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## Transplacental Fetal Treatment Improves the Outcome of Prenatally Diagnosed Complete Atrioventricular Block Without Structural Heart Disease

Edgar T. Jaeggi, MD; Jean-Claude Fouron, MD; Earl D. Silverman, MD, FRCPC; Greg Ryan, MB; Jeffrey Smallhorn, MBBS; Lisa K. Hornberger, MD

**Background**—Untreated isolated fetal complete atrioventricular block (CAVB) has a significant mortality rate. A standardized treatment approach, including maternal dexamethasone at CAVB diagnosis and  $\beta$ -stimulation for fetal heart rates  $<55$  bpm, has been used at our institutions since 1997. The study presents the impact of this approach.

**Methods and Results**—Thirty-seven consecutive cases of fetal CAVB since 1990 were studied. Mean age at diagnosis was  $25.6 \pm 5.2$  gestational weeks. In 33 patients (92%), CAVB was associated with maternal anti-Ro/La autoantibodies. Patients were separated into those diagnosed between 1990 and 1996 (group 1;  $n=16$ ) and those diagnosed between 1997 and 2003 (group 2;  $n=21$ ). The 2 study groups were comparable in the clinical presentation at CAVB diagnosis but did differ in prenatal management (treated patients: group 1, 4/16; group 2, 18/21;  $P<0.0001$ ). Overall, 22 fetuses were treated, 21 with dexamethasone and 9 with  $\beta$ -stimulation for a mean of  $7.5 \pm 4.5$  weeks. Live-birth and 1-year survival rates of group 1 were 80% and 47%, and these improved to 95% for group 2 patients ( $P<0.01$ ). The 21 patients treated with dexamethasone had a 1-year survival rate of 90%, compared with 46% without glucocorticoid therapy ( $P<0.02$ ). Immune-mediated conditions (myocarditis, hepatitis, cardiomyopathy) resulting in postnatal death or heart transplantation were significantly more common in untreated anti-Ro/La antibody-associated pregnancies compared with patients treated with steroids (0/18 versus 4/9 live births;  $P=0.007$ ).

**Conclusions**—A standardized treatment approach, including transplacental fetal administration of dexamethasone and  $\beta$ -stimulation at heart rates  $<55$  bpm, reduced the morbidity and improved the outcome of isolated fetal CAVB. (*Circulation*. 2004;110:1542-1548.)

**Key Words:** heart block ■ fetus ■ cardiotoxic agents ■ steroids ■ pregnancy

Isolated congenital complete atrioventricular block (CAVB) is caused predominantly by maternal anti-Ro and anti-La autoantibodies.<sup>1</sup> These antibodies enter the fetal circulation in the middle of the second trimester and may trigger immune-mediated inflammation of the atrioventricular (AV) nodal and myocardial tissues in a susceptible fetus. Subsequent replacement of the AV node and necrotic myocytes with fibrosis commonly results in CAVB and, if severe enough, in endocardial fibroelastosis (EFE) and dilated cardiomyopathy.<sup>2-4</sup> Fetal CAVB develops in 1% to 2% of anti-Ro/La antibody-positive pregnancies, typically between 20 and 24 weeks of gestation.<sup>5,6</sup> Viral infections and long-QT syndrome might be responsible for autoantibody-negative cases of isolated CAVB.<sup>7,8</sup> There is a significant risk of death, particularly in association with fetal hydrops, poor ventricular function, heart rates  $<55$  bpm, and/or premature delivery.<sup>9-11</sup> Most published data on outcome reflect the “natural” course

of prenatally diagnosed heart block, covering eras before the use of antenatal therapies. Transplacental treatment strategies using antiinflammatory and  $\beta$ -mimetic agents are aimed at preventing or modulating risk factors associated with a poor outcome. The use of dexamethasone therapy is based on the assumption that the cause of isolated CAVB is an inflammatory carditis. We hypothesized that the use of dexamethasone with and without  $\beta$ -sympathomimetics would improve fetal outcome. To test this hypothesis, we compared the outcome of fetuses diagnosed with CAVB before (1990–1996) and after (1997–2003) the routine use of maternal dexamethasone at 2 large perinatal centers.

### Methods

The clinical presentation, management, and evolution of all cases of isolated fetal CAVB encountered at our institutions since 1990 were reviewed. CAVB was considered to be “isolated” if no or only minor

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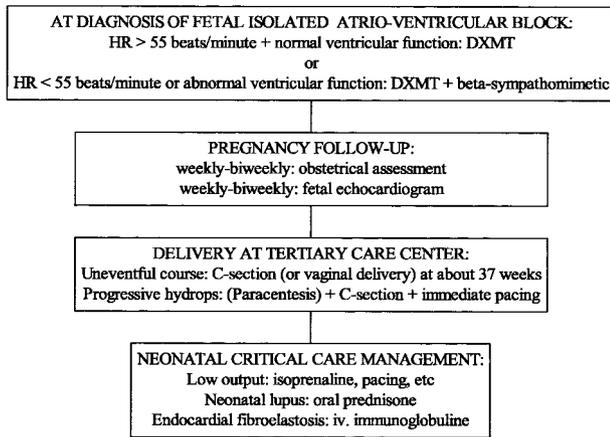
From the Divisions of Cardiology (E.T.J., J.S., L.K.H.) and Rheumatology (E.D.S.), Department of Pediatrics, The Hospital for Sick Children, and the Fetal Medicine Unit (G.R.), Mount Sinai Hospital, University of Toronto, Toronto; and the Division of Cardiology, Department of Pediatrics, Sainte-Justine Hospital, University of Montreal, Montreal (J.C.F.), Canada. Dr Hornberger is now at the University of California, San Francisco Children's Hospital, Department of Pediatrics, Division of Cardiology, The Fetal Cardiac Program, San Francisco, Calif.

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**Figure 1.** Protocol used since 1997 for management of prenatally diagnosed isolated CAVB (DXMT indicates dexamethasone; HR, heart rate).

anatomic cardiac anomalies were diagnosed prenatally or postnatally. All patients were examined by at least one of the investigators at each institution. The Institutional Review Boards of the Hospital for Sick Children and the Sainte-Justine Hospital approved this retrospective study.

Management during the 2 study eras reflects the standard of care at each institute. Since 1997, pregnancies were managed according to a treatment protocol as outlined in Figure 1. At the time of diagnosis of heart block, maternal dexamethasone (4 or 8 mg/d for 2 weeks, followed by 4 mg/d) was initiated and, when possible, maintained for the duration of the pregnancy, tapering at times (2 mg/d) in the third trimester. If the average heart rate declined below 55 bpm, a  $\beta$ -sympathomimetic agent was added. A combined pediatric cardiology, rheumatology, and obstetrics team closely monitored the affected pregnancies, with delivery being near 37 weeks of gestation in uncomplicated pregnancies and neonatal care being in the critical care unit.

By contrast, between 1990 and 1996, most pregnancies with isolated CAVB were followed up by serial echocardiography without an attempt to alter the perinatal outcome by transplacental therapy. If prenatal treatment was elected during this era (n=4), it was inconsistent with the present management protocol. For example, none of the 3 patients with fetal heart rates <55 bpm received glucocorticoid and  $\beta$ -sympathomimetic therapy, and dexamethasone was given only temporarily during midgestation to the remaining patient with a faster heart rate.

AV block was defined as complete if there was no mechanical relationship between atrial and ventricular contractions on M-mode or Doppler echocardiography. The gestational age at detection of heart block was taken as the earliest documentation of the conduction anomaly. Fibrosis of the endomyocardium was identified as areas of persistently increased echogenicity of endocardial surfaces. It was graded either as mild, if EFE appeared to be limited to small areas, or as severe, if there was extensive involvement of one or both ventricles. A diagnosis of EFE was based on echocardiography and, if applicable, on necropsy.<sup>3</sup>

Collected data included the presence of maternal anti-Ro/La antibodies, gestational ages at diagnosis of AV block, disease-related complications, type and duration of treatment, morbidity, and outcome. The videotaped recordings of all echocardiographic examinations were reviewed to determine the evolution of cardiac rhythm, rates, and function and disease-related findings. A response to  $\beta$ -sympathomimetic therapy was defined as a persisting increase in fetal heart rate >5 bpm for at least 2 weeks after initiation. ECGs were reviewed for the degree of AV block, heart rates, and QRS and QT intervals.

To determine whether therapy altered the outcome, we created 2 study populations on the basis of the era of diagnosis of CAVB and whether the fetus received steroid treatment.

## Statistical Analysis

Data were expressed as frequencies or mean and SD. Comparisons between groups were performed with the  $\chi^2$  or Fisher's exact test for categorical variables and the Student's *t* test for continuous variables. Kaplan-Meier estimates were used to plot survival curves, and log-rank tests were used to compare those with and without fetal treatment.

## Results

### Clinical Features

Table 1 details the characteristics of 37 patients in chronological order of CAVB diagnosis. Maternal anti-Ro/La autoantibodies were found in 33 pregnancies (92%), but only 5 mothers had previously diagnosed autoimmune disease. Of the 4 patients without circulating autoantibodies, 1 had congenital long-QT syndrome, with the pathogenesis of the rest being unknown. Most mothers were referred for fetal bradycardia, but 3 with maternal autoantibodies were seen before developing AV block. Patients 32 and 35 had normal fetal echocardiograms at 20 weeks of gestation. Patient 26 was assessed at 21 weeks for fetal arrhythmia and was found to have multiple isolated premature beats.

All 37 patients had CAVB at the time of diagnosis of the AV conduction defect. Fetal hydrops, initially present in 3 of the 37 patients (8%) (patients 11, 19, and 34), was associated with mild (n=1) or severe (n=2) EFE and slow ventricular rates ranging from 34 to 55 bpm. Of the 34 nonhydropic fetuses, 9 had isolated mild pericardial effusions, which did not progress. One patient (patient 15) with a moderate pericardial effusion developed hydrops related to immune-mediated hemolytic anemia between 32 and 34 weeks. EFE was diagnosed in 8 fetuses and 1 infant, in all patients secondary to anti-Ro/La antibodies. Four patients (patients 3, 11, 19, and 34) had diffuse biventricular EFE with reduced contractility. In the remaining 5 fetuses, fibrosis was more localized and affected predominantly the papillary muscles (patients 24, 25, and 36), the left ventricular septum (patient 12), or the left atrial septum and free wall (patient 35). Of the 5 fetuses with mild EFE, patient 12 developed significant myocardial dysfunction perinatally.

### Management

Table 2 describes the characteristics of the patients, divided into the 2 study eras. The only statistically significant difference between the 2 populations was that patients seen since 1997 were more likely to have received transplacental fetal therapy than those diagnosed earlier. Table 3 specifies the therapy that fetuses received.

Three pregnancies with immune-mediated CAVB were terminated (patients 11, 34, and 36), 2 presenting with severe EFE and hydrops. Patient 36 was treated with dexamethasone and salbutamol (40 mg/d) for 2 weeks before termination of pregnancy at 23 gestational weeks. Echocardiography revealed moderate tricuspid valve regurgitation, EFE of the tricuspid valve papillary muscles, a heart rate of 47 bpm, and no evidence of congestive heart failure. Fifteen (44%) of the 34 patients with ongoing pregnancies were diagnosed between 1990 and 1996. During this era, 4 mothers were treated with dexamethasone (n=3) or a  $\beta$ -agonist (n=1). By contrast, 18 (95%) of 19 ongoing pregnancies with isolated

**TABLE 1. Characteristics of 37 Patients Diagnosed Prenatally With Isolated Complete AV Block (1990–2003)**

Patient	Year	GA	Antibodies	Hydrops	EFE	A Rate	V Rate	Prenatal Treatment	GA Birth	Postnatal Treatment	Outcome
1	1990	20	Ro/La	–	–	158	72	–	†		FD
2	1990	35	Ro	–	–	130	40	–	37	Isoprenaline, PPM	Alive
3	1991	20	Ro	–	+	140	56	–	37	PPM	Htx 3 years
4	1991	27	Ro/La	–	–	140	60	–	27	Isoprenaline, dopa, steroids, PPM	NND
5	1991	37	Ro/La	–	–	125	50	–	37	PPM	Alive
6	1993	27	Ro/La	–	–	95	48	Dexa	39	Isoprenaline, TPM, PPM	Alive
7	1994	20	Ro/La	–	–	137	60	–	35†		FD
8	1994	23	Ro	–	–	141	53	Dexa	35†		FD
9	1994	28	Negative	–	–	132	60	–	37	PPM	Alive
10	1994	26	Ro/La	–	–	155	80	–	37	No treatment	Alive
11	1995	20	Ro	+	+	175	55	–	20†		TOP
12	1995	36	Ro	–	(+)	140	45	–	37	Isoprenaline, PPM, steroids, ECMO	NND
13	1995	35	Negative	–	–	130	40	–	37	Isoprenaline, TPM	NND
14	1996	18	Ro	–	–	140	60	Dexa	34	No treatment	Alive
15	1996	32	Ro	+	–	135	54	$\beta$ -S	38	Isoprenaline, dopa, TPM, PPM, frusemide	NND
16	1996	24	Ro/La	–	–	135	45	–	28	Isoprenaline, PPM	D 6 months
17	1997	26	Ro/La	–	–	145	70	Dexa	37	No treatment	Alive
18	1997	18	Ro/La	–	–	133	61	Dexa	33	Isoprenaline, dopa, TPM	Alive
19	1997	26	Ro/La	+	+	120	38	Dexa, $\beta$ -S	28†		FD
20	1997	22	Ro/La	–	–	135	64	Dexa	37	No treatment	Alive
21	1997	28	La	–	–	150	82	Dexa	30	Dopa, PPM, steroids	Alive
22	1998	31	Ro/La	–	–	145	50	Dexa, $\beta$ -S	37	Isoprenaline, PPM	Alive
23	1998	24	Ro/La	–	–	140	60	Dexa	36	Isoprenaline, PPM	Alive
24	1999	25	Ro	–	(+)	135	57	Dexa, $\beta$ -S	35	Isoprenaline, dopa, PPM, steroids, IVIG	Alive
25	1999	29	Ro	–	(+)	130	50	Dexa, $\beta$ -S	34	Isoprenaline, PPM, steroids, IVIG	Alive
26	1999	23	Ro/La	–	–	145	80	Dexa	39	No treatment	Alive
27	2000	23	Ro	–	–	165	60	Dexa	36	PPM	Alive
28	2000	19	Negative	–	–	138	50	Dexa, $\beta$ -S	37	Isoprenaline, PPM	Alive
29	2000	31	Ro/La	–	–	131	50	Dexa, $\beta$ -S	35	Isoprenaline, PPM	Alive
30	2000	25	Ro/La	–	–	135	65	Dexa	35	Steroids	Alive
31	2000	29	Negative	–	–	123	64	Dexa, $\beta$ -S	34	Isoprenaline, PPM	D 3 years
32	2001	24	Ro/La	–	–	140	60	–	38	PPM	Alive
33	2001	20	Ro	–	–	165	55	Dexa	31	Isoprenaline	Alive
34	2002	26	Ro/La	+	+	135	54	–	26†		TOP
35	2002	21	Ro	–	(+)	150	80	Dexa, IVIG	36	Steroids, IVIG	Alive
36	2003	20	Ro	–	+	164	65	Dexa, $\beta$ -S	23†		TOP
37	2003	28	Ro/La	–	–	135	47	Dexa, $\beta$ -S	37	Isoprenaline, PPM	Alive

A indicates atrial;  $\beta$ -S, maternally given  $\beta$ -sympathomimetic agent; D, death; Dexa, maternally given dexamethasone; Dopa, dopamine; ECMO, extracorporeal membrane oxygenation; EFE, endocardial fibroelastosis [diffuse, severe, +; localized, mild, (+)]; FD, fetal death; GA, gestational age (weeks) at CAVB diagnosis; GA birth, gestational age at birth (weeks); †fetal death (weeks of gestation); Htx, heart transplantation; hydrops: +, present; –, absent; IVIG, intravenous immune globulin; NND, neonatal death; PPM, permanent pacemaker; TPM, temporary pacemaker; TOP, termination of pregnancy; and V, ventricular.

CAVB seen since 1997 were treated: 18 mothers received dexamethasone, in 8 in combination with  $\beta$ -mimetic therapy because of fetal heart rates <55 bpm. In 1 patient (patient 34), the treatment protocol was modified at the appearance of left atrial fibroelastosis at 25 weeks of gestation, and 1 intravenous dose of immune globulin was given to the mother.<sup>12</sup> Oral dexamethasone was initiated at a mean gestational age of  $25 \pm 4.3$  weeks (range, 20 to 32 weeks) and continued for  $7.4 \pm 4.5$  weeks (range, 2 to 15 weeks).

We next examined whether the use of oral maternal  $\beta$ -sympathomimetic therapy improved fetal heart rate. Three types of  $\beta$ -agonists were used to treat a total of 9 patients. Drug selection was mainly a function of availability of medication. Ventricular rates ranged between 38 and 52 bpm when  $\beta$ -sympathomimetic treatment was started between 20 and 33 weeks. Administration was continued for a mean of  $7.3 \pm 4.6$  weeks (range, 3.5 to 17). Four (44%) of these fetuses responded to ritodrine (patients 19 and 27) or salbutamol

**TABLE 2. Characteristics of Fetuses Diagnosed With Isolated Complete AV Block Between 1990–1996 (n=16) and 1997–2003 (n=21)**

Era of Diagnosis	1990–1996	1997–2003	P
Gestational age at diagnosis, wk	27±6.5	24.7±3.7	NS
Atrial rates, bpm*	139±17	141±12	NS
Ventricular rates, bpm*	55±11	60±11	NS
Fetal hydrops*	1/16 (6)	2/21 (10)	NS
Severe/mild endocardial fibroelastosis	2/1 (19)	2/4 (29)	NS
Termination of pregnancy	1/16 (6)	2/21 (10)	NS
Transplacental therapy with dexamethasone†	3/15 (20)	18/19 (95)	< 0.0001
Fetal death†	3/15 (20)	1/19 (5)	NS
Gestational age at delivery, wk	35.5±3.9	35.3±2.2	NS
Birth weight, kg	2.5±0.8	2.3±0.7	NS
Caesarian section	8/12 (67)	15/18 (83)	NS
Neonatal isoprenaline treatment	7/12 (58)	10/18 (56)	NS
Temporary pacemaker as a neonate	3/12 (25)	1/18 (6)	NS
Permanent pacemaker as a neonate	6/12 (50)	10/18 (56)	NS
Age at neonatal pacemaker implantation, d	5.5±5.9	5.8±9	NS
LVEF% of neonatal survivors	65±7	70±10	NS
Postnatal follow-up, y	5.2±5	3.4±1.8	NS

All values are presented as mean±SD or as ratio and percentage. LVEF% indicates left ventricular ejection fraction (in %), determined by biplane Simpson’s rule.

\*Findings at diagnosis of CAVB.

†Only cases with pregnancy continuation.

(patients 15 and 37), with an increase in the ventricular rate of 8 to 19 bpm. The heart rate was unaffected by β-stimulation in the other 5 patients. Of the 16 serially followed-up patients who did not receive β-stimulation, 5 (31%) experienced a spontaneous increase above the initial ventricular rate of >5 bpm and 4 (25%) a decrease of >5 bpm, whereas the rate remained stable in 7 patients.

Adverse effects attributed to transplacental drug therapy included oligohydramnios in 4 pregnancies (19%) treated with dexamethasone. In 3 of them (patients 24, 30, and 33), the oligohydramnios prompted iatrogenic premature delivery, whereas in 1 (patient 17), dexamethasone was successfully discontinued at 32 weeks. One mother (patient 26) developed arterial hypertension, and dexamethasone was discontinued at 35 weeks, 4 weeks before delivery.

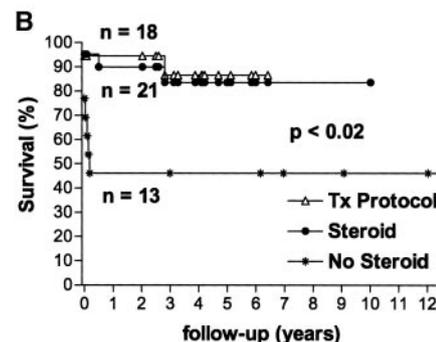
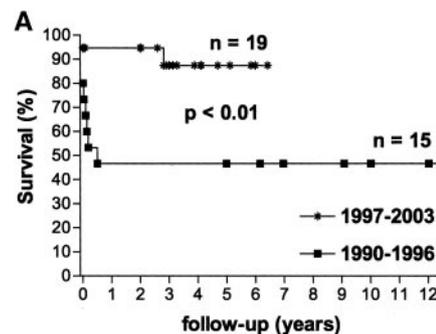
**Outcome**

The impact of era of diagnosis and fetal therapy on freedom from death is shown in Figure 2. Kaplan-Meier survival estimates differed among study eras (log rank  $\chi^2=7, P<0.01$ ) and among pregnancies with and without transplacental

steroid administration (log rank  $\chi^2=6.35, P<0.02$ ). There was no difference in the prevalence of predictors of adverse outcome or in neonatal management between the groups (Table 2). Symptomatic bradycardia and ventricular rates of

**TABLE 3. Characteristics of Transplacental Fetal Treatment (n=22; 1990–2003)**

Medication	No. of Patients Treated
Dexamethasone only (4–8 mg/d)	13
Dexamethasone+ritodrine (30–60 mg/d)	5
Dexamethasone+terbutaline (10 mg/d)	2
Dexamethasone+salbutamol (30–40 mg/d)	1
Salbutamol only (10 mg/d)	1



**Figure 2.** A, Era of diagnosis of fetal isolated CAVB and freedom from death. B, Transplacental fetal treatment with (Steroid) and without (No Steroid) dexamethasone and freedom from death. Survival was best with protocol-guided approach (Tx Protocol).

**TABLE 4. Survival of Isolated CAVB With Average Fetal Heart Rates Below and Above 55 bpm: Impact of Prenatal Management (3 Patients With Termination of Pregnancy Were Excluded)**

Heart Rate	Patient Numbers	Intrauterine Death	Neonatal Death	Survival >1 Month, n (%)
<55 bpm	n=16			
No treatment	6	0	3	3/6 (50)
Dexamethasone or $\beta$ -sympathomimetic	3	1	1	1/3 (33)
Dexamethasone and $\beta$ -sympathomimetic	7	1	0	6/7 (86)
>55 bpm	n=18			
No treatment	7	2	1	4/7 (57)
Dexamethasone	11	0	0	11/11 (100)

Survival of the fetal and neonatal periods of cases managed according to the treatment guidelines (17/18=94%) vs incompletely or untreated (8/16=50%) cases:  $P=0.006$ .

<50 to 55 bpm (AHA/ACC class I [1] and I [5] indications) were the principal causes for permanent pacemaker implantation in 19 of a total of 21 patients who have required such an intervention to date.<sup>13</sup>

#### **Impact of Era of Diagnosis**

Live birth and 1-year survival rates of fetuses diagnosed before 1997 were 80% (95% CI, 60% to 100%) and 47% (95% CI, 22% to 72%), respectively. During this era, 3 fetuses (patients 1, 7, and 8) died between 21 and 35 weeks of gestation, none with signs of heart failure at the last echocardiogram. Another 4 died in the neonatal period, either because of long-QT syndrome with torsade de pointes (patient 13), myocarditis with ventricular dysfunction, prematurity and respiratory failure (patient 4), EFE with ventricular dysfunction and sepsis (patient 12), or immune-mediated liver fibrosis (patient 15). The mother of the last patient received salbutamol but no corticosteroids. Patient 3 developed a dilated cardiomyopathy after birth and underwent cardiac transplantation at 3.4 years of age. This patient is coded as being alive in the survival estimates.

By comparison, of the 19 ongoing pregnancies diagnosed since 1997, 95% (95% CI, 85% to 100%) of the fetuses survived to birth and were still alive by 1 year of age. The only intrauterine death occurred in patient 19, diagnosed at 26 weeks with hydrops, severe EFE, and a bradycardia of 38 bpm. Despite a sustained increase in the ventricular rate to 55 bpm on ritodrine and dexamethasone, this fetus remained hydropic and died at 28 weeks. Overall, 18 of 19 fetuses with a diagnosis of isolated CAVB since 1997 survived the neonatal period, compared with 8 of 15 diagnosed before 1997 ( $P<0.02$ ). An additional 2 babies born in the most recent era died unexpectedly at 6 months and 3 years of age, both without signs of myocardial disease at necropsy.

#### **Impact of Transplacental Therapy**

We next determined whether the use of dexamethasone with and without  $\beta$ -sympathomimetic therapy was important for fetal outcome. In an initial analysis, we included 3 patients with incomplete transplacental steroid treatment: Patients 6 and 8 did not receive a  $\beta$ -mimetic despite low fetal heart rates, and patient 14 was treated for only 3 weeks with steroids. The total of treated fetuses ( $n=21$ ) had a live birth

and 1-year survival rate of 95% (95% CI, 86% to 100%) and 90% (95% CI, 78% to 100%), compared with 77% (95% CI, 54% to 100%) and 46% (95% CI, 19% to 75%) survival, respectively, without steroid therapy ( $P=0.015$ ). However, when fetuses were managed according to the treatment protocol (dexamethasone at CAVB diagnosis, plus a  $\beta$ -sympathomimetic at heart rates <55 bpm), the 1-year survival increased to 95%. Moreover, immune-mediated complications, specifically hepatitis, myocarditis, or EFE, led to postnatal death or cardiac transplantation in 4 of 9 survivors who did not receive antenatal steroids but in none of the 18 live births after maternal dexamethasone administration ( $P<0.01$ ). The impact of fetal heart rate and choice of antenatal therapy on outcome is shown in Table 4.

### **Discussion**

In complete AV block, the fetal heart needs to accommodate the bradycardia and electromechanical AV dissociation by increasing stroke volumes. Although cardiac output often remains sufficient, it may be hampered by the presence of additional myocardial disease. We and others have previously reported that there is a high morbidity and mortality in fetuses with isolated CAVB.<sup>9-11</sup> These data were based primarily on the "natural" history of fetal AV conduction defects, because very few received potentially helpful fetal therapy.

Transplacental fetal treatment would ideally be used to prevent the development of isolated CAVB. Unfortunately, aside from the presence of maternal anti-Ro/La antibodies, there are no known markers that predict which fetus will develop an AV conduction defect. The vast majority of pregnant women with anti-Ro/La antibodies are healthy and do not deliver infants with CAVB.<sup>5,6</sup> Therefore, prophylactic treatment of all pregnancies at risk of CAVB with fluorinated steroids is not justified. It is also difficult to predict the outcome for fetuses with heart block, unless poor prognostic factors are manifest at the diagnosis of CAVB. In our study, although most cases of fetal hydrops and EFE were detected at the time of diagnosis of CAVB, in 25% of patients, these manifestations became apparent only on repeat echocardiograms. Furthermore, other maternal antibody-induced abnormalities, such as myocarditis and hepatitis, were diagnosed only after delivery. Thus, findings linked with adverse out-

come may develop or become detectable weeks after diagnosis of heart block. These factors have led to our routine use of dexamethasone in pregnancies complicated by isolated fetal CAVB, as previously proposed.<sup>11</sup>

Several previous retrospective studies have suggested that the use of glucocorticoids might temper immune-mediated fetal cardiac damage and indirectly improve cardiac contractility in suspected fetal myocarditis.<sup>14</sup> Saleeb et al<sup>15</sup> demonstrated that treatment with fluorinated steroids resulted in resolution of incomplete AV block, effusions, and fetal hydrops. However, no outcome benefit was found compared with untreated fetuses with less severe immune-mediated complications. By contrast, the present study demonstrated for the first time that the routine use of dexamethasone given to mothers at the time of diagnosis of fetal heart block, in combination with  $\beta$ -sympathomimetic therapy for persistent fetal bradycardia <55 bpm, significantly improved survival compared with untreated fetuses. Our findings are consistent with observations in children and adults with acute and chronic myocarditis and inflammatory dilated cardiomyopathy who show benefit from immunosuppressive steroid treatment.<sup>16–18</sup> Frustaci et al<sup>16</sup> found that active lymphocytic myocarditis responded well to immunosuppressive treatment if cardiac autoantibodies were detectable in the patient's serum. Because isolated fetal CAVB is caused predominantly by maternally transmitted cardiac autoantibodies and has been associated with lymphocytic infiltrates,<sup>3</sup> a beneficial effect of glucocorticoid might be anticipated.

Our findings imply that prolonged administration of dexamethasone does not permanently reverse complete AV conduction block but may render the affected fetus less likely to develop significant additional disease manifestations, thus improving overall outcome. Immune-mediated conditions causing postnatal death or requiring cardiac transplantation were observed only in the untreated group. By contrast, 3 of 4 treated patients with EFE have remained well, without myocardial dysfunction or progressive EFE, at 1 to 4 years of age.

The development of oligohydramnios may be a dose-related complication of steroid therapy. There were no deaths associated with oligohydramnios, but the decreased amniotic fluid prompted premature deliveries in the majority of these patients. Oligohydramnios is usually an indicator of placental insufficiency. However, in this setting, it must be carefully interpreted in the context of other tests of fetal well-being, particularly those relating to placental function: ie, umbilical and uterine arterial Doppler, other components of the biophysical profile, and placental texture. The amniotic fluid volume needs to be carefully monitored throughout gestation, and a decrease in dexamethasone dose may be required. Other potential side effects of the use of corticosteroids in pregnancy, including neurodevelopmental and growth issues, require further evaluation.

It has been suggested that  $\beta$ -sympathomimetic therapy to increase the fetal cardiac output should be given to mothers of fetuses with a heart rate <55 bpm. Different  $\beta$ -agonists had been tried in a small number of pregnancies, showing an inconsistent effect on fetal heart rates.<sup>19–21</sup> This is in agreement with our own data: In nearly half of patients,

$\beta$ -stimulation did not affect the fetal heart rate. In fact, compared with treated fetuses, fetal heart rate increased spontaneously in a similar percentage of fetuses without  $\beta$ -sympathomimetic therapy by >5 bpm when followed serially. However, fetuses treated with  $\beta$ -agonists had lower baseline heart rates and had no further decrease in heart rate, in contrast to untreated patients. Moreover, because cardiac output and ventricular fractional shortenings were not assessed routinely by echocardiography, the impact of the  $\beta$ -stimulation and immune suppression on the myocardial function of the "nonresponders" is unclear. Ultimately, survival of fetuses with critically lowered heart rates was improved with  $\beta$ -stimulation if treatment was combined with dexamethasone. No major adverse effects were associated with  $\beta$ -sympathomimetic therapy. The use of  $\beta$ -agonists, such as salbutamol and isoprenaline, should be avoided in patients with long-QT syndrome, because sympathetic stimulation alters ventricular depolarization, may dramatically prolong QTc, and may trigger cardiac events. Assessment of QT intervals by magnetocardiography may be useful in the diagnosis of fetal long-QT syndrome and influence the choice of management of isolated CAVB.<sup>8</sup>

Limitations to our study need to be addressed. Treatment was not randomized but rather depended on the era of diagnosis of CAVB. The contribution of a varied team approach of pregnancy management to the differing outcome is unknown. Although dexamethasone was the only fluorinated steroid used, various  $\beta$ -agonists in different dosages were used. The number of treated patients with heart rates <55 bpm was too small to analyze the efficacy of different  $\beta$ -agonists or to demonstrate a difference in outcome compared with untreated or incompletely treated fetuses. The long-term adverse impact of low heart rates, maternal autoantibodies, and high-dose steroid administration on the developing human fetus needs further investigation.

In summary, our study for the first time demonstrates that the introduction of transplacental glucocorticoid and  $\beta$ -mimetic fetal therapy in the management of isolated CAVB has at least contributed importantly to a significant improvement in fetal and neonatal morbidity and mortality. Further improvement in pregnancy monitoring and screening for maternal anti-Ro and anti-La antibodies will lead to the detection of CAVB secondary to maternal autoantibodies at younger gestational ages than previously reported. Therefore, it may be possible to begin glucocorticoid therapy closer to the onset of immune-mediated damage of cardiac tissue. The efficacy and safety of this approach should be further addressed in a large-scale, randomized trial.

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