Prospective Evaluation of Fetuses With Autoimmune-Associated Congenital Heart Block Followed in the PR Interval and Dexamethasone Evaluation (PRIDE) Study

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We evaluated the efficacy of dexamethasone (DEX) in anti-SSA/Ro–exposed fetuses newly diagnosed with congenital heart block. Previous use of DEX has been anecdotal with varying reports of therapeutic benefit. This was a multicenter, open-label, nonrandomized study involving 30 pregnancies treated with DEX (22 with third-degree block, 6 with second-degree block, 2 with first-degree block) and 10 untreated (9 with third-degree block, 1 with first-degree block). Initial median ventricular rates, age at diagnosis, and degree of cardiac dysfunction were similar between groups. Six deaths occurred in the DEX group. There was no reversal of third-degree block with therapy or spontaneously. In fetuses treated with DEX, 1/6 with second-degree block progressed to third-degree block and 3 remained in second-degree block (postnatally 1 paced, 2 progressed to third degree); 2 reverted to normal sinus rhythm (NSR; postnatally 1 progressed to second degree). DEX reversed the 2 fetuses with first-degree block to NSR by 7 days with no regression at discontinuation. Absent DEX, the 1 with first-degree block detected at 38 weeks had NSR at birth (overall stability or improvement in 4 of 8 in the DEX group vs 1 of 1 in the non-DEX group). Median gestational birth age was 37 weeks in the DEX group versus 38 weeks in the non-DEX group ($p = 0.019$). Prematurity and small size for gestational age were restricted to the DEX group. Pacemaker use and growth parameters at birth and 1 year were similar between groups. In conclusion, these data confirm the irreversibility of third-degree block and progression of second- to third-degree block despite DEX. A potential benefit of DEX in reversing first- or second-degree block was supported in rare cases but should be weighed against potential steroid side effects such as growth restriction. © 2009 Elsevier Inc. (Am J Cardiol 2009;103:1102–1106)

Although evidence is limited and uncontrolled, maternal dexamethasone (DEX) has been utilized to treat fetal congenital heart block (CHB) in the anticipation that it may decrease the degree of block and/or prevent or ameliorate an associated cardiomyopathy.[1] Accordingly, a multicenter study was initiated to prospectively evaluate the efficacy of DEX in anti-SSA/Ro–exposed fetuses newly diagnosed with varying degrees of CHB. This study was part of the PR Interval and Dexamethasone Evaluation (PRIDE) study, in which the unaffected fetuses were reported separately.[2] Randomization of the treatment was not feasible given the rapidity with which institutional review board (IRB) approval was required. Thus, therapeutic decisions were made by the physicians and patients.

Methods

Patients entered this prospective, multicenter, observational study from December 2000 to April 2006. A total of 40 pregnant women with anti-SSA/Ro antibodies (with/without anti-SSB/La antibodies) were enrolled from 33 centers across the United States by participating clinicians who included rheumatologists, pediatric cardiologists, and obstetricians. The study was approved by the IRB of the New York University School of Medicine (New York, New York). Written informed consent was obtained from all subjects who agreed to have medical records and echocardiographic tapes evaluated.

Although the initial study was designed to be a randomized controlled trial of DEX 4 mg/day compared with placebo, this was not feasible because (1) it proved impossible to obtain IRB approval from the many sites within a week of identification of an affected fetus and (2) the first several women refused randomization. There-

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fore, the decision to treat with DEX was made by the managing physicians.

At study entry, all patients fulfilled the following criteria, namely (1) presence of anti-SSA/Ro and/or anti-SSB/La antibodies documented by a commercial laboratory or in the research laboratory of JPB and (2) presence of any degree of fetal heart block diagnosed echocardiographically. Exclusion criteria included the presence of structural heart disease associated with heart block (e.g., heterotaxia, complete atrioventricular septal defect) or the absence of acceptable quality imaging as determined in the core laboratory.

Data were obtained on maternal health status and previous and current pregnancies. Mothers could be clinically asymptomatic or have a rheumatic disease. Rheumatologic diagnoses were assigned based on case-report forms filled out by the participating obstetricians and cardiologists performing the echocardiographies and verified by telephone interviews and review of medical records when available. The following categories were assigned in the majority of cases: (1) asymptomatic if a patient denied any clinical symptoms that would be consistent with systemic lupus erythematosus (SLE) or Sjögren syndrome (SS); (2) undifferentiated autoimmune syndrome (UAS) if insufficient criteria for SLE or SS; (3) SLE if 4 American College of Rheumatology criteria were satisfied[3]; (4) possible, probable, or definite SS if patients had at least dry eyes and/or dry mouth plus evidence of objective criteria in addition to autoantibodies according to the European classification[4]; and (5) SLE and SS.

Fetal echocardiographic protocols were established focusing on the evaluation of structural heart disease, presence of hydrops fetalis or abnormal fluid collections, assessment of systolic ventricular function by M-mode or 2-dimensional echocardiography, presence of valvular regurgitation by Doppler, and qualitative tissue characteristics on 2-dimensional echocardiogram.[2]

Heart rate and rhythm were determined by Doppler or M-mode echocardiography, allowing for the detection of second- or third-degree CHB. To detect first-degree block, the fetal mechanical Doppler PR interval was determined during 1:1 conduction, according to a method previously developed and validated.[5–7] Briefly, from an apical 5-chamber or left ventricular long-axis view, the pulsed Doppler sample volume was placed in the left ventricular outflow tract between the anterior leaflet of the mitral valve and the aortic valve. The pulsed Doppler signal thus obtained showed simultaneously the mitral valve inflow and the aortic outflow signals. An interval was then measured from the onset of the mitral a wave (mechanical atrial systole) to the beginning of aortic flow (mechanical ventricular systole). A PR interval of $\geq$150 ms (3 SD above the mean) was considered first-degree block.

All submitted fetal and postnatal echocardiograms and electrocardiograms were over read in the core laboratory. Any disputed results were adjudicated by consensus opinion. Electrocardiograms and echocardiograms were requested at birth and at 1 year of age. Growth parameters at birth and 1 year were evaluated.

All sera were initially evaluated in the clinical immunology laboratory of the New York University Hospital for Joint Diseases. Specifically, screening evaluation for the presence of antibodies to anti-SSA/Ro and/or anti-SSB/La was done by enzyme-linked immunosorbent assay (Diamedix Corporation, Miami, Florida). In this commercial test, the cutoff for normal has been established at 19 EU for anti-SSA/Ro and SSB/La antibodies. However, patients with anti-SSA/Ro titers $<$35 EU were not included in the study. In addition to evaluation by commercial enzyme-linked immunosorbent assay, sera were evaluated by enzyme-linked immunosorbent assay using the recombinant proteins 48-kD SSB/La, 52-kD SSA/Ro, and 60-kD SSA/Ro, which were synthesized and purified as previously described.[2,8]

Table 1
Clinical parameters for groups treated and not treated with dexamethasone

	DEX (n = 30)	No DEX (n = 10)	p Value
Age at diagnosis (gestational wks)			
No. of subjects	30	10	
Mean	22.1	24.8	
Median	21.5	23.5	0.09
Range	18–30	20–38	
Ventricular rate (beats/min)			
No. of subjects	28*	9*	
Mean	69	62	
Median	60	60	0.9
Range	48–120	50–70	
Cardiac manifestations other than purely conduction system disease			
No. of subjects	30	10	
Manifestation	7 (23%)†	2 (20%)‡	1.0
Age at birth (gestational wks)			
No. of subjects	26§	10	
Mean	36.3	38.2	
Median	37	38	0.02
Range	28.5–40	36.5–40	
Pacemaker			
No. of subjects§	26	10	
Paced	11 (42%)	5 (50%)	0.72

* Excludes first-degree block (2 in DEX group, 1 in no-DEX group).
† Three pericardial effusions, 1 cardiomegaly, and 3 atrioventricular valve regurgitations.
‡ One scalp edema and 1 atrioventricular valve regurgitation.
§ Excludes 4 deaths.

Continuous variables such as gestational age and ventricular rate at diagnosis were compared between treatment groups using the Mann-Whitney test (Instat 3, GraphPad, San Diego, California). Categorical variables were compared using Fisher's exact test (Instat 3). A p value $<$0.05 was considered statistically significant.

Results

Forty mothers identified with a fetus with CHB were enrolled. Maternal health status was as follows: 11 women were asymptomatic, 10 had SS, 6 had SLE, 1 had SLE/SS, 1 had discoid lupus, 10 had UAS, and 1 had rheumatoid arthritis. Recurrent fetal disease was common: 4 women (10%) had a previous offspring with CHB, and 5 women (13%) had a previous infant with the characteristic rash of neonatal lupus. All mothers with a previously affected child were in the DEX group.