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DEPARTMENTS

PEDIATRIC CARDIOLOGY TODAY

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INITIAL EXPERIENCE WITH BOSENTAN THERAPY IN PATIENTS WITH EISENMENGER'S SYNDROME

By Douglas D. Christensen, MD

Eisenmenger's Syndrome is a progressive, cyanotic congenital heart condition leading to irreversible pulmonary vascular disease with profound cyanosis and exercise intolerance. Though less common nowadays due to earlier surgical intervention for many congenital heart lesions, Eisenmenger's Syndrome can still be a complication in some children—especially in developing nations. Current treatments for Eisenmenger's Syndrome include: phlebotomy, supplemental oxygen and vasodilator therapy. The latter approach is usually achieved with continuous intravenous prostacyclin. Prostacyclin therapy, however, carries associated risks and inconveniences, including dislodged central venous lines, infections, infusion pump malfunctions, and the inconvenience of a permanent delivery system. While lung or heart-lung transplantation with repair of the congenital defect have been used in the treatment of Eisenmenger's Syndrome, these patients have the highest peri-operative mortality and the lowest 1-month survival rates among all lung transplant patients.

> ***"After treatment with Bosentan therapy, seven out of the ten patients showed an improvement in NYHA classification of one or more grades. "***

Bosentan is an orally active, nonpeptide, competitive antagonist of both ETA and ETB (endothelin type A and B) receptors, with a slightly higher affinity for the ETA receptor. Bosentan competes with Endothelin-1 (ET-1), a neurohormone that binds at the ETA and ETB receptors, leading to constriction of the pulmonary arteries when it binds to ETA receptors and vasodilatation when it binds to ETB receptors. Concentrations of ET-1 are elevated in the plasma and lung tissue of pulmonary artery hypertension patients, suggesting a pathogenic role of ET-1 in this disease. Serious adverse effects of Bosentan use include potential liver injury and teratogenicity. Other adverse events reported include headache, nasopharyngitis, flushing, hypotension, palpitations, dyspepsia, edema, fatigue and pruritus. While Bosentan has been used in adult and pediatric patients for the treatment of

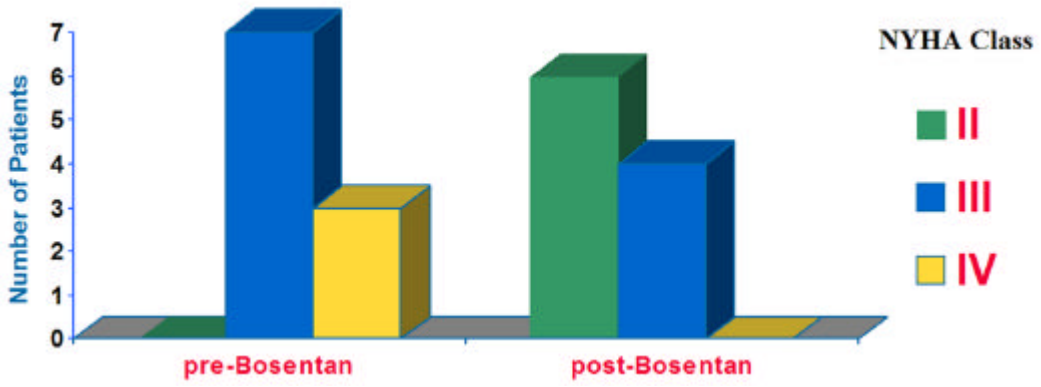

Table 1: New York Heart Association (NYHA) Classification (Class II, III, IV).

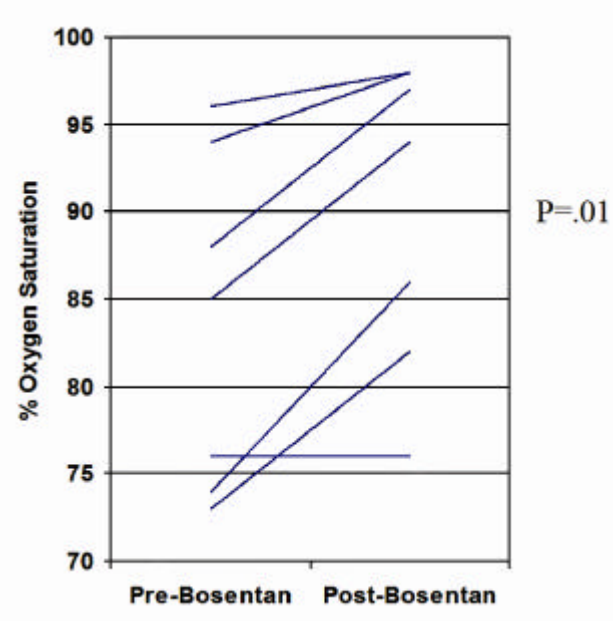

Table 2: Oxygen Saturation (Pre-Bosentan and Post Bosentan)

primary pulmonary artery hypertension, its use has not been reported in patients with Eisenmenger's Syndrome.

"This study suggests... that Bosentan therapy for Eisenmenger's Syndrome results in improved oxygenation and improved subjective functional status with no apparent adverse effects."

The purpose of this study was to report our initial experience with Bosentan therapy in patients with Eisenmenger's Syndrome. We conducted a retrospective chart review on ten patients (two males, eight females), aged between 23 and 68 years (mean 46.4 years) who were diagnosed with Eisenmenger's Syndrome. The diagnoses of congenital heart disease leading to Eisenmenger's Syndrome included: atrial septal defect (n=3), ventricular septal defect (n=4) and Tetralogy of Fallot (n=3). The main symptoms in all patients were dyspnea and exercise intolerance and all patients had severe functional limitation as assessed by the New York Heart Association (NYHA) functional status classification—in which higher grades are associated with greater limitations. Seven patients were classified in NYHA class III and three patients were in class IV. There were no patients in class II. Baseline pulse oximetry on room air was measured with a range of 72 to 96% (median 76%). Five of the ten patients were receiving supplemental oxygen (1-3 L/min by nasal cannula). All patients were being treated with concomitant medications which included diuretics (n=5), ACE inhibitors (n=4), Carvedilol (n=4), digoxin (n=3) and calcium channel blockers (n=2). All patients were started on Bosentan 62.5mg PO once a day. Liver function tests were monitored over two months and the dose was increased to the optimal dose of 125mg PO once a day. Thereafter liver function tests were monitored every three months. Clinic follow-up was performed every three months and room air oxygen saturation levels and NYHA functional status were recorded.

After treatment with Bosentan therapy, seven out of the ten patients showed an improvement in NYHA classification of one or more grades. Three patients had no change in NHYA classification (Table 1). Time of follow-up ranged from 2 to 14 months. Oxygen saturation levels at initiation of therapy were median of 76 % with a range from 72-96%. These levels increased after treatment from 2-14 months to median of 88%, (p=.01). (Table 2) There were no significant changes in liver function tests and no reports of other adverse effects. During the study period no patients discontinued Bosentan therapy and there were no deaths or interim hospitalizations.

This study suggests, therefore, that Bosentan therapy for Eisenmenger's Syndrome results in improved oxygenation and improved subjective functional status with no apparent adverse effects. We speculate that Bosentan therapy may be a valuable adjunct for standard medical therapy for the treatment of pulmonary hypertension in Eisenmenger's Syndrome and may obviate the need for lung or heart-lung transplantation in some patients.

For comments to this article, send email to: Comments@PediatricCardiologyToday.com

~PCT~

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Organizations Related to Eisenmenger's Syndrome

American Heart Association (AHA)
www.americanheart.org

American Organ Transplant Association
www.a-o-t-a.org

CHASE - Hospital for Sick Children
www.chasekids.org/links.html

Genetic Alliance
www.geneticalliance.org

Little Hearts, Inc.
www.littlehearts.net

March of Dimes Birth Defects Foundation
www.marchofdimes.com

NIH/National Heart, Lung and Blood Institute Information Center (NLBI)
rover.nhlbi.nih.gov

National Foundation For Transplants
www.transplants.org

National Transplant Assistance Fund
www.transplantfund.org

Second Wind Lung Transplant Association
www.2ndwind.org

PROFILE: CONGENITAL HEART INFORMATION NETWORK AND THE NATIONAL HEART DEFECT AWARENESS DAY - FEBRUARY 14, 2004

A group of dedicated family members, patients, friends and medical professionals are hoping the annual *National Heart Defect Awareness Day* will help raise awareness about congenital heart defects (CHD), the most common birth defect worldwide.

Last year the *National Heart Defect Awareness Day* had well over 100 hospitals, practices, organizations and various civic groups throughout the world participate in activities, celebrations, and media events.

In 1999, Jeanne Imperati, a Connecticut mother of a child with a congenital heart defect, conceived the idea for an annual awareness day to reduce childhood deaths, and increase funding to support CHD related causes and research. "Few people realize more babies are born with congenital heart defects - approximately 40,000 - than with Spina Bifida, Down's Syndrome and hearing loss. Yet, heart defects are sometimes overlooked and not routinely diagnosed in newborns."

In 1998 in the United States, 55,000 hospital admissions for treatment of CHD were recorded, a statistic which includes an estimated 20,000 operations performed for repair or palliation per year. (*American College of Cardiology, 32nd Bethesda Conference: Care of the Adult With Congenital Heart Disease*).

"An untold number of children and young adults are put at risk each year due to a lack of early screening for heart defects and childhood onset heart disease," said Mona Barmash, the founder of Congenital Heart Information Network, which sponsors the *National Heart Defect Awareness Day.*

Local coordinators nationwide are planning activities in recognition of National *Heart Defect Awareness Day 2004*. If you or your hospital or practice are already planning Awareness Day activities or would like more information visit www.tchin.org/aware, or call +215.493.3068.

~PCT~

The Congenital Heart Information Network

C.H.I.N., a 501(c)3 organization provides reliable information, support services and resources to families of children with congenital defects and acquired heart disease, adults with congenital heart defects, and the professionals who work with them.

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Alan D. Tong, MD, FACC
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CLINICAL TRIAL ABSTRACTS (CLINICALTRIALS.GOV)

Pediatric Heart Disease Clinical Research Network

~ currently recruiting patients~

Sponsored by National Heart, Lung, and Blood Institute (NHLBI)

Purpose: To evaluate novel treatment methods and management strategies to benefit children with structural congenital heart disease, inflammatory heart disease, heart muscle diseases, and arrhythmia.

Condition: Arrhythmia; Defect, Congenital Heart; Pediatric Heart Disease; Kawasaki Disease

Treatment or Intervention: Drug: Steroid therapy; Device: Biventricular pacing

Study Type: Interventional

Study Design: Diagnostic, Randomized

Further Study Details: Background: Treatment of congenital and acquired pediatric heart disease involves medical, surgical, and catheter-based approaches. Medical therapy is employed widely to treat various pediatric heart diseases including arrhythmias, heart failure, myocarditis, and coronary artery aneurysms arising after Kawasaki Disease. Few drugs used as "standard therapy", however, have been tested in randomized controlled trials in pediatrics. Emerging adult therapies, such as immune modulation in heart failure, may benefit children but are virtually untested in pediatric populations. In addition, pediatric heart failure can arise from multiple causes, including structural heart defects, heart muscle disease and inflammation, post-operative injury and edema, and poorly-controlled arrhythmias. Many structural congenital heart abnormalities are successfully corrected surgically. However, the optimal timing and approach for complex congenital structural malformations including the several malformations that lead to single ventricle physiology are not known, and the risks and benefits of devices compared to surgical repair of certain defects have not been studied systematically. In addition, the acute and chronic post-operative course can be complicated by conditions such as post-cardiopulmonary bypass syndrome (especially in infants), arrhythmias including those implicated in sudden death, neurodevelopmental deficits, ventricular dysfunction and heart failure, and coagulapthy leading to the need for reoperation. Treatment strategies for these conditions are not supported by systematic prospective clinical studies.

Most treatment decisions concerning many pediatric heart disease are not evidence-based. In the past 25 years, fewer than 40 randomized clinical trials have been conducted, of which nearly half dealt with patent ductus arteriosus in preterm infants. The major barriers to clinical studies in pediatric heart disease include the heterogeneity of conditions, the small numbers of individuals with a particular malformation or condition at any one center, differences in treatment approaches to particular problems, the absence of systematic centralized databases, and the lack of resources to provide national coordination of collaborative efforts. The network approach is an effective, flexible way to study adequate numbers of patients with uncommon diseases, such as congenital cardiovascular malformations.

Design Narrative: The network will establish and maintain the infrastructure for a data coordinating center and multiple clinical centers to conduct multiple clinical trials. Protocols under development include: Biventricular Pacing for Children with Dilated Cardiomyopathy and Heart Failure; Acetylcholinesterase (ACE) Inhibition in the Treatment of Mitral Valve Regurgitation After Repair of Complete Atrioventricular Canal Defects. Two recently developed and approved protocols have begun recruitment. They include: Trial of Pulse Steroid Therapy for Kawasaki Disease, and The Relationship Between Functional Health Status and Laboratory Parameters of Ventricular Performance After the Fontan Procedure. The approved Infant Single Ventricle Study will start recruitment in the Fall of 2003.

Eligibility: Both genders, ages up to 21 years.

Criteria: Varies with protocol

Location and Contact Information: Locations throughout the U.S. and Canada (MA, NY, NC, PA, SC, UT, Ontario)

Study chairs or principal investigators: Page Anderson, Duke University *ander005@mc.duke.edu*

W. Gersony, Columbia Presbyterian Med. Ctr.

Brian McCrindle, Hospital for Sick Children *brian.mccrindle@sickkids.ca*

LuAnn Minich, Primary Children's Medical Ctr. *pclminic@ihc.com*

Jane Newburger, Children's Hospital Boston *newburger@tch.harvard.edu*

J. Saul, Med. Univ. of S.C. *saulp@musc.edu*

Lynn Sleeper, New England Research Institute

Victoria Vetter, CHOP *vetter@email.chop.edu*

Study ID Numbers 138
Study Start Date September 2001;
Estimated Completion Date August 2006
Record last reviewed August 2003
NLM Identifier NCT00023517
ClinicalTrials.gov processed this record on 2003-12-02

Family Studies of Hypertrophic/ Dilated Cardiomyopathy

~ currently recruiting patients~

Sponsored by: National Heart, Lung, and Blood Institute (NHLBI)

Purpose: This study will examine blood cells of patients (and their relatives) with hypertrophic cardiomyopathy or dilated cardiomyopathy for genes that may cause or modify the disease. Cardiomyopathy causes thickening or stretching of the heart muscle that can

cause chest pain, shortness of breath, palpitations, and fainting. Cardiomyopathy sometimes runs in families and is caused by an abnormal gene or genes.

Patients diagnosed with hypertrophic cardiomyopathy or dilated cardiomyopathy, or both, may enroll in this study. Relatives of patients will also be studied.

Participants will have a review of their medical history and a brief physical examination, including and electrocardiogram (EKG) and echocardiogram-an ultrasound test of the heart. A small blood sample will be obtained for DNA (genetic) study.

Condition: Hypertrophic Cardiomyopathy; Congestive Cardiomyopathy

Study Type: Observational

Study Design: Screening

Further Study Details: Hypertrophic cardiomyopathy (HCM) is an important cause of sudden death in apparently healthy young individuals but its clinical manifestations are highly variable both within and between families. Linkage analysis and/or a candidate gene approach has been used to localize 10 genes, which when mutated, can cause HCM. Recently, mutations in disease genes for HCM have been shown to cause dilated cardiomyopathies. Thus, biased screening studies with HCM genes against patients with either hypertrophic or dilated cardiomyopathies are warranted. Clinical observations as well as experiments in our laboratory have demonstrated the contribution of modifier genes to the severity of any one individual's disease. Both biophysical and genomics studies in our laboratory are yielding a list of candidate modifier genes. The purpose of this protocol is to determine allele frequency of existing and newly identified genes for which there is mechanical, genomic or conceptual evidence that these genes modify or cause cardiac hypertrophy/dilation. Evidence for the effect of any one allele is established through a combination of association, linkage and/or mechanical analysis studies. The latter studies involve analysis of normal and transgenic animal skeletal/cardiac tissue from animals produced under the oversight of the Animal Use Committee.

Eligibility: Both genders are eligible for study

Inclusion and exclusion: See ClinicalTrial.gov

Expected Total Enrollment: 1000

Location and Contact Information: National Heart, Lung and Blood Institute (NHLBI), 9000 Rockville Pike, Bethesda, Maryland, 20892, United States; Recruiting Patient Recruitment and Public Liaison Office 1-800-411-1222 *prpl@mail.cc.nih.gov*

Study ID Numbers 020283; 02-H-0283
Study Start Date August 21, 2002
Record last reviewed October 23, 2003 Last Updated October 23, 2003
NLM Identifier NCT00045825
ClinicalTrials.gov processed this record on 2003-12-02

Evaluation of Argatroban Injection in Pediatric Patients Requiring Anticoagulant Alternatives to Heparin

~ currently recruiting patients~

Sponsored by: Texas Biotechnology Corp.

Purpose: The purpose of this study is to evaluate the safe and effective dose of Argatroban for prophylaxis and/or treatment of thrombosis in pediatric patients with current or previous diagnosis of heparin-induced thrombocytopenia (HIT) and thrombosis syndrome (HITTS), or who in the opinion of the investigator require alternative anticoagulation due to an underlying condition.

Condition: Thrombocytopenia; Thrombosis

Treatment or Intervention: Drug: Argatroban

Phase: Phase IV

Study Type: Interventional

Study Design: Treatment, Non-Randomized, Open Label, Uncontrolled, Single Group Assignment, Safety/Efficacy Study

Eligibility: Both genders, ages 4 Months - 16 Years.

Expected Total Enrollment: 24

Criteria: See ClinicalTrial.gov

CLINICALTRIALS

www.ClinicalTrials.gov

Clinical Trial Abstracts has been abstracted from the ClinicalTrials.gov Database (The NIH, Dept. of Health and Human Services, through the National Library of Medicine). *See www.ClinicalTrials.gov for additional up-to-date detail.*

ClinicalTrials.gov provides regularly updated information about federally and privately supported clinical research in human volunteers. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers. You may search the database by a number of criteria.

Search ClinicalTrials.gov:

Key Words or Specific Information

Key Words Search

Focused Search- search by disease, location, treatment or sponsor.

Browse

Browse by Condition - studies listed by disease or condition

Browse by Sponsor - studies listed by funding organization

Resource Information at ClinicalTrials.gov

Understanding Clinical Trials - information explaining and describing clinical trials

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

USEFUL WEBSITES
Associations and Societies

The Association for European Paediatric Cardiology (AEPC)
www.aepc.org/home.htm

Association of American Medical Colleges (AAMC)
www.aamc.org/start.htm

The British Cardiac Society
www.bcs.com/index.html

British Heart Foundation
www.bhf.org.uk/

British Pharmacopoeia Commission
www.pharmacopoeia.org.uk/

Canadian Cardiovascular Society
www.ccs.ca/

The Canadian Pediatric Cardiology Association (CPCA)
www.cardioped-canada.org/cpca.asp

The Canadian Generic Pharmaceutical Association (CGPA)
www.cdma-acfpp.org/index.html

Canadian Paediatric Society (CPS)
www.cps.ca/

Cardiovascular and Interventional Radiological Society of Europe (CIRSE)
www.cirse.org/

Location and Contact Information: Lara Bjorkquist, 713-578-6522 lbjorkquist@tbc.com

Locations throughout the U.S. (CA, IL, SC)

Study ID Numbers ARG-401
Record last reviewed January 2003
NLM Identifier NCT00039858
ClinicalTrials.gov processed this record on 2003-12-02

Study of Energy Expenditure in Infants With Ventricular Septal Defects

~ currently recruiting patients~

Sponsored by: National Center for Research Resources (NCRR), Indiana University

Purpose: Objectives: Compare the total daily energy expenditure in infants with ventricular septal defects vs. healthy control infants.

Condition: Heart Septal Defects, Ventricular

Study Type: Observational

Study Design: Natural History

Further Study Details: Protocol Outline: Height, weight, and vital signs (including oxygen saturation by pulse oximetry) are measured on Day 1. Resting energy expenditure, oxygen consumption (VO2), carbon dioxide production (VCO2), and resting respiratory exchange quotient (RQ) are measured using open circuit respiratory calorimetry on Day 1. Patients undergo assessment of total daily energy expenditure using the doubly labeled water method comprised of oral deuterium and oral oxygen O 18 with the next scheduled feeding on Day 1. Urine samples are collected prior to isotope administration, then serially for approximately 12 hours after isotope administration on Day 1, and then daily on Days 2-7. These samples are analyzed by mass spectrometry. On Day 1, patients also undergo echocardiogram to confirm size of defect and measure the degree of pulmonary/systemic blood flow ratio and pulmonary artery pressures.

Eligibility: Healthy Volunteers of both genders, ages 3 - 4 months.

Criteria: See ClinicalTrial.gov

Expected Total Enrollment: 20

Location and Contact Information: Indiana Univ., Indianapolis, IN U.S.A.

Study chairs or principal investigators: Catherine Leitch, Study Chair, Indiana Univ. 317-274-4920

Study ID Numbers NCRR-M01RR00750-9045; IU-9607-08; IU-9511-16
Study Start Date August 1994
Record last reviewed May 2002
NLM Identifier NCT00006272
ClinicalTrials.gov processed this record on 2003-12-02

Dexamethasone in Lupus Congenital Heart Block of Newborns

~ currently recruiting patients~

Sponsored by: National Institute of Arthritis and Musculoskeletal and Skin Diseases

Purpose: This study has two parts. The goal of the first part is to find out the usefulness of giving medications known as fluorinated steroids to pregnant women whose unborn children have a heart condition called congenital heart block (CHB). CHB occurs in some babies with neonatal lupus, a form of lupus that affects newborns but usually disappears by the time the infant is 3-6 months old. We will look at whether giving a steroid drug, such as dexamethasone, to pregnant women improves the heart function and general health of newborns who have autoantibody-associated CHB. This form of CHB is linked to the presence of certain blood proteins (antibodies) in the mother. Women enrolled must have antibodies to SSA/Ro and/or SSB/La and must be carrying a fetus with first, second, or third degree CHB diagnosed during gestation. It will be the decision of the physician and the mother as to whether a medication such as dexamethasone will be administered.

The second part of the study will examine pregnant women who are at high risk for having babies with CHB to identify the earliest signs of heart problems in the unborn child that can be detected using ultrasound testing. We will follow 100 mothers considered at high risk for having a child with CHB by doing

weekly echocardiograms (a noninvasive method that uses ultrasound to produce images of the heart) of the fetus from the 16th week of pregnancy. From week 28 to 34, echocardiograms will be performed every other week.

Condition: Congenital heart block; Neonatal lupus; Atrioventricular nodal dysfunction; Myocardial injury

Treatment or Intervention: Drug: Dexamethasone or other steroid, Physician's choice

Phase: Phase II

Study Type: Observational

Study Design: Screening, Longitudinal, Defined Population, Prospective Study

Further Study Details: The PRIDE (PR Interval and Dexamethasone Evaluation) study in CHB (congenital heart block) consists of two trials. The first is a prospective look at the course of CHB diagnosed in utero (in the presence or absence of treatment with steroids such as dexamethasone). Based on the seminal observation that isolated congenital CHB is strongly associated with maternal antibodies (Abs) to SSA/Ro and SSB/La ribonucleoproteins (RNP), we anticipate that we will elucidate pathogenetic mechanisms and develop appropriate treatments (the lauded "bench-to-bedside" approach) for CHB.

We will enroll 50 women, irrespective of disease activity, who are identified as carrying a fetus with CHB. Treatment will be the decision of the physician and patient. The study seeks to gather data culled from these decisions by closely following the subsequent course of the pregnancy. This will be accomplished by review of medical records and analysis of echocardiograms. By examining data from one particular category (for example, all patients receiving dexamethasone or all those not receiving any medical treatments), common outcomes will be assessed.

The primary outcomes we will evaluate include neonatal ventricular rate and ejection fraction at birth and presence or absence of abnormal fluid collection as assessed on the final fetal echocardiogram and obstetrical ultrasound before delivery. Secondary outcome measures include the degree of AV nodal block at birth, gestational age at birth, birth weight, cardiothoracic ratio, and death.

The second trial is observational, and its purpose is to identify the earliest noninvasive echocardiographic marker of AV nodal dysfunction and/or myocardial injury. It is important for two reasons: (1) it will identify whether the "subclinical" incidence of tissue injury exceeds overt injury manifest as advanced AV dissociation, a point that addresses basic research questions about the pathogenicity of anti-Ro/La Ab. (2) it will provide the optimal opportunity for reversibility of block if early lesions can be identified and shown to progress, a point critical to management.

We will follow 100 mothers considered at high risk for having a child with CHB, as defined by (1) presence of anti-Ro and/or anti-La Ab documented prior to pregnancy and a previous child with neonatal lupus or (2) presence of anti-Ro and/or anti-La Ab documented prior to pregnancy and a healthy child or no previous pregnancy. We will follow these women by weekly echocardiograms from 16 weeks of gestation with special attention to the mechanical PR interval. Mothers of children who develop first-, second-, or third-degree block will be entered into the first trial.

Eligibility: Healthy females, ages 16 - 50 years old

Criteria: See ClinicalTrial.gov

Expected Total Enrollment: 150

Location and Contact Information: Elaine Kiang, 212-598-6513 prideinchb@yahoo.com

Throughout the U.S. (CT, NY)

Study chairs or principal investigators : Jill P. Buyon, Principal Investigator, Hospital for Joint Diseases

Study ID Numbers NIAMS-055; R01 AR46265
Study Start Date October 2000; Estimated Completion Date October 2004
Record last reviewed September 2003
NLM Identifier NCT00007358
ClinicalTrials.gov processed this record on 2003-12-02

MEDICAL CONFERENCES

NewEra Cardiac Care Conference
January 9 - 11, 2004, Dana Point, CA
www.amainc.com/cardiac_care.html

International Congress XVII - Endovascular Interventions
February 8-12 2004, Scottsdale, AZ
www.amainc.com/index.html

Joint Interventional Meeting
February 12-14, 2004, Rome, Italy
www.jim-vascular.com/

ACC '04 (Annual Scientific Session)
March 7-10, 2004, New Orleans, LA
www.acc.org/2004ann_meeting/home/home.htm

29th Annual Scientific Meeting - 2004 SIR "The World of Intervention"
March 25-30, 2004, Phoenix, AZ
www.sirweb.org/annualMeeting/annualMeetingHome.shtml

39th Annual Meeting - Association for European Paediatric Cardiology
May 19-22, 2004 - Munich, Germany
http://www.i-plan.de/aepc/gi/index.html

14th World Congress in Cardiac Electrophysiology and Cardiac Techniques
June 16-19, 2004, Nice-France
http://www.cardiostim.fr/?Jpto=116&KM_Session=1ac0fda6f5e517af5d591a1a1705a5fa&Lang=GB&Tpl=program

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