Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 57, No. 6, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.09.044

Use of Intravenous Gamma Globulin and Corticosteroids in the Treatment of Maternal Autoantibody-Mediated Cardiomyopathy

Sara M. Trucco, MD,* Edgar Jaeggi, MD,§ Bettina Cuneo, MD,¶ Anita J. Moon-Grady, MD,*† Earl Silverman, MD,‖ Norman Silverman, MD,‡ Lisa K. Hornberger, MD*

San Francisco, Sacramento, and Palo Alto, California; Toronto, Ontario, Canada; and Oak Lawn, Illinois

Objectives This study sought to evaluate the outcome of maternal autoantibody-mediated fetal cardiomyopathy/endocardial fibroelastosis following intravenous gamma globulin (IVIG) and corticosteroid therapy.

Background We have previously shown that 85% of fetuses and infants with maternal autoantibody-mediated fetal cardiomyopathy/endocardial fibroelastosis suffer demise or need for transplant. In an attempt to improve this outcome, in 1998, we began to empirically treat affected patients with IVIG and corticosteroids.

Methods We reviewed the clinical records and echocardiograms of 20 affected patients encountered in our institutions and treated with IVIG and corticosteroids from 1998 to 2009.

Results All 20 were initially referred at a median gestational age of 23 weeks (range 18 to 38 weeks). Nineteen mothers were anti-Ro antibody positive, 8 anti-La antibody positive, and 7 had clinical autoimmune disease. Endocardial fibroelastosis was seen in 16 and was not obvious in 4 others with reduced ventricular function, and 16 (80%) had reduced or borderline ventricular shortening fraction (≤30%) before or after birth. Eighteen had atrioventricular block at referral (16 in 3°). During pregnancy, maternal IVIG was given in 9 and dexamethasone in 17. After birth, 17 infants received IVIG (n = 14) and/or corticosteroids (n = 15). Twelve underwent pacemaker implantation. Four with hydrops at presentation died perinatally, despite initial improvement in function in 3. At a median follow-up of 2.9 years (1.1 to 9.8 years), 16 (80%) patients are currently alive with normal systolic ventricular function and 6 are not paced.

Conclusions Treatment of maternal autoantibody-mediated fetal cardiomyopathy/endocardial fibroelastosis with IVIG and corticosteroids potentially improves the outcome of affected fetuses. Further studies are needed to determine the optimal dose and timing of IVIG administration. (J Am Coll Cardiol 2011;57:715–23) © 2011 by the American College of Cardiology Foundation

Anti-Ro(SSA) and anti-La(SSB) antibodies are found in patients with autoimmune diseases including systemic lupus erythematosus (SLE) and Sjögren syndrome (1), but may also be identified in pregnant women without autoimmune disease (2). Neonatal lupus erythematosus results when these maternal autoantibodies (MAb) pass through the placenta and deposit on fetal tissues, including the heart (3,4). Clinical fetal myocardial disease is observed in 1% to 2% of pregnancies with MAb, typically between 20- and 24-weeks gestational age (GA) (5). In most affected fetuses, myocardial damage is largely confined to the conduction system with evolution of atrioventricular block (AVB). Approximately 20% of affected fetuses, however, can develop more diffuse myocardial disease manifested as cardiomyopathy (CM) and usually associated with endocardial fibroelastosis (EFE) (2,6,7), and this may occur with or without clinical conduction system abnormalities. The prognosis for fetuses and infants with diffuse MAb-CM/EFE is generally poor, with death or need for cardiac transplantation in 85% despite successful pacemaker therapy (6–8). A standard treatment approach in pregnancies with MAb-related fetal disease, including maternal dexamethasone and beta-sympathomimetic therapy in conjunction with more aggressive surveillance and perinatal management, has been shown to decrease morbidity and improve outcomes (9). A closer look at our previous series, however, reveals that fetuses who developed MAb-CM/EFE despite dexamethasone and beta-

From the *Pediatric Cardiology, University of California, San Francisco, San Francisco, California; †Pediatric Cardiology, University of California, Davis, Sacramento, California; ‡Pediatric Cardiology, Stanford University, Palo Alto, California; §Pediatric Cardiology, The Hospital for Sick Children, Toronto, Ontario, Canada; ‖Rheumatology, The Hospital for Sick Children, Toronto, Ontario, Canada; and the ¶Pediatric Cardiology, Hope Children's Hospital, Oak Lawn, Illinois. The authors have reported that they have no relationships to disclose. Thomas P. Graham Jr., MD, served as a Guest Editor for this paper.

Manuscript received May 15, 2010; revised manuscript received September 28, 2010, accepted September 29, 2010.

Abbreviations and Acronyms

AVB = atrioventricular block
CM = cardiomyopathy
DDD = dual mode, dual pacing, dual sensing
EFE = endocardial fibroelastosis
GA = gestational age
Ig = immunoglobulin
IVIG = intravenous gamma globulin
MAb = maternal autoantibodies
SF = shortening fraction
SLE = systemic lupus erythematosus
VVI = ventricular inhibited

sympathomimetics were responsible for 80% of all fetal deaths and 44% of post-natal deaths or cases requiring cardiac transplantation (9).

In 1998, a new treatment strategy of administrating intravenous gamma globulin (IVIG) and corticosteroids, either before or after birth, following a diagnosis of fetal MAb-CM/EFE was initiated. Use of IVIG was justified based on our discovery of diffuse immunoglobulin (Ig) G deposition, IgM, and T-cell infiltration throughout the myocardium, suggesting MAb induces a fetal immune response leading to CM/EFE (6,7). In fact, of the patients with MAb-CM/EFE described in our previous report (6), the only fetal survivor received IVIG shortly after birth. Additionally, the use of IVIG and corticosteroids to treat other inflammatory disorders, such as SLE and Sjögren syndrome, has been well described (10,11). We hypothesized that fetuses and infants with MAb-CM/EFE treated with IVIG and corticosteroids would have better outcomes than those treated with corticosteroids alone. This study reports the outcomes of this novel treatment strategy as experienced in 4 fetal and neonatal treatment centers with comparison to historical controls.

Methods

This study was a multicenter, retrospective review that included patients from the University of California, San Francisco; the Hospital for Sick Children, Toronto, Ontario; the University of California, Davis, Sacramento; and the Heart Institute for Children, Oak Lawn, Illinois. We included all fetuses and infants of mothers with anti-Ro and/or anti-La antibodies with evidence of MAb-CM/EFE defined by the presence of obvious EFE by echocardiography and/or myocardial systolic dysfunction. All were treated with IVIG and corticosteroids before or after birth. Fetuses and infants with and without AVB and those with simple congenital heart defects were included. Patients with isolated AVB without CM or EFE, and those with more complex structural heart disease were excluded.

The clinical presentation, management, and outcome of 20 consecutive cases of MAb-CM/EFE encountered from 1998 to 2009 were reviewed. Clinical data collected included GA at diagnosis of fetal heart disease; AVB severity; timing, type, and dose of therapy; GA at birth; age at pacemaker insertion, subsequent interventions, and at most recent follow-up; age at time of death; and cause of death. Maternal data collected included MAb positivity, presence of clinical autoimmune disease, age at pregnancy, previously affected children, and medications and doses received during pregnancy.

Echocardiographic parameters collected pre-natally included atrial and ventricular rates, ventricular systolic function, severity of tricuspid and mitral insufficiency, and the presence of any structural heart defects. In cases where the fetus was not in AVB, the AV interval (reflecting PR interval) was also measured using previously validated Doppler techniques (12). Fetal 3° AVB was diagnosed in cases where there was no mechanical relation between atrial and ventricular contraction (13). Ventricular shortening fraction (SF) was calculated with comparison to normal values and considered abnormal if <28% or borderline in 3° AVB if 28% to 30% (14). Endocardial fibroelastosis was suspected when echogenic areas within the endocardium of atria and ventricles, papillary muscles, and chordae were identified (6), and it was further categorized by severity (Fig. 1). Post-natal echocardiograms were also reviewed to document valve insufficiency, degree and location of EFE, ventricular function (SF by M-mode and ejection fraction, available consistently in last exam, by biplane Simpson), and presence of structural heart disease. Autopsy findings were reviewed. The research ethics boards of the participating institutions approved this investigation.

Statistical analysis. Simple statistics were calculated using Microsoft Excel for Mac (version 11.2.3, Microsoft Corp., Redmond, Washington).

Results

Clinical features. Table 1 details the characteristics of the 20 patients encountered. Eighteen were from singleton pregnancies and 2 were dichorionic, diamniotic twins. The 19 pregnancies were diagnosed with fetal cardiac disease at a median GA of 23 weeks (range 18 to 33 weeks). Fetal echocardiography referral was for fetal bradycardia in 17 (85%) and suspected CM/EFE in 3 (15%). Median maternal age was 29 years (22 to 38 years). Nineteen mothers were anti-Ro and 8 anti-La antibody positive. For one other with SLE referred at 38 weeks for delivery, specific antibody type was not available. Seven mothers had clinical autoimmune disease: 5 SLE, 1 hypothyroidism, one rheumatoid arthritis. Twelve were clinically asymptomatic. One mother had a previous infant with AVB.

At initial referral, 16 fetuses had 3° AVB, 1 had 2° AVB, 1 had 1° AVB, and 2 had a normal atrial rhythm with a normal AV interval. Endocardial fibroelastosis was identified in 16 (13 pre-natally, 3 post-natally) and was considered qualitatively severe in 3, moderate in 6, and mild in 7. MAb-CM/EFE was suspected in 4 others with myocardial systolic dysfunction but without obvious myocardial echogenicity. Reduced or borderline left, right, or biventricular SF was present in 11 fetuses at presentation or pre-natal follow-up. Five with 3° AVB developed hydrops (2 with small effusions, 3 with moderate-large effusions and/or ascites), and 1 in 3° AVB had an isolated pericardial effusion