Fetal arrhythmias are estimated to occur in 1-2% of gestations. The majority of these are PVCs and PACs which are generally considered benign. More serious arrhythmias can occur including SVT, atrial flutter, and VT. Management of fetal arrhythmias has been limited by our inability to effectively monitor and diagnose them. The gold standard has been Doppler M mode echocardiography which can demonstrate the timing of atrial and ventricular contractions. Echo, however, does not give information about the electrical activity of the heart and is labor intensive. The fetal ECG can be obtained from the maternal abdomen but there is significant artifact in the form of myopotentials and the maternal ECG. Of particular interest, the maternal ECG (based on voltage potential) does not attenuate and is 10-100 times as strong as the fetal signal. In addition, useful signals are difficult to obtain after 27 weeks, probably due to the insulating properties of the vernix caseosa. Fetal

Figure 1. SARA, consisting of 151 gradiometers arranged to comfortably fit the gravid abdomen.
magnetocardiography (fMCG) is a new technique that is particularly useful for evaluating fetal arrhythmias.

When an electric or ionic current flows through a conductor, a magnetic field is generated perpendicular to the current. As cardiac tissue depolarizes, small currents are generated across the advancing wave front and consequently an electromagnetic field is generated perpendicular to the current. This field can be detected and is the basis of fMCG. The field generated by the fetal heart is on the order of 0.5-10 pT, or approximately one millionth the strength of the earth’s magnetic field. By comparison, the maternal signal is approximately 50 pT. The device used to measure these biomagnetic fields is called a Superconducting Quantum Interference Device or SQUID magnetometer. SQUIDs must be super cooled and shielded from all electromagnetic interference.

One clear advantage of fMCG is that the signal strength is inversely proportional to the square of the distance from the source. Consequently, if the receiver is placed close to the fetus, the maternal signal will considerably smaller. The University of Arkansas for Medical
The result is a signal that is analogous to a surface ECG. (Figure 2) If further resolution is needed, signal averaging can be performed. Fetal magnetocardiography offers some exciting possibilities including the more accurate diagnosis of fetal arrhythmias, monitoring for fetal toxicity with drugs such as Flecaïnide, Sotalol, and Amiodorone leading to safer use of antepartum antiarrhythmics, and prenatal diagnosis of channelopathies such as the Long QT syndrome without the need for amniocentesis. This technology is currently expensive and cumbersome due to the need for super cooling and electro-magnetic shielding. However, work is currently under way towards the development of a “high” temperature SQUID that does not require super cooling.
Advances in diagnostic imaging and surgical technique have allowed most congenital heart disease to be anatomically repaired, even in infancy. However, until recently, the possibility of prevention of congenital heart disease seemed remote. Widespread use of sonographic obstetrical screening, in combination with improved acquisition and interpretation of fetal echocardiograms, now allows us to diagnose many cardiac anomalies by midgestation, and also to observe their prenatal progression. Not unexpectedly, the capacity for early diagnosis has generated considerable interest in prenatal therapeutic intervention.

Several fundamental principles underlie the field of fetal intervention. The fetal diagnosis must be certain, and there must be an understanding of how the disease will evolve through the remainder of gestation. The resultant condition at birth must be associated with significant mortality or morbidity. Finally, a procedure must be available that can correct the initial lesion and thereby improve the outcome at birth; this procedure must offer sufficient benefit to the child to justify the risk to both mother and fetus.

Hypoplastic left heart syndrome (HLHS), though rare, remains the congenital cardiac defect associated with the most deaths in the first year of life. Characterized by a left ventricle (LV) inadequate to support the systemic circulation, the syndrome may result from one of a number of primary left heart lesions. Included among this list of causative primary lesions is valvar aortic stenosis (AS). In fact, fetal echocardiographic observation has demonstrated that AS associated with LV dysfunction, when diagnosed in the second trimester, progresses to HLHS[1]. Thus, critical AS diagnosed...
the mid-trimester fetus presents an ideal target lesion for prenatal intervention.

The mechanisms through which AS becomes HLHS are poorly understood. It is hypothesized that increased LV afterload and decreased coronary perfusion lead to LV myocardial damage. Initially, this LV injury is manifest as LV dilation and systolic dysfunction. With impaired LV filling, pulmonary venous return is diverted at the atrial level. The resultant decrease in left heart flow leads to growth arrest, and ultimately, hypoplasia. Consistent with this hypothesis, the echocardiographic hallmarks of critical AS of the fetus include:

1. primary AS as evidenced by thickened valve tissue and a narrowed antegrade flow jet,
2. severe LV dysfunction,
3. echogenicity of the LV myocardium,
4. left to right flow at the atrial septum, and,
5. retrograde flow in the ascending aorta (Figure 1).

Authors had described a percutaneous fetal aortic valvuloplasty procedure as early as 1991[2]. Although the work of several groups had resulted in a total of 12 procedures reported through the year 2000, the experience yielded limited technical success and a high rate of fetal mortality3. The procedure did, however appear to be technically feasible. With the benefits of improved imaging, instruments, and intraoperative obstetrical management, we believed the procedure could be performed more safely and with better technical results.

In March 2000, we began to offer fetal aortic valvuloplasty to mothers of fetuses with critical AS at less than 26 weeks gestation, as part of an innovative therapy protocol at the Children’s Hospital, Boston, and the Brigham and Women’s Hospital. Candidates were required to meet all of the echocardiographic criteria described above, with at least 3 experienced fetal echocardiographers attributing a high likelihood of progression to HLHS. Furthermore, the LV had to be deemed “salvageable”, that is, without significant hypoplasia (length within 2 S.D. of normal for gestational age) at the time of diagnosis.

Between March 2000 and March 2004, twenty mothers elected to undergo the procedure. All gave informed consent for the procedure after meeting with pediatric cardiologists, fetal surgeons, perinatologists, and anesthesiologists. The aortic valvuloplasty was performed successfully in 14 cases, giving a technical success rate of 70%.

The procedure is performed with the mother under general anesthesia. In many cases, the procedure can be performed percutaneously. When transabdominal fetal positioning fails, a limited laparotomy is performed. Not only does the laparotomy afford greater access for fetal manipulation, but it also allows higher resolution imaging directly on the uterine surface.

Once ideal fetal position is established, the fetus is given intramuscular anesthetic and muscle relaxant. A 19 G needle introduced into the maternal abdomen is guided under ultrasound through the fetal chest wall and into the LV cavity. Once inside the LV, the needle is used as an introducer for a standard PTCA catheter over a wire. The balloon diameter is intended to be ~120% the diameter of the valve annulus. The wire is used to probe for the aortic valve orifice. Once the wire has

Figure 2. This graph depicts the change in dimension of left heart structures (mitral and aortic valves and ascending aorta) in fetuses that had a technically successful in-utero aortic valvuloplasty compared to those with an unsuccessful procedure and those that declined the procedure. Only fetuses with pregnancies carried to near term delivery (>33 weeks gestation) were included. The data reflects the first and last measurements made during gestation.

“Widespread use of sonographic obstetrical screening, in combination with improved acquisition and interpretation of fetal echocardiograms, now allows us to diagnose many cardiac anomalies by midgestation, and also to observe their prenatal progression.”
crosed the valve, the balloon is advanced, and the balloon is inflated straddling the valve (Figure 2). All of the equipment is then withdrawn.

Using this technique, we have not observed maternal complications related either to anesthesia or to the catheterization procedure. A variety of fetal complications have occurred; the most common complications being bradycardia and small pericardial effusions. The fetal bradycardia responds to either intramuscular or intracardiac epinephrine. Effusions often resolve spontaneously, but can also be drained at the conclusion of the procedure. Although we have not seen fetal demise intraoperatively, 3 fetuses were found to have expired within 72 hours of the procedure.

Of 14 fetuses who underwent successful aortic valve dilation between 21 and 29 weeks gestation, 3 were born with 2 ventricle circulations. The remainder of the liveborn fetuses who underwent either successful or unsuccessful aortic valvuloplasty procedures had a diagnosis of HLHS at birth. Although only 3 fetuses did not require a Stage I palliation, technically successful fetal aortic valve dilation was associated with significant growth of left heart structures including the mitral valve, aortic valve, and ascending aorta (Figure 3)[4].

The lack of maternal complications and the possible prevention of HLHS in 3 fetuses have encouraged us to cautiously pursue this intervention. We are in the process of developing a protocol to investigate more closely the impact of successful aortic valve dilation on the growth of left heart structures in utero.

While critical AS is currently the most common diagnosis referred for fetal cardiac intervention, indications will likely expand as additional procedures become available and practiced. One additional disease that has been proposed as a target for fetal therapy is pulmonary atresia with intact ventricular septum. Perforation and dilation of the pulmonary valve can be performed using a technique similar to that used for aortic valve procedures. The difficulty in offering intervention to this group of fetuses lies in the clinical spectrum of the disease, and our inability to predict the postnatal morbidity based on prenatal appearance. Although it seems likely that pulmonary atresia can be treated prenatally, we first need to be able to identify those fetuses who would have the poorest postnatal outcomes, and would therefore have the most to gain from fetal intervention.

In fact, the emergence of a second indication for fetal intervention has, in our center, been driven primarily by the identification of a uniquely high risk set of neonates. Infants born with HLHS and an intact atrial septum have a failing circulation until left atrial (LA) decompression can be achieved. These infants as have markedly elevated mortality rates, compared to others with HLHS. We hypothesized that a prenatal procedure to create an atrial septal defect would aid in postnatal stabilization and thereby improve neonatal outcomes. By decompressing the LA in utero, one might attenuate secondary tissue/organ damage occurring in the lung, and might favorably impact longer term survival.

We have performed 7 of these procedures; 6 of 7 have been technically successful. As with the aortic valve procedure, we have not experienced any maternal complications. Furthermore, we have been able to access the atrial septum in all cases without the use of a laparotomy. Due to the technique and equipment used, the newly created atrial defects are small, but appear to persist through gesta-

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“The potential for echocardiographic diagnosis in utero has already favorably impacted care of children with congenital heart disease. A therapeutic arm has been added to the field with regard to management of fetal arrhythmias.”
tion[5]. Although we have not yet demonstrated clinical effect, we expect that the introduction of equipment and techniques dedicated to this procedure will improve our ability to make large defects in the atrial septum, and will ultimately lead to clinical benefit.

Fetal cardiology is emerging as one of the most rapidly growing fields in our specialty. The potential for echocardiographic diagnosis in utero has already favorably impacted care of children with congenital heart disease. A therapeutic arm has been added to the field with regard to management of fetal arrhythmias. Now we are developing the means of modifying structural disease in utero. It is our hope that with the continuing collaborative efforts of fetal imagers, obstetricians, fetal surgeons, and interventionalists, we can add prevention to the management of some forms of congenital heart disease.

Reference List

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Corresponding Author:
Audrey C. Marshall, MD
Cardiology
Assistant in Cardiology
Harvard Medical School Appointment
Assistant Professor
Harvard Medical School
Children’s Hospital Boston
audrey.marshall@cardio.chboston.org

Wayne A. Tworetzky, MD
Cardiology
Services/Programs
Assistant in Cardiology
Harvard Medical School Appointment
Assistant Professor in Pediatrics,
Harvard Medical School
Children’s Hospital Boston
wayne.tworetzky@cardio.chboston.org

MEDICAL CONFERENCES

28th Annual Management of the Tiny Baby
February 2-4, 2006; Lake Buena Vista, Florida USA
www.pediatrix.com

Pediatric Critical Care Medicine 2006 - A Review for Board Preparation, Recertification and Comprehensive Update
March 25-28, 2006; McLean, VA USA
www.cbcbiomed.com

2006 PAS (Pediatric Academic Societies) Annual Meeting
April 29–May 2, 2006; San Francisco, CA USA
www.pas-meeting.org

20th Annual Conference of the Southern Association of Neonatologist
May 18-21, 2006; Marco Island, FL USA
www.southeastneo.org/ID1/conference.php3

2006 AAP National Conference & Exhibition
October 7-10. Atlanta, GA USA

Europaediatrics
Oct 7-10, 2006; Barcelona, Spain
www.kenes.com/europaediatrics/

NANN 22nd Annual Educational Conference—Neonatal Nursing Excellence: Growing and Knowing
November 8-11, 2006; Nashville, TN USA
www.nann.org/i4a/pages/index.cfm?pageid=803

November 8–11, 2006; Miami Beach, FL USA
neonatology.med.miami.edu/conference/default.htm
Use of Sucrose to Relieve Pain During Eye Exams in Infants

This study is currently recruiting patients.

Sponsors and Collaborators: Weill Medical College of Cornell University

Purpose: The purpose of this study is to see if an oral sucrose solution can comfort premature infants during their necessary eye exams. We believe that the use of this solution prior to the eye exams will lead to a decrease in pain as measured by rise in heart rate and fall in oxygen saturation. In addition this will lead to a decrease in events in the 12 hours following examination. Events include episodes when the infants temporarily stop breathing, has a drop in their heart rate, or has a drop in their oxygen levels.

Condition: Apnea of Prematurity; Retinopathy of Prematurity; Pain Control

Treatment or Intervention: Drug- sucrose solution

Study Type: Interventional

Study Design: Prevention, Randomized, Double-Blind, Placebo Control, Cross-over Assignment, Efficacy Study

Eligibility: Ages 5 Weeks and above; both male and female,

Criteria

Inclusion Criteria: All premature infants admitted to the Neonatal Intensive Care Unit requiring serial dilated examinations to assess for retinopathy of prematurity will be candidates for this study. This includes all infants with a birthweight of less than 1500g and infants between 1500g and 2000g who require supplemental oxygen.

Exclusion Criteria: Any infant who is unable to safely suckle 0.5cc of fluid will be excluded from the study. This includes infants that are being maintained on ventilators and those with serious gastrointestinal complications that may be exacerbated by an oral fluid bolus. Any infant being maintained on narcotics for any reason will not be eligible for the study. All infants with major congenital anomalies will be excluded.

Location and Contact Information: Please refer to this study by ClinicalTrials.gov identifier NCT00161694

Tamara L Rousseau, MD; 212-746-3530; tlrousseau2001@yahoo.com; NYPH- Weill Cornell Medical Center, New York, New York, 10021, United States

Study chairs or principal investigators: Tamara L Rousseau, MD, Principal Investigator, Neonatology Fellow at NYPH-Weill Cornell Medical Center

Study to Test the Pain-Relieving Effect of Laughing Gas in Infants

This study is currently recruiting patients.

Sponsors and Collaborators: University of California, Los Angeles; UCLA Department of Neonatology

Purpose: to study infants in the Neonatal Intensive Care Unit (NICU) who are undergoing a heel stick for blood sampling, a standard procedure in patient care. Currently, these infants do not get any pain relief for this procedure. Several recent clinical studies have shown the usefulness of nitrous oxide (laughing gas) for treating pain for minor procedures in children 0 to 18 years, but these effects have not been exclusively studied in the newborn and infant populations. Animal studies have questioned the analgesic (pain-relieving) effect of nitrous oxide in very young animals. It is unclear if this also applies to humans. The purpose of this study is to investigate whether or not nitrous oxide has an analgesic (pain-relieving) effect in infants undergoing minor procedures in the neonatal period (less than 3 months).

Condition: Analgesic Affect

Treatment or Intervention: Drug- Nitrous Oxide

Phase III
Study Type: Interventional

Study Design: Randomized, Single Blind, Active Control, Single Group Assignment

Eligibility: Ages up to 3 Months, Both Genders

Criteria

Inclusion Criteria: Full-term babies up to three months old scheduled for heel stick blood draw.

Exclusion Criteria: preterm, difficult airway (micrognathia, cranio-facial malformation, choanal atresia, Pierre Robin syndrome, or Treacher Collins syndrome), sedated, intubated (including tracheostomy), have an oxygen requirement (FiO2>40%), anemia, bone marrow suppression, or cardiac defect

Location and Contact Information: UCLA Medical Center, Los Angeles, California, 90095, United States; Recruiting; Samuel Wald, MD 310-206-0085; swald@mednet.ucla.edu

Samuel Wald, MD, Principal Investigator

Study chairs or principal investigators: Samuel Wald, MD, Principal Investigator, UCLA Department of Anesthesiology

More Information

Study ID Numbers: 05-04-029-01
Last Updated: November 7, 2005
Record first received: November 7, 2005
ClinicalTrials.gov Identifier: NCT00250692
Health Authority: United States: Institutional Review Board
ClinicalTrials.gov processed this record on 2005-11-16

Study of MEDI-524 (Numax), for the Prophylaxis of Serious Respiratory Syncytial Virus (RSV) Disease in High-Risk Children

This study is currently recruiting patients

Purpose: The primary objective of this study is to compare the safety and efficacy of MEDI-524 to palivizumab when administered monthly by intramuscular (IM) injection for the reduction of the incidence of RSV hospitalization among children at high risk for serious RSV disease.

Condition: Respiratory Syncytial Virus Infections

Intervention: Drug: MEDI-524

Phase III
This study is recruiting throughout the world

Guisela Torres; 301-398-4222
torresg@medimmune.com

Study chairs or principal investigators: Genevieve Lonsosky, MD, Study Director, MedImmune, Inc.

Study Type: Interventional

Study Design: Prevention, Randomized, Double-Blind, Active Control, Parallel Assignment, Safety/Efficacy Study

Further Study Details: Primary Outcomes: The primary objective of this study is to compare the safety and efficacy of MEDI-524.

Secondary Outcomes: To compare the incidence of medically-attended lower respiratory illnesses (LRIs) between treatment groups; To compare the incidence of RSV-specific medically-attended LRI in a subset of patients; To compare the frequency and incidence of medically-attended otitis media (OM) infections between treatment groups; To compare the frequency of prescribed antibiotics for medically-attended LRI and medically-attended OM infections; To describe the trough serum concentrations of MEDI-524; To describe the immunogenicity of MEDI-524

Eligibility: Ages 6 Months - 24 Months, both Genders

Criteria

Inclusion Criteria:
- 24 months of age or younger at randomization (child must be randomized on or before his/her 24-month birthday) with a diagnosis of chronic lung disease (CLD) of prematurity requiring medical intervention/management (i.e., supplemental oxygen, bronchodilators, or diuretics) within 6 months before randomization—or
- 35 weeks gestational age or less at birth and 6 months of age or younger at randomization (child must be randomized on or before his/her 6-month birthday)

Exclusion Criteria:
- Hospitalization at the time of randomization (unless discharge is anticipated within 10 days)
- Mechanical ventilation or other mechanical support (including continuous positive airways pressure [CPAP])
- Life expectancy < 6 months
- Active RSV infection (a child with signs/symptoms of respiratory infection must have negative RSV testing)
- Known renal impairment or hepatic dysfunction
- Chronic seizure or evolving or unstable neurologic disorder
- Congenital heart disease [CHD] (children with uncomplicated CHD [e.g., patent ductus arteriosus (PDA), small septal defect] and children with complicated CHD that are currently anatomically and hemodynamically normal can be enrolled)
- Known immunodeficiency
- Mother with HIV infection (unless the child has been proven to not be infected)
- Known allergy to Ig products
- Receipt of palivizumab, RSV-IGIV, or other RSV-specific monoclonal antibody, or any other polyclonal antibody (for example, hepatitis B Ig, IVIG, VZIG) within 3 months prior to randomization
- Anticipated use of palivizumab or IVIG during the study (blood transfusions permitted)
- Previous receipt of RSV vaccines
- Participation in other investigational drug product studies

Location and Contact Information:

This study is recruiting throughout the world

Guisela Torres; 301-398-4222
torresg@medimmune.com

More Information

Study ID Numbers: MI-CP110
Last Updated: November 4, 2005
Record first received: August 10, 2005
ClinicalTrials.gov Identifier: NCT00129766
Health Authority: United States: Food and Drug Administration
ClinicalTrials.gov processed this record on 2005-11-16

Clinical Trial - Perinatal and Neonatal Medicine

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You may Browse by Condition, Disease or by Sponsor

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What's New - studies in the news
MEDLINEplus - authoritative consumer health information
Genetics Home Reference - consumer information about genes and genetic conditions
NIH Health Information - research supported by the NIH
Comprehensive Prenatal Test Expands Detection of Genetic Disorders

A new chromosomal test developed at Baylor College of Medicine (BCM) in Houston can now alert pregnant women to an array of fetal disorders otherwise undetectable by conventional tests. This testing is discussed in a commentary and editorial in today’s edition of the journal Nature.

“It’s the beginning of a sea change in prenatal diagnosis,” said Dr. Arthur Beaudet, chair of molecular and human genetics at BCM. “You are going to be able to detect a range of the most severe conditions, and in the future this can be cheaper than current methods hopefully using a very noninvasive approach.” The new test can find more disorders and is as at least as fast as previous techniques.

The technique could even lead to more general use of prenatal screening for these disorders, said Beaudet.

The new test uses a gene chip or microarray to analyze various areas of the human genome for abnormal regions that contain too many or too few copies of the genetic material. These gains or losses in DNA can lead to devastating genetic conditions that present serious disabilities for the lives of children born with them.

The microarray or gene chip is like a map that is covered with tiny dots consisting of DNA from known locations on each of the 46 chromosomes. DNA from the patient is labeled one color (for example, red), and DNA from a normal person (control) is labeled another color (in this example, green). The two DNAs are then mixed and added to the microarray. The appropriate part of the genome seeks out the appropriate dot of DNA on the chip and attaches to it. If the DNA in both patient and control is normal, then the two colors of the dye even out and that dot turns yellow. If there is too much DNA (as happens when there are three instead of two copies of a region or an entire chromosome), then the dot is more red because there is more of the patient’s DNA. If there is too little, the dot is greener because there is more of the control’s DNA and less of the patient’s.

Beaudet says the new test can accurately identify a number of chromosomal disorders early in pregnancy that previous screens could not. Among the disorders that this technique will detect are Di-George, Williams, Angelman, and Prader-Willi syndromes. It also detects a variety of gains or losses towards the ends (telomeres) of the chromosomes, which are important causes of many developmental disability syndromes.

For women already having amniocentesis or chorionic villus sampling, the new test can be an added analysis on the sample with no added risk. The risk of amniocentesis and chorionic villus sampling to the fetus is even less than has been suggested in the past. The procedure-related risk of amniocentesis is probably only 1:400-500, says Dr. Joe Leigh Simpson, chair of OB/GYN at BCM. Investigators at the University of California at San Francisco have suggested that it is cost-effective to offer traditional amniocentesis to all pregnant women.

“Offering the test to all pregnant women becomes even more attractive using the newer form of prenatal testing because it combines tests for many additional diseases,” Beaudet said. Women may increasingly be offered the choice of going straight to amniocentesis or chorionic villus sampling rather than the blood tests and ultrasound tests that are currently used to estimate risks of Down syndrome and decide which women are candidates for amniocentesis.

The comprehensive BCM test is expected to cost approximately $1,900 in addition to the usual costs for amniocentesis and prenatal testing. Procuring the same results using separate, conventional tests would cost around $20,000. More information about the test can be obtained by calling 1-800-411-4363.
When caring is critical...