the mother and fetus.

In contrast to obstetric anesthetic practice, general anesthesia is the technique of choice for open fetal surgery. Induction and maintenance of general anesthesia for the parturient has the potential to cause a number of problems. First and foremost is aspiration pneumonitis. Pregnancy decreases lower esophageal sphincter tone, alters the anatomic relationship of the esophagus to the diaphram and stomach, and increases intragastric pressure. Thus, a rapid sequence induction is always performed for endotracheal intubation.

Pregnancy also markedly affects maternal pulmonary function. The gravid uterus reduces functional residual capacity while oxygen consumption increases to meet the demands of the fetus. This increases the risk of hypoxia during periods of apnea (during a rapid sequence induction). Also, decreases in capillary oncotic pressure and increases in capillary permeability increase the risk of pulmonary edema, especially postoperatively when magnesium sulfate is used for tocolysis.

Both the cardiovascular system and central nervous system are affected by pregnancy. A decrease in preload during supine positioning (supine hypotension syndrome) can cause maternal hypotension and fetal hypoxia. Thus, it is important to maintain left tilt to displace the uterus from the vena cava. The Minimal Alveolar Concentration (MAC) is significantly lower during pregnancy and sensitivity to muscle relaxants is increased. Thus, lower doses of volatile anesthetics and muscle relaxants are needed.

Fetal Anesthetic Considerations

Table 1 summarizes fetal diseases eligible for fetal surgery at the present time. Lesions requiring open/hysterotomy at midgestation result in severe disability or death if left untreated. Ex-utero intrapartum therapy (EXIT) is done at or near term via hysterotomy for infants with complete airway obstruction to establish an airway before cord clamping. Fetoscopic surgery is a minimally invasive technique for the evaluation and treatment of twin-twin transfusion syndromes and bladder outlet obstruction. All of these fetal diseases typically compromise or disturb cardiovascular function. The combination of immature organ function and cardiovascular disease predispose the fetus to anesthetic related difficulty.

Maintenance of fetal cardiovascular stability is the primary concern of anesthetic management. The fetal cardiovascular system is less able to compensate for hypoxia and hypovolemia then a full term infant. Lacking a functional pulmonary system to increase oxygen tension, the fetus relies on increased cardiac output and blood flow redistribution to improve tissue oxygenation. The starling curve is decreased in a fetus compared to a neonate resulting in less cardiac output for a given stroke volume. Thus, cardiac output is more dependent on heart rate. High vagal tone and low baroreceptor sensitivity causes the fetus to respond to stress with a decrease in heart rate. Circulating blood volume is quite low in the fetus, the average midgestation fetus has an estimated blood volume between 40-60 ml. Minimal surgical blood loss can precipitate hypovolemia. Thus, assessing fetal cardiovascular stability requires intraoperative monitoring of fetal echocardiography, fetal pulse oximetry and fetal blood gases to maximize fetal safety.

Incomplete myelination and less synaptic activation make the fetus more sensitive to volatile inhalation agents (MAC is decreased), analgesics and muscle relaxants. High cutaneous heat and evaporative losses require warm ambient temperatures during fetal exposure, limited fetal surgical time, and use of warm irrigation fluids to prevent hypothermia. Additionally, altered coagulation factors predispose to bleeding and cause difficulty in surgical hemostasis. Attention to these issues is paramount in decreasing fetal morbidity related to the surgical procedure.

Utero-placental anesthetic consideration

Fetal survival depends on transfer of oxygen from the mother to the fetus. Uterine and umbilical artery blood flow and placental barriers to diffusion influence fetal oxygenation. Maternal systemic blood pressure and myometrial tone affect uterine artery blood flow. Although volatile anesthetics decrease myometrial tone they also tend to decrease maternal blood pressure. Thus, maintenance of maternal artereial pressure is critical (maternal systemic pressure within 10% of baseline). On the other hand, umbilical artery blood flow is influenced by fetal cardiac output and vascular resistance, both intrinsic and extrinsic (compression by “nuchal cord”). Therefore, preservation of fetal cardiac output is important to maintain placental perfusion and fetal oxygenation.

Control of myometrial tone is also necessary during open fetal surgery for operative exposure and is provided for by general inhalation anesthesia. Epidural anesthesia provides no uterine relaxation, although it may help prevent premature labor in the postoperative period.[6] The use of magnesium sulfate, terbutatline, nifedipine and indomethacin are used alone or in combination to maintain uterine quiescence in the postoperative period.

FETAL SURGERY

Open Fetal Surgery

Open fetal surgeries are usually performed on the midgestation fetus with myelomeningocele, congenital diaphragmatic hernia, congenital cystic adenomatoid malformation, or sacrococcygeal teratoma. To qualify as a surgical candidate, a mother must undergo extensive medical and psychosocial screening, have a fetus with disease that merits intervention, and be at low maternal risk for anesthesia and surgery. This surgery is contraindicated for mothers with serious medical diseases or fetuses with other disabling/lethal congenital abnormalities.

Preoperative Evaluation and Preparation

In the pre-anesthetic evaluation, particular attention is paid to maternal and family history of anesthetic problems, airway examination, maternal size/weight, placental location, and fetal cardiovascular function. The mother must be able to comply with the intensive demands postoperatively including strict bed rest and compliance with medications. The fetus is evaluated by ultrasound, echocardiography, an MRI, and karyotype analysis. When the decision for surgery is made, a multi-disciplinary team consisting of surgery, anesthesia, obstetrics, genetics, social work, and nursing meet to discuss the plan and obtain consent.

Patients are admitted to the hospital either the night before or the day of surgery. In preparation for surgery, the operating room is warmed to 80°F, type specific and O^- PRBC's are made available for the mother and fetus, respectively. Monitors include two pulse-oximeters (maternal and fetal) and an arterial pressure transducer. Epinephrine, atropine, vecuronium, and fentanyl, prepared in sterile 1 cc syringes, are given to the scrub nurse for possible fetal administration. After assuring NPO status, a single large bore intravenous catheter is inserted. Sodium bictrate per oral and metoclopramide IV are administered to the mother to decrease the risk of aspiration pneumonitis. An indomethacin suppository is administered for postoperative tocolysis. A lumbar epidural is inserted and tested with lidocaine 1.5% with epinephrine 1:200,000. The parturient is then positioned with left tilt to minimize supine hypotension syndrome.

Intraoperative Management

A rapid sequence induction facilitated with sodium thiopental and succinylcholine is performed followed by tracheal intubation. General anesthesia is maintained with 0.5 MAC volatile anesthetic (isoflurane or desflurane) and 50% nitrous oxide. A radial arterial line, second intravenous line, nasogastric tube and foley catheter are inseted. Fetal status is monitored by echocardiography. Intravenous fluid is restricted (500cc total) to reduce the risk of postoperative pulmonary edema.

Open hysterotomy procedures require low uterine tone to maintain fetal perfusion and optimize fetal exposure. Before skin incision nitrous oxide is turned off and the inhalation agent is increased to 2.0 MAC to provide uterine relaxation and fetal anesthesia by the time of uterine and fetal incision. Ephedrine or phenylephrine is administered as necessary to maintain maternal SBP within 10% of baseline.

Fetal anesthesia is provided by placental passage of volatile anesthetics. Equilibration between mother and fetus takes a while with isoflurane, reaching approximately 70% of maternal levels in one hour.[7] Before fetal incision, the fetus receives fentanyl 10-20mcg/kg intramuscularly to supplement the anesthesia and provide postoperative analgesia. It is important to monitor the time from uterine incision as after 60 minutes, the fetus becomes progressively acidotic.[8]

Assessing fetal well-being is a difficult task. For CCAM, CDH and SCT repairs, fetal arterial saturation is monitored by pulse-oximetry. The pulse-oximeter is placed on the fetal hand and wrapped with foil to decrease ambient light exposure. Normal fetal arterial saturation is 60-70%, although values greater than 40% represent adequate fetal oxygenation. Echocardiography is also used to monitor fetal heart rate and stroke volume. Fetal distress, manifested by bradycardia, decreased saturations, or decreased stroke volume, is often a result of partial umbilical cord occlusion. Fetal arterial or venous blood gases may be obtained by the surgeons through umbilical vessel puncture to help guide therapy during periods of fetal distress. O- blood can be administered for blood loss.

Following closure of the uterus, the anesthetic is converted to a regional based technique. As the final stitches are placed in the uterus, the volatile anesthetic is decreased to 0.5 MAC and the epidural is dosed with local anesthetic and opioid (15-20cc bupivicaine 0.25% and morphine 0.05mg/kg). Tocolysis is instituted via a magnesium sulfate intravenous load (6 grams) and infusion (2-3 grams/hour). The patient is extubatated after skin closure and transferred to the obstetric floor for observation.

Postoperative management

Key goals for postoperative management include prevention of premature labor and maintaining maternal comfort. Magnesium sulfate is the drug of choice in the early postoperative period (2-3 days) for tocolyisis while a patient controlled epidural infusion is used for analgesia. Indomethacin is continued for 48 hours postoperatively; ductus arteriosus diameter is monitored daily. It is also suspected that a well-functioning epidural assists in the prevention of preterm labor.[6] Following discontinuation of the epidural and magnesium sulfate, the first line of tocolysis is nifedipine per oral. If this fails terbutaline is administered by a subcutaneous route and maintained by an external pump. The patient is advised to be on strict bed rest for the remainder of her pregnancy. The patient is an obligate cesarean section for both this delivery and all subsequent deliveries due to the high uterine incision these surgeries require.

Ex-utero intrapartum therapy (EXIT)

The EXIT procedure is used to secure the airway or to resect pulmonary masses for diseases in which the fetus has a congenital or acquired obstructive airway lesion. These procedures require general anesthesia to relax the uterus. Culmination of the procedure is the delivery of the fetus, who may require additional surgery and have anesthetic issues arising from its status as an immediate newborn.

Preoperative Management

Maternal preparation for EXIT is similar to that for open fetal surgery. Most of these patients are followed for an extended period of time since the fetal lesions were discovered on prenatal ultrasounds. This gives time for the counseling and testing that was mentioned above for open procedures.

Anesthetic preparation is the same for the EXIT as for the open procedure with three notable exceptions: no tocolytics, no epidural and one additional operating room. Tocolytics are unnecessary since the procedure ends in delivery. An epidural is not used since PCA is used for postoperative analgesia. Resuscitation equipment, neonatologists and a second operating room are readied for delivery. Additionally, the risk of aspiration and supine hypotensive syndrome are higher in the term gestation mother with a large gravid uterus.

Intraoperative Management

Anesthesia for the EXIT is via an inhalation based technique. After a rapid sequence induction and orotracheal intubation, a second intravenous line, a nasogastric tube and foley catheter are placed. An arterial line is not required. Low-level inhalation agent is used before maternal skin incision and high-level inhalation agent is used thereafter. Ephedrine and phenylephrine are used for maternal blood pressure maintenance. For rapid emergence of the baby after delivery, our preference of inhalation agent is desflurane because of its low blood gas solubility.

During hysterotomy it is important for the surgeons to only partially expose the fetus and maintain the uterine volume at an appropriate level for placental perfusion to be maintained. This allows approximately 1 hour of operative time for the surgeons before the fetus becomes acidotic.[8] Fentanyl 10-20 mcg/kg intramuscularly is given to supplement fetal analgesia and provide postoperative analgesia. Fetal status is closely monitored via a pulse-oximeter, echocardiography, and visual inspection. Fetal blood gases are obtained as needed and O- blood administered if necessary. When oxygenation of the fetus is assured, the umbilical cord is clamped and the fetus delivered.

After delivery it is important to quickly reverse uterine relaxation. Volatile agents are turned off after cord clamping. Due to the anesthetic induced uterine relaxation, uterine atony and significant blood loss is a risk. Thus, the timing of cord clamping with respect to administration of oxytocin, methergine and prostaglandin $F_{2\zeta}$ for the uterus to regain tone and prevent uterine atony must be coordinated between anesthesiologist and surgeon. Blood loss is monitored and cross-matched blood is administered if needed. Morphine IV is administered for postoperative analgesia and the trachea extubated after surgical closure.

Postdelivery/Postoperavitve Management:

Following surgery/delivery there are two patients to care for. The mother is brought to a postpartum ward. The immediate disposition of the newborn infant is based on surgical need; a second operating room is available in case further surgery is needed. If surgery is not required immediately, a neonatology team assists in resuscitating and transporting the neonate to intensive care. When further surgery is necessary, there are several unique considerations. It is essential to dry and clean the newborn because of temperature considerations and the inherent difficulty of monitors sticking to the newborn. Also, these infants are provided an anesthetic for surgery. For this one must keep in mind the lower MAC requirements of the newborn and the existence of a transitional circulation.

Fetoscopic Assisted Surgery

Fetoscopic surgical procedures are the most common fetal intervention done at our institution. These procedures involve the percutaneous placement of small trocars and laparoscopes into the uterus. Umbilical cord ligation and selective ablation of fetal connecting vessels is done for twin pregnancies complicated by twin reversed arterial perfusion sequence (TRAP) and twin-twin transfusion syndrome (TTTS) where one death of one or both twins is imminent and conventional therapy has failed. Bladder outlet can be treated using a fetoscopic-guided laser to ablate posterior urethral valves. Anesthetic management of the cases depends on the location the placenta, umbilical cord and amniotic membranes.[5]

Preoperative management

Due to the emergent nature of these procedures (especially for TTTS and TRAP) parturients may not receive as extensive preoperative evaluation as those undergoing open and EXIT procedures.

Patients are admitted to the hospital the day of surgery. The room is prepared as for an open procedure in the rare event a hysterotomy is required for the surgical access. In the preoperative area, the mother receive sodium bicitrate per oral, metoclopramide intravenously and if at high risk for preterm labor indomethacin per rectum. Following placement of standard ASA monitors, a lumbar epidural is inserted and tested. The parturient is then positioned with left tilt.

Intraoperative management

The location of the placenta, umbilical cord and amniotic membranes influences the difficulty of surgical exposure. Fetoscopic surgery involves the insertion of small trocars through the abdominal wall into the uterus and amniotic sac to access the umbilical cord. An anterior placenta carries the risk of spearing the highly vascular placenta. However, since the umbilical cord structures are also anterior, ultrasound guidance allows makes access easier to the umbilical cord. In the patient with an anterior placenta, epidural anesthesia is often sufficient due to the ease of surgery. A complicating factor is severe polyhydramnios, which can make surgical exposure difficult, requiring general anesthesia to enable uterine manipulation to access the umbilical cord. In a parturient with a posterior placenta, the uterus is easily accessible but the umbilical cord is often difficult to expose. Thus, a posterior placenta often requires more uterine manipulation than an anterior placenta. Fetal movement with uterine manipulation also increases the difficulty of the surgery.

The risk for preterm labor increases with hysterotomy for the fetal procedure or a maternal history of preterm labor. Preoperative uterine activity and intraoperative uterine manipulation guides the choice between a balanced general anesthetic, a deep general anesthetic (2 MAC isoflurane), and the use of postoperative epidural analgesia. Deep inhalation anesthesia relaxes the uterus, while epidural analgesia postoperatively may decrease the risk of preterm labor.[6]. Prophylaxis of preterm labor also includes intraoperative administration of magnesium sulfate. Indomethacin is occasionally used for patients at high risk of preterm labor when cardiac failure is not present in the remaining fetus.

Anesthetic choice is guided by potential advantages and disadvantages for the mother and the fetus (table 2). Epidural anesthesia is used for the majority of these cases and has the advantage of minimal effects on fetal hemodynamics,[9] on uteroplacental blood flow[10], and postoperative uterine activity.[6] The disadvantages include lack of uterine relaxation, lack of fetal anesthesia, and difficulty manipulating the uterus and cord while the fetus may be moving. A balanced inhalation-opioid anesthetic has the advantage of allowing uterine manipulation with an immobile-anesthetized fetus, yet should have less fetal cardiovascular depression then deep inhalation anesthesia. General anesthesia also eliminates concerns associated with an awake patient: anxiety, combativeness, nausea and emesis. The potential disadvantage of this technique is an inability to fully relax the uterus to access difficult cord positions. Deep inhalation anesthesia has the advantage of profound uterine relaxation allowing externalization of the uterus and hysterotomy based procedures. The disadvantage of this technique is fetal cardiovascular depression, and decreased uteroplacental blood flow.[3;8]

Postoperative management

As with the open hysterotomy cases, the most important aspect of postoperative management is tocolysis. Epidurals are removed after the surgery for these patients, unless they undergo hysterotomy based procedures. Thus, magnesium sulfate followed by either nifedipine or terbutaline are the mainstay of tocolytic management. Discharge from the hospital on postoperative day 2-3 is expected following this procedure.

Conclusion

Anesthesia for fetal surgery is an evolving field. The anesthetic techniques that have emerged are safe for mother and fetus. Due to the myriad of anesthetic and surgical issues these cases generate, it is essential to have good communication and cooperation between surgeons and anesthesiologists from the preoperative period to the postoperative period. This will allow development of a cohesive anesthetic and surgical plan that can be used for the safe perioperative management of the fetal surgery patient.

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Table 1: Surgical approaches to fetal lesions: timing and cause for treatment

Surgical Approach	Fetal Lesion/Anomaly	Reason for Treatment	Gestational Age
Open/Hysterotomy	Congenital diaphragmatic hernia	Lung hypoplasia	18-25
	Congenital Cystic Adenomatoid Malformation	Hydrops fetalis, lung hypoplasia	18-25
	Myelomeningocele	Aminotic fluid neurotoxicity	22-26
	Sacrococcygeal teratoma	Hydrops fetalis	18-25
Ex-Utero Intrapartum Therapy	Congenital or iatrogenic high airway obstuction	Secure airway	Near term
	Giant fetal neck mass	Secure airway, resect mass	Near term
Fetoscopic surgery	Twin-twin transfusion	Impending fetal demise, hydrops fetalis	Midgestation
	Twin reversed arterial perfusion sequence	Impending fetal demise, hydrops fetalis	Midgestation
	Bladder outlet obstrucion	Hydronephrosis and renal hypoplasia	Midgestation

Table 2: Implications of anesthetic technique for fetoscopic surgery

	Fetal Depression	Uteroplacental Blood Flow	Uterine Relaxation
Regional Anesthesia	-	-	-
Balanced General Anesthetic +/- Epidural	+	+/-	+/-
Deep General Anesthetic With Epidural	++	++	++

Designing a Clinical Trial of Fetal Surgery: The Myelomeningocle Saga

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Chief Neurosurgery, Children's Hospital of Philadelphia

Introduction:

Until recently, three options were available to the parents of a fetus diagnosed with a myelomeningocele: termination, continuation of the pregnancy until term with cesarean or vaginal delivery, or early delivery by induced labor or planned cesarean section. Developments in diagnostic imaging, surgical techniques applicable to the fetus, and drugs for the prevention of premature labor over the past 10 years have provided a fourth option: *in utero* closure. The current application of fetal surgery to the human is a triumph of the scientific model. Years of animal work provided the rationale for the currently performed procedures, and led to our ability to perform them with relative safety. The efficacy of fetal surgery, however, remains unproven, particularly for myelomeningocele. This will ultimately only be determined by a multicenter, randomized, prospective clinical trial. Such a trial has been proposed, and is currently under review by the National Institutes of Health. The design of this trial required compromise among the centers that will participate.

Background:

Animal studies have demonstrated that prenatal coverage of the lesion may preserve neurological function. Michejda created a spina bifida-like lesion in eight Macaca mulatta fetuses by performing intrauterine lumbar laminectomy and displacing the spinal cord from the central canal. This condition was repaired in utero in five monkeys. At delivery, the five animals whose lesion was covered developed normally, while those with open lesions were paraplegic with lower extremity somatosensory loss and incontinence. Studies performed in the rat model showed that those animals in which the defect remained uncovered were born with a severe deformity and weakness of the hind limbs and tail. In contrast, repaired rats were normal at birth. Histological studies of the exposed spinal cord revealed findings similar to those described in children with myelomeningocele. Similar studies have been performed in fetal pigs and lambs with identical results. It has recently been shown in an open spinal canal fetal lamb model that hindbrain herniation can be prevented by mid-gestational repair of the surgically created myelomeningocele. It is now hypothesized that the neurological defects seen in children with myelomeningocele result from both the congenital myelodysplasia as well as from intrauterine spinal cord injury resulting from prolonged exposure of neural elements to the intrauterine environment.

The clinical experience to date:

In 1994, the first human cases of myelomeningocele repair in utero were performed using a fetoscopic approach. This approach did not result in satisfactory repair of the lesion and was abandoned. In 1997, the first cases were carried out by hysterotomy. As of August 25th, 2001, 182 women had received open fetal repair of myelomeningocele at three centers: University of California San Francisco (UCSF), Children's Hospital of Pennsylvania (CHOP) and Vanderbilt. Selection criteria varied between the centers.The group at Vanderbilt began operating primarily on late gestation fetuses to avoid the risk of a severely premature fetus should labor prove uncontrollable, and they had no exclusion criteria based on fetal leg function or ventricular size. The CHOP criteria were more selective: only fetuses of 25 weeks of gestation or less with ventricular size less than 17 mm and intact leg fuction by dynamic ultrasound were considered for fetal surgery.

The CHOP cases resulted in 3 fatalites due to premature delivery, whereas those at Vanderbilt include two fetal deaths and two neonatal deaths. In addition, one infant from Vanderbilt died at 10 months of causes unrelated to the surgery or prematurity. At UCSF, there was one fetal death and one death from complications of prematurity.

One of the unexpected results of the fetal surgery experience to date is the apparent decrease in the need for shunts in these children. At CHOP, only 29% of children have required shunts, compared with a series of 416 patients followed in the Spina Bifida Clinic, in whom 84% had a shunt by one year of age. Even if the fetal and control patients are stratified by spinal level, the requirement for shunt is signicantly less in the fetal group for all levels. This result is encouraging, since the morbidity associated with shunt dependent hydrocephalus is significant over the lifetime of a patient. Still, bias associated with selection, and perhaps different criteria for shunting the fetal patients might account for this result.

Both CHOP and Vanderbilt have demonstrated a marked improvement in the degree of hindbrain herniation following in utero repair. MRIs done three weeks after fetal closure of myelomeningocele showed improvement in all patients, and, on the MRI obtained six weeks postnatally, all were Grade 1 (normal).

In 34 patients with in utero repair at CHOP, several had neurological function substantially better than might have been expected after conventional repair. Fifteen of 34 patients evaluated had newborn lower extremity function better than expected by at least two spinal levels based on anatomic level as determined by the initial MRI. Interestingly, all these patients were operated at less than 25 weeks' gestation, suggesting that earlier repair of the myelomeningocele may result in improved lower extremity function.

Thus, the preliminary pilot data suggest possible benefits to prenatal surgery for myelomeningocele: reversal of the hindbrain hernia, decreased need for shunts, and preservation of leg function in early gestation repairs when normal leg function was demonstrated by ultrasound prior to fetal surgery. But selection bias and other factors make comparison with historical controls difficult. The benefits of fetal surgery must be evaluated in view of the risks to the fetus and the mother.

Design of the trial

The major issues in the design of a prospective trial may be summarized as follows:

1. What selection criteria would be used? The three centers all had different approaches. The CHOP data would suggest that early gestation (less than 26 weeks) is most appropriate. The CHOP and Vanderbilt data would favor a ventricular size cut-off of 15 mm.
2. What is the primary endpoint of the study? The clearest benefit to date appears to be decreased requirement for shunting. The pilot data would suggest that approximately 200 patients would answer this question. The reviewers at NIH have favored leg function as the primary endpoint. This would be more difficult to assess, and pilot data are lacking.
3. How to avoid the "back door." Many other centers have expressed interest in beginning fetal myelomeningocele programs. How can this be discouraged until benefit is proven? How can the 3 centers currently performing this operation be encouraged to join the trial, and not offer fetal surgery to patients who randomize to the conventional arm?
4. How to deal with the press, and issues of marketing while the trial is ongoing?
5. How to deal with the "control patients," to ensure that they receive the best possible neurosurgical and obstetric care, so as to not disadvantage this group? Must they also be treated at the study institution to ensure this, despite the inconvenience and expense?
6. How to assure an equitable distribution of patients among the 3 centers to keep everyone happy, and yet not place undue hardship on patients from different geographic locations?

These issues required a number of compromises. The trial as currently proposed, is as follows:

The study is an unblinded randomized controlled clinical trial of 200 patients. Patients diagnosed with myelomeningocele at 16 to 25 weeks gestation will be referred to the Data and Study Coordinating Center (DSCC) for initial screening and information. Those eligible and interested will be assigned by the DSCC to a Fetal Surgery Unit where final evaluation and screening will be carried out. Patients who satisfy the eligibility criteria and consent to randomization will be centrally randomized to one of the following two management protocols:

- Intrauterine repair of the myelomeningocele at 18^0 to 25^6 weeks, discharge to nearby accommodation on tocolytics when stable for preterm labor, weekly prenatal visits and biweekly ultrasounds conducted at to the FSU; cesarean delivery at 37 weeks following demonstration of lung maturity.
- Return to local perinatologist for prenatal care, with monthly ultrasounds reported to the FSU; return to the Fetal Surgery Unit at 37 weeks gestation for cesarean delivery following demonstration of lung maturity; neonatal repair of the myelomeningocele.

Inclusion Criteria

1. Myelomeningocele at level T1 through S1 with hindbrain herniation. Lesion level will be confirmed by ultrasound and hindbrain herniation will be confirmed by MRI at the Fetal Surgery Unit.
2. Maternal age ∅18 years
3. Gestation age at randomization of 18^0 to 25^6 weeks gestation as determined by clinical information and evaluation of first ultrasound. If the patient's last menstrual period is deemed sure and her cycle is 26 to 32 days, and if the biometric measurements from the patient's first ultrasound confirm this LMP within ∂ 10 days, the LMP will be used to determine gestational age. In all other cases (i.e. if the LMP is unsure, if she has an irregular cycle or her cycle is outside the 26-32 day window or if the measurements from her first ultrasound are more than 10 days discrepant from the ultrasound), the ultrasound determination will be used. Once the EDC has determined for the purposes of the trial, no further revision is made.
4. Normal karyotype with written confirmation of culture results. Results by fluorescence in situ hybridization (FISH) will be acceptable if the patient is at 24 weeks or more**.**

Exclusion Criteria

1. Non-resident of the United States
2. Multifetal pregnancy
3. Abnormal fetal echocardiogram
4. Fetal anomaly other than myelomeningocele or an anomaly related to myelomeningocele
5. Documented history of incompetent cervix
6. Short cervix< 20mm measured by ultrasound
7. Preterm labor in the current pregnancy
8. Past history of recurrent preterm labor
9. Maternal-fetal Rh isoimmunization, Kell sensitization or a history of neonatal alloimmune thrombocytopenia
10. Maternal HIV or Hepatitis-B status positive or unknown because of the increased risk of transmission to the fetus during fetal surgery
11. Uterine anomaly such as large or multiple fibroids or mullerian duct abnormality
12. Other maternal medical condition which is a contraindication to surgery or general anesthesia
13. Patient does not have a support person (e.g., husband, partner, mother)
14. Inability to comply with the travel and follow-up requirements of the trial
15. Patient does not meet other psychosocial criteria (as determined by the case social worker) to handle the implications of surgery

Current status:

The trial has the support of the pediatric neurosurgical community. There has been an informal agreement that no new programs will begin pending the results of the trial. The NIH has the current proposal under review, and has expressed some reservations about using incidence of shunting as the primary endpoint.

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3:00 - 4:00 pm

PRO/CON: STANDARDS IMPROVE QUALITY OF CLINICAL CARE

Moderator: Aubrey Maze, MD

PRO: Burton S. Epstein, MD
CON: Frederic A. Berry, MD

Pro: Practice Guidelines Improve the Quality of Clinical Care

Burton S. Epstein, M.D.

The objective of this discussion is to provide the evidence that practice guidelines have had a measurable impact on the quality of clinical patient care. In doing so, I shall summarize the background, justification, process and success of the effort.

The scope of the license to practice medicine does not limit the right/privilege of the physician to practice independently as he/she sees fit. Neither does certification by the American Board of Anesthesiology determine the mode of practice. While practicing the specialty of Anesthesiology in the years 1958-1985, I received documents from the ASA titled either "Technical" or "Educational" Bulletin. ASA's Administrative Procedure No.5 requires that each bulletin "include a disclaimer prepared by legal counsel to reflect variations in anesthesia practice --- and the need to preserve the individual anesthesiologist's right to exercise medical judgment appropriate to a particular circumstance" **(1)**.

In 1985, ASA President H. Ketcham Morrell issued a formal recommendation to the Board of Directors and House of Delegates. He said, "I believe we owe it to our membership as well as the American public for ASA to set down guidelines concerning standards of care as a very minimum effort. Eventually, I envision, and even suggest, that there will be published a document that describes what are considered to be the minimum standards of care for patients receiving care in all of its various modalities." I was asked to chair this new Ad Hoc Committee on Standards of Care and did so for nine years. Following are my reflections on the evolution of Practice Parameters by the ASA during the past 15 years.

Before considering the drafting of its first Standard on Basic Intra-Operative Monitoring, the Committee considered the potential influence on:

- Uniformity and accountability of patient care throughout the U.S.
- Development of guidelines within Departments of Anesthesia and the facilities in which they practice
- Development of Standards for anesthesia care by accrediting bodies and state regulatory agencies
- Availability and affordability of malpractice insurance
- Providing a basis for expert witnesses in a legal case for comparing adherence to a previously determined national benchmark

Our Committee concluded that ASA should develop some rules to guide its members in their practice, that we should set them for ourselves and that we should not have them arbitrarily imposed on us by outside forces. In addition, the process for determining the ground rules must be open for public scrutiny and subject not only to review but also to modification. Furthermore, unlike the basis for some legal actions, we determined that it was not prudent to

wait for the "preponderance of evidence" or "beyond a reasonable doubt" to impede the initial development process. Available data would be analyzed and the presence or absence of evidence distinguished from the opinions of experts.

ASA "Standards for Basic Intra-Operative Monitoring" was implemented in 1986 and exists today as "Standards for Basic Anesthetic Monitoring." Since 1986, only one other ASA Standard (Postanesthesia Care) has been developed which remains in place. ASA has recognized that evidence for issuing further standards (rules) is lacking. As a result, other Practice Parameters **(2)** have supplanted Standards. These include Guidelines (recommendations) and Advisories (reports) as well as Statements, Positions or Protocols.

Most Practice Guidelines are developed by a rigid process that compares evidence to the opinions (consensus) of experts. The cost for developing each Guideline is approximately $100,000 dollars. The reader must be aware of the use of the terms in the Guidelines such as, "should," "may," and "consider vs. "shall," in the language of Standards. The analysis of the literature in the development of Guidelines clearly displays the strength of the data with the terms, "suggests" (qualitative) vs. "supports" (quantitative) vs. "insufficient." Concluding recommendations separate the data from the opinions of the consultants.

With these safeguards in place, ASA has continued to make great strides in providing a degree of uniform, safe care to our patients. "Guidelines for Non-Operating Room Anesthetizing Locations" and for "Office-Based Anesthesia" have been developed by consensus. "Practice Parameters" developed by a more formal, evidence-based process include "Practice Guidelines for Management of the Difficult Airway," "Preoperative Fasting," and "Sedation and Analgesia by Non-Anesthesiologists." All have been subject to review and have received approval from the ASA House of Delegates.

In my opinion, the greatest impact in the development of "Practice Parameters" has been in the two directed at management of the airway and the role of monitoring. Both have resulted in the implementation of educational endeavors, have improved patient management and have had a positive influence on decisions to purchase equipment and the hiring of additional, trained personnel. Anesthesiologists are better able to design and implement a plan for management of the patient with a difficult airway. By using pulse oximetry and capnography, anesthesiologists are no longer implicated as the cause of hypoxia and hypoventilation by exclusion after cardiac arrest, brain damage and death. Malpractice claims for death or brain damage related to inadequate "ventilation" (oxygenation) have essentially disappeared **(3).** I agree with the conclusion of the report of the AMA Council of Scientific Affairs that outcome research is not supportive of the use of pulse oximetry but the benefits exceed the risk **(4).** There is no doubt that the pulse oximeter has had a measurable impact on the quality of patient care.

A particular parameter may only address one component of anesthesia care. In aggregate, however, parameters allow for a more uniform level of care regardless of the type of anesthesia provided, the provider and the setting in which it is administered. The risk of administration of anesthesia to the patient has been reduced markedly and we have been commended by prestigious organizations, such as the Institute of Medicine, for our efforts in improving patient safety **(5).**

While many other specialties have experienced an alarming amount of losses in malpractice claims, malpractice insurance carriers have collected data that indicate the continued success of anesthesiologists in controlling their losses. The largest insurer in the state of Massachusetts, Pro Mutual Group, has reduced the risk ("relativity") category of anesthesiologists from a previous high in 1988 of 5 on a scale of 5 to 1.6 **(6)**. The largest insurer in the state of New York rates anesthesiologists as 1.02 on a scale of 8. The lowest category of 1.0 is assigned to Internal Medicine. The ASA Director of the component societies of Arizona, Nevada and New Mexico noted in the September Annual Report to the ASA House of Delegates, "---practice parameters, guidelines and advisories have, up to this point, proven to be valuable resources in defending malpractice litigation involving anesthesiologists" **(7).**

We should be proud of our efforts to improve the quality of clinical patient care through the development of practice parameters. We should continue to identify new areas in risk management, for which additional practice parameters may be appropriate.

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