Autoimmune-Associated Congenital Heart Block: Demographics, Mortality, Morbidity and Recurrence Rates Obtained From a National Neonatal Lupus Registry

JILL P. BUYON, MD, RUDI HIEBERT, BS, JOSHUA COPEL, MD,* JOSEPH CRAFT, MD,* DEBORAH FRIEDMAN, MD, FACC,† MARGARET KATHOLI, LE LA A. LEE, MD,‡ THOMAS T. PROVOST, MD,§ MORRIS REICHLIN, MD,∥ LISA RIDER, MD,¶ ANN RUPEL, BA, SUSAN SALEEB, BS, WILLIAM L. WESTON, MD,‡ MARY LOUISE SKOVRON, PhD

New York, New York; New Haven, Connecticut; Denver, Colorado; Baltimore and Bethesda, Maryland; and Oklahoma City, Oklahoma

Objectives. The present study describes the demographics, mortality, morbidity and recurrence rates of autoimmune-associated congenital heart block (CHB) using information from the Research Registry for Neonatal Lupus.

Background. Isolated CHB detected at or before birth is strongly associated with maternal autoantibodies to 48-kD SSB/La, 52-kD SSA/Ro and 60-kD SSA/Ro ribonucleoproteins and is a permanent manifestation of the neonatal lupus syndromes (NLS). Available data are limited by the rarity of the disease.

Results. The cohort includes 105 mothers whose sera contain anti-SSA/Ro or anti-SSB/La antibodies, or both, and their 113 infants diagnosed with CHB between 1970 and 1997 (56 boys, 57 girls). Of 87 pregnancies in which sufficient medical records were available, bradyarrhythmia confirmed to be CHB was initially detected before 30 weeks of gestation in 71 (82%) (median time 23 weeks). There were no cases in which major congenital cardiac anatomic defects were considered causal for the development of CHB; in 14 there were minor abnormalities. Twenty-two (19%) of the 113 children died, 16 (73%) within 3 months after birth.

Cumulative probability of 3-year survival was 79%. Sixty-seven (63%) of 107 live-born children required pacemakers: 35 within 9 days of life, 15 within 1 year, and 17 after 1 year. Forty-nine of the mothers had subsequent pregnancies: 8 (16%) had another infant with CHB and 3 (6%) had a child with an isolated rash consistent with NLS.

Conclusions. Data from this large series substantiate that autoantibody-associated CHB is not coincident with major structural abnormalities, is most often identified in the late second trimester, carries a substantial mortality in the neonatal period and frequently requires pacing. The recurrence rate of CHB is at least two- to three-fold higher than the rate for a mother with anti-SSA/Ro-SSB/La antibodies who never had an affected child, supporting close echocardiographic monitoring in all subsequent pregnancies, with heightened surveillance between 18 and 24 weeks of gestation.

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Congenital heart block (CHB) has emerged as an important model of passive autoimmunity. The association between acquired conduction defects in an otherwise normally developing fetal heart and maternal autoantibodies to SSA/Ro and SSB/La ribonucleoproteins is well established, even in mothers who are completely asymptomatic (see Buyon [1] and Tseng and Buyon [2] for review). Cardiac injury is presumed to arise from the active transplacental transport of maternal IgG autoantibodies into the fetal circulation (3). Other neonatal abnormalities affecting the skin, liver and blood cells are also reported to be associated with maternal anti-SSA/Ro-SSB/La antibodies and are collectively grouped under the heading of neonatal lupus syndromes (NLS) (see Lee [4,5] for review), so termed because the cutaneous lesions resemble those seen in systemic lupus erythematosus (SLE) (6,7). To date, established third-degree block is irreversible. However, the noncardiac manifestations are transient, resolving at ~6 months after birth coincident with the disappearance of maternal autoantibodies from the infant’s circulation.

It has been estimated that only 1 of every 15,000 to 20,000...
live births results in a baby with isolated CHB (8). Although many mothers of children with CHB are asymptomatic, women with rheumatic diseases such as SLE or Sjögren’s syndrome (SS) are more likely to have affected offspring. In one retrospective study, the rate was 7 of 259 live births of mothers with SLE, and in those with anti-SSA/Ro antibodies the rate was 6 of 79 (9). In a prospective study, none of 26 pregnant patients with lupus with anti-SSA/Ro or anti-SSB/La antibodies, or both, gave birth to a child with CHB (10). These studies indicate the rarity of this disease; accordingly, available clinical data are limited. To date the largest cohort of isolated CHB reported by a rheumatology group comprised 64 affected families; however, anti-SSA/Ro or anti-SSB/La antibodies, or both, were identified in only 60% of 53 mothers tested (11).

Given the recognized importance of NLS, a National Research Registry was established in September 1994, to provide a source of well documented cases, inclusive of mothers and their families, available to researchers interested in basic science or clinical studies, or both. The present study summarizes demographies, mortality, morbidity and recurrence rates of 113 children with CHB whose 105 mothers have anti-SSA/Ro or anti-SSB/La antibodies, or both, and are currently enrolled in the Registry. This information should provide critical data for family counseling, research strategies and management of pregnancies at risk of developing autoimmune-associated CHB or in which CHB has been detected.

## Methods

**Research Registry for Neonatal Lupus and case ascertainment.** The Research Registry for Neonatal Lupus was established by the National Institute for Arthritis, Musculoskeletal and Skin Diseases in September 1994. The purpose of this registry is to document cases of NLS for basic and clinical research. Cases are considered potential candidates for enrollment in the Registry if a mother has a child with any manifestation of NLS such as atrioventricular (AV) block, characteristic skin rash, hemolytic anemia, leukopenia, thrombocytopenia or cholestatic liver disease. Because it is well established that autoimmune-associated CHB is independent of whether the mother has SLE or SS or is totally asymptomatic (1,2,12), there were no entry restrictions based on maternal disease status. To be eligible, mothers must live in the United States or be U.S. citizens residing abroad.

Referrals to the Registry are generally from obstetricians, pediatricians, rheumatologists and pediatric cardiologists. A separate mailing describing the Registry has been sent to all board-certified pediatric cardiologists. Periodic announcements are made at professional specialty meetings and in medical journals. Additional advertisements appear in newsletters targeted to patients with SLE or SS, such as *Lupus Lifestyles* and *Moisture Seekers*, respectively, which account for several self-reported cases.

In contrast to SLE, a disease in which there are criteria established by the American College of Rheumatology (13), no such formal criteria yet exist for classification as NLS. However, for the purposes of the Registry, a case is considered to be definite NLS if the following two criteria are met: 1) maternal antibodies to the 52-kD SSA/Ro, 60-kD SSA/Ro or 48-kD SSB/La ribonucleoproteins are identified (see later); and 2) heart block (see later) or characteristic skin rash is diagnosed. The present study includes only mothers and their children with heart block (in the presence or absence of cutaneous manifestations). The affected births occurred during 1970 to 1997.

Forty-four of the enrolled mothers were known to one of us (J.P.B.) before establishment of the Registry and comprised part of a previously reported cohort (12).

**Sources of information.** The data presented here were obtained both from patients and from medical records.

*Information obtained directly from the mother and her family.* Consent (approved by the institutional review board of the Hospital for Joint Diseases) to participate in the Registry is obtained from all mothers. Enrollment questionnaires include general information such as ethnic background, names of all family members (affected child, siblings, mother and father), dates of birth of all family members, gender of affected and unaffected siblings, address and phone numbers of all family members, and address and phone numbers of all physicians caring for family members.

For all pregnancies, data are sought regarding medications taken during the pregnancy, history of any maternal illnesses, time of detection of heart block, gestational length of the pregnancy and mode of delivery. A complete obstetric history of all pregnancies preceding and following the affected pregnancy is similarly included. The unintended loss of a fetus before 6 months of gestation is included in the database only if medical attention was sought. Information on cutaneous, hematologic, and hepatic abnormalities and time of onset is requested. Subsequent health status of an affected child includes mortality, availability of an autopsy and timing of pacemaker insertion. Information on enrolled families is updated at 6-month intervals by mailed questionnaires.

*Information obtained from the medical records.* To the extent possible, information obtained from the enrollment questionnaire is verified from the medical records of both the mother and her affected children. Records from the child’s pediatrician, cardiologist, rheumatologist and dermatologist,
as well as the mother’s internist/rheumatologist and obstetrician, are requested with patient permission. Complete blood count, chemistry profile, sedimentation rate and urinalysis are recorded. All medical records are reviewed and abstracted by the same investigator (J.P.B.).

Information from questionnaires and abstracted medical records is stored in a computer database. The database for the Registry has been formatted to combine information recorded from the mother’s enrollment questionnaire and abstracted from the requested medical records.

**Verification of CHB and time of onset.** A child is classified as having CHB if the Registry has a copy, or physician’s note that reports the results, of an obstetrical sonogram, echocardiogram (in utero or after birth), electrocardiogram (ECG), Holter monitor or autopsy that verifies the presence of CHB. When echocardiographic reports are reviewed, the degree of block and presence or absence of effusions or hydrops are noted. All cases reported had either second- or third-degree block, except one child who had first-degree block detected at 10 years of age and whose sibling had third-degree block diagnosed in utero.

Whenever a perinatal echocardiogram is available, CHB is categorized as to whether structural lesions are present. Associated structural abnormalities are classified in one of two categories: 1) those that could account for AV block because of fibrous disruption between the atrium and AV node or because of absence of the penetrating bundles of the AV node such as atrioventricular septal defects, single ventricle, developmental tricuspid valve disease, L-transposition of the great arteries (ventricular inversion) or heterotaxia (14); and 2) miscellaneous structural cardiac lesions not considered causally related to heart block, such as ventricular septal defect (VSD), patent ductus arteriosus (PDA) (if it persists >3 days after full-term delivery or >1 month after premature delivery) or atrial septal defect (ASD) (if it requires surgery or persists >28 days after birth). In the absence of structural abnormalities noted on an in utero echocardiograms, CHB is considered isolated if postnatal echocardiograms are unavailable, although it is acknowledged that persistent ASD or nonphysiologic PDA cannot be ruled out.

The time of detection of CHB is taken as the earliest documentation of a bradyarrhythmia (subsequently verified to be secondary to AV block) in the mother’s prenatal medical record. Because the Registry includes women currently pregnant with affected fetuses as well as those whose pregnancies occurred almost four decades ago, there are differences in prenatal care and availability of records. It is understood that the time of detection may or may not reflect true onset. The extent of medical care and other unspecified factors could affect the likelihood of observing CHB in the fetus. The time of detection is reported in estimated weeks of gestation for children whose CHB was detected in utero up through and including 40 weeks of gestation. For children whose AV block was initially observed postnatally, time of first detection is reported as age after birth. In 26 (23%) of 113 cases, CHB could be unambiguously established but prenatal records were insufficient to reliably report time of detection.

**Verification of maternal autoantibody status.** Sera from 83 of the mothers of children with CHB were sent to the Registry and confirmed to contain antibodies to SSA/Ro or SSB/La, or both, by enzyme-linked immunosorbent assay (Diamedix Corporation) and SDS-immunoblot, as previously described (15). In 22 mothers, records from a commercially approved laboratory were used for documentation of anti-SSA/Ro or anti-SSB/La antibodies, or both.

**Recurrence.** A recurrent case is defined as any child with CHB or a rash characteristic of NLS whose mother is known to have anti-SSA/Ro or anti-SSB/La antibodies, or both, and an immediately preceding pregnancy that resulted in a child with CHB.

**Statistical analysis.** Data are presented as frequency distributions. Differences between proportions were evaluated using Fisher exact test in a 2 by 2 table. Mortality is presented in terms of a cumulative survival rate, computed from life-table analysis.

### Results

**Demographics.** As of July 1, 1997, 142 mothers and their 166 affected offspring are enrolled in the Registry. On the basis of initial answers to a standardized questionnaire sent to each mother, 106 children have only cardiac conduction abnormalities, 35 have only cutaneous manifestations, and 22 were characterized by their mothers as having both CHB and skin rash. Three children were noted to have hepatic or hematologic manifestations of NLS, or both, without cardiac or cutaneous involvement. Of the 119 mothers whose children have CHB (with or without cutaneous disease), 105 have documented anti-SSA/Ro or anti-SSB/La antibodies, or both, 10 are negative, and medical records and sera remain unavailable for 4. The 105 mothers who are antibody positive and their 113 children with CHB make up the cohort presented in this study. In 88 (78%) of the 113 children, antibodies were detected either in the cord blood of the affected baby or in the mother within 1 year of that child’s birth. The clinical status of the mothers was varied and included SLE, SS and no detectable rheumatic disease.

As detailed in the map in Figure 1, the 105 mothers of children with CHB are from 30 states across the continental United States; the largest number, 23 (22%), are from New York. As demonstrated in Figure 2, the great majority of mothers are white, comprising 76% of the group. To date there are only two Asians.

Of the 113 offspring with CHB, 56 are boys and 57 girls. Of the 95 children without associated cutaneous lesions, 48 are boys and 47 girls. Of the 18 children reported by their mothers to have associated skin rashes consistent with NLS, 8 are boys and 10 girls.

**Time of detection of CHB.** Identifying the time of detection of CHB should provide a basis from which to decide on pregnancy surveillance, and guide bench research with regard
to fetal vulnerability. Time of detection was defined as the first prenatal record of bradyarrhythmia, most often noted on routine sonogram and subsequently confirmed to be AV block by echocardiogram. Medical records of 87 pregnancies were of sufficient quality for analysis. As shown in Figure 3, the timing of heart block does not appear to occur randomly during gestation. No cases were detected before 17 weeks. In 71 (82%) of the fetuses, bradycardia was identified before 30 weeks of pregnancy. Detection was most frequently clustered between 20 and 24 weeks. Fourteen (16%) cases were first identified in the third trimester, five of which were noted at the time of delivery. The median time of in utero detection was 23 weeks. Of the 85 fetuses diagnosed with CHB during pregnancy, 15 were born between 1970 and 1987, 8 of whom were diagnosed before 30 weeks of gestation. Seventy pregnancies occurred between 1988 and 1997, in which 63 were diagnosed with CHB before 30 weeks (p < 0.003, earlier detection of CHB in pregnancies between 1988 and 1997 compared with pregnancies before 1988).

In one child represented in Figure 3 as having conduction abnormalities detected at birth, sonogram in the late second trimester did reveal a transient bradycardia but it was not confirmed to be AV block by echocardiogram. At birth an ECG demonstrated borderline first-degree AV block. At 18 months this child had second-degree block and required a pacemaker because baseline heart rate fell below 60 beats/min and Holter monitoring revealed periods of complete AV block. In one fetus treated with dexamethasone after echocardiogram confirmed second-degree AV block at 21 weeks of gestation, an ECG at birth revealed predominant first-degree block that regressed to second-degree block (2:1) by 8 months of age. In another fetus diagnosed with second-degree block at 20 weeks of gestation and treated with dexamethasone, an ECG at birth revealed first-degree block that remains stable at 4 years of age.

Only two children in the cohort were diagnosed with CHB after birth. One child was diagnosed with third-degree block at 2 years 7 months of age during a hospital stay for pneumonia. No birth or early childhood records were available. One child, whose younger sibling was diagnosed with CHB in utero, was diagnosed with first-degree block at 10 years of age after a routine ECG was done during evaluation of a wrist injury.

**Associated structural lesions.** Eighty-four medical records of the 113 children with CHB were of sufficient quality to allow classification with regard to the presence or absence of structural defects. These records included one or more of the following: echocardiograms that were performed late enough during gestation to reliably evaluate cardiac anatomy or after 3 months of age or autopsy reports. No child has major anatomic cardiac abnormalities that would be considered causal for the development of CHB. Fourteen children have miscellaneous structural lesions not known to be associated with the development of CHB. These include three with persistent PDA requiring surgical repair; six with an ASD; one with a small VSD; one with pulmonic stenosis; one with a dysplastic pulmonary valve; one with a hypoplastic right ventricle and polyvalvular dysplasia with tricuspid and pulmonary valve nodules; and one in which the chordae tendineae of the septal and posterior leaflets of the tricuspid valve were fused to the right ventricular endocardium. In one child with trisomy 21 there were no developmental anatomic defects of the heart.

**Mortality and gestational age at birth.** Of the 113 offspring, 22 (19%) have died (12 boys, 10 girls) (Figure 4). Six of these deaths occurred in utero. Ten neonates died in the first 3 months after birth. Six children died between 3 months and 3 years of age. Twenty-two children are older than 10 years. None of the 67 children between 3 and 10 years old remaining in the cohort have died.

Not unexpectedly, survival relates to gestational age at birth (Table 1). Fourteen (52%) of 27 offspring born before 34 weeks of gestation have died. In contrast, the mortality is markedly reduced in those children born at later gestational ages. Specifically, only 8 (9%) of 86 children born at or after 34 weeks have died (p < 0.001 between the two groups). When pregnancies <34 weeks of gestation were evaluated by era, those occurring before 1988 had a mortality rate of 67% (4 of 6), compared with 48% (10 of 21) in pregnancies during or after 1988. This difference in proportion is not statistically significant (p = 0.65).

Those infants who survive the neonatal period have an excellent prognosis. The cumulative probability of survival at 3 years is 79% (Figure 5).
Pacemaker. With regard to the morbidity of CHB, 67 (63%) of the 107 children born alive have required pacemakers, 35 within the first 9 days of life. Fifteen additional children have been paced in the first year, and 17 after 1 year. One infant has had a cardiac transplant at 8 months of age because of intractable cardiomyopathy.

Recurrence rates. As shown in Table 2, 49 mothers have had pregnancies that lasted longer than 6 months, subsequent to the birth of a child with CHB. In 36 (73%) of these pregnancies there were no AV conduction abnormalities or reported cutaneous manifestations of NLS in the children. Eight (16%) next pregnancies resulted in a second child with heart block, two in association with a skin rash. In one of these families the first child had first-degree block detected at 10 years of age and the second child had CHB detected in utero. In three additional families, the next younger siblings had cutaneous manifestations alone. Thus, the probability of having a second affected child with any manifestation of NLS was 22%.

One subsequent pregnancy ended at 30 weeks, but the fetus was not known to have any conduction abnormalities. Another subsequent pregnancy resulted in the birth of a boy who died at 2 months of age. Although there were no documented conduction abnormalities, he had severe aortic stenosis and cardiomyopathy, which on biopsy was found to be associated with immunoglobulin deposition.

There were three sets of twins in the cohort. Two sets were dizygotic, with only one twin in each set having CHB. Histologic analysis of the third set revealed a twin (diamniotic, dichorionic) placenta. Detailed genetic analysis strongly suggested monozygosity. One twin had CHB and the other was healthy.

Discussion

Although NLS is rare, its discussion is an integral part of all pregnancy counseling of women with SLE, SS or undifferentiated autoimmune syndromes. Pregnant women who have...
anti-SSA/Ro or anti-SSB/La antibodies, or both, regardless of their clinical status, are at risk of having infants with CHB. The present study comprises the largest cohort of mothers with anti-SSA/Ro or anti-SSB/La antibodies, or both, and their children with CHB compiled to date. Such information is critical to family counseling regarding expectations for future childbearing and determining possible prophylactic or therapeutic modalities, or both.

Demographics. There was a striking ethnic predominance in the mothers of affected children, 76% being white. This is of potential interest because SLE is more prevalent among minorities (16). Although the data may be subject to referral bias, it is not readily explained by either geographic location or access to better medical care. Alternatively, the absence of a minority predominance may be real and further emphasizes that autoimmune-CHB is not “lupus” in a neonate and does not unequivocally imply maternal lupus. Several studies have convincingly demonstrated that the majority of mothers whose pregnancies are complicated by CHB are asymptomatic (11,12,17) or have undifferentiated autoimmune syndromes more closely related to SS than SLE (17). Many women come to the attention of a rheumatologist solely on the basis of identification of heart block in their offspring.

Table 1. Mortality by Gestational Age and Era of Birth

<table>
<thead>
<tr>
<th>Gestational Age at Birth (wk)</th>
<th>1970–1987</th>
<th>1988–1997</th>
<th>All Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Births</td>
<td>Deaths*</td>
<td>Births</td>
<td>Deaths*</td>
</tr>
<tr>
<td>26–28</td>
<td>1 1</td>
<td>2 1</td>
<td>3 2</td>
</tr>
<tr>
<td>29–31</td>
<td>4 3</td>
<td>13 9</td>
<td>17 12</td>
</tr>
<tr>
<td>32–33</td>
<td>1 0</td>
<td>6 0</td>
<td>7 0</td>
</tr>
<tr>
<td>34–37</td>
<td>8 1</td>
<td>38 3</td>
<td>46 4</td>
</tr>
<tr>
<td>38–40</td>
<td>13 1</td>
<td>24 3</td>
<td>37 4</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>2 0</td>
<td>1 0</td>
<td>3 0</td>
</tr>
<tr>
<td>Total</td>
<td>29 6</td>
<td>84 16</td>
<td>113 22</td>
</tr>
</tbody>
</table>

*Mortality rate was 21% (6 of 29) in pregnancies occurring before 1988 versus 19% (16 of 84) in pregnancies during or after 1988. This difference in proportion is not statistically significant (p = 0.99).

No gender-based difference in the frequency or prognosis of CHB was demonstrated, in contrast to the reported female predominance of cutaneous manifestations of NLS (4,5). The latter observation has guided the basic research question of whether sequestered intracellular antigens can translocate to the cell surface under the influence of hormones. This would account for the accessibility of fetal antigen to cognate maternal antibody. There is currently great interest in the role of estrogen and the induction of cell surface expression of SSA/Ro and SSB/La on cultured keratinocytes. Hormonal modulation of SSA/Ro and SSB/La has been reported in keratinocytes (18). Most recently, Wang and Chan (19) demonstrated that 17beta-estradiol at concentrations of $10^{-8}$ to $10^{-7}$ mol/liter induced up to a fivefold increase in the expression of the full-length 52-kD SSA/Ro and 60-kD SSA/Ro mRNA in human keratinocytes isolated from neonatal foreskins, compared with untreated cells in which basal expression was low. In contrast, estradiol had no effect on cultured cardiocytes (J.P.B., manuscript submitted). The apparent discordance in mRNA expression and translocation of SSA/Ro-SSB/La proteins in keratinocytes compared with cardiocytes after exposure to estradiol may contribute, in part, to clinical differences observed for gender predominance, reversibility and timing of these two manifestations of NLS.

Table 2. Outcome of 49 Pregnancies Immediately Subsequent to Birth of a Child With Congenital Heart Block

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Pregnancies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>36 (73%)</td>
</tr>
<tr>
<td>Manifestations of NLS</td>
<td></td>
</tr>
<tr>
<td>CHB only</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>CHB and rash</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Rash only</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Fetal demise</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Neonatal death*</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

*Aortic stenosis and severe cardiomyopathy. CHB = congenital heart block; NLS = neonatal lupus syndromes.
Identification of AV conduction abnormalities. Inasmuch as fetal arrhythmias can now be evaluated prenatally by echocardiographic and Doppler ultrasound techniques, AV block is most frequently identified during the fetal period. In our experience and that of others, bradycardia, as determined by fetal echocardiography, has been noted after the fetus had an initially normal heart rate (20,21). With rare exception, in pregnancies occurring after the late 1980s, CHB is detected before the 30th week of gestation, most often between 20 and 24 weeks (12,20,22–26). One hypothesis is that this gestational period coincides with, or immediately follows, a time in which there is surface accessibility of otherwise intracellularly sequestered target antigens or increased expression of a fetal factor, or both. mRNA expression of an alternative transcript of the leucine zipper is deleted, is maximally expressed in the human heart between 14 and 16 weeks of gestation (27). This approximates the time in fetal life (after functional maturity of the cardiac conducting system) when placental transfer of maternal antibodies into the fetal circulation becomes effective, just before the clinical detection of bradycardia. Because the AV node may already be fibrosed by the time bradycardia is first estimated, the time in fetal life (after functional maturity of the heart between 14 and 16 weeks of gestation (27). This approximates the time in fetal life (after functional maturity of the cardiac conducting system) when placental transfer of maternal antibodies into the fetal circulation becomes effective, just before the clinical detection of bradycardia. Because the AV node may already be fibrosed by the time bradycardia is first identified at the bedside, it is reasonable to speculate that the pathologic process has occurred earlier.

Outcome in affected children. Although it has been suggested that isolated CHB is a generally benign condition (see Michaelsson and Engle [8] for review), one-fifth of the affected children reported here have died. The mortality rate was greatest in the neonatal period and, as expected, was associated with an earlier gestational age at birth. In the study reported by McCune et al. (28), in which the average follow-up was 4.5 years (range 0.25 to 9.5), 3 (21%) of 14 children died in the neonatal period. In our first report, 31% (17 of 55) of the children died, 12 within the first 3 months after birth (12). From data generated in Europe, Julkunen et al. (29) reported 6 (18%) deaths in 34 children and Brucato et al. (30) reported 3 (19%) in 16. By contrast, in the study by Michaelsson and Engle (8) done in 1972 inclusive of 418 cases in which CHB occurred without other evidence of heart disease, the overall mortality rate was 8%. Approximately half of the children included were diagnosed after 12 months of age. Children with heart block dying soon after birth may have been missed and inclusion of children with late diagnoses could thus have led to lower estimates of mortality. In fact, among the 122 infants diagnosed at birth, there were 18 deaths (15% mortality rate), further supporting that early infancy is the time of greatest risk of death. Most deaths were reported to be due to cardiac failure. One critical limitation is that maternal autoantibody status was not specified. Because the demonstration of autoantibodies was a prerequisite for inclusion in the present study, the groups are not equivalent. It is unknown whether autoimmune-associated CHB is a more severe disease, because insufficient data are available to directly compare outcome in children whose mothers are well documented to have anti-SSA/Ro or SSB/La antibodies, or both, with children whose mothers do not have these autoantibodies. Finally, in a more recent study of 102 patients with isolated CHB (no maternal antibody status mentioned) >15 years of age, the mortality rate was 11% (31).

The dependency of permanent pacing carries the potential of significant morbidity. Pacemakers were implanted in the majority of the children in this cohort, often in the first months after birth. This is consistent with published reports (30,31) and our earlier series in which mean follow-up extended into the second decade (12). Indications for placement of pacemakers in children include daytime heart rate averaging <50 beats/min, especially when associated with episodes of junctional exit block or a flat junctional response to exercise (32), a prolonged QT interval (33) and a wide QRS complex (34).

Several reports describe rheumatic diseases developing in children with NLS (35–37). Although these data raise concern, firm conclusions cannot be drawn from anecdotal reports. Although the number of older children is limited, none in the present cohort has developed a rheumatic disease, including one patient 27 years old.

Management. An additional lesson provided by the Registry is that incomplete blocks are not fixed. Although one fetus with second-degree block did revert to normal sinus rhythm after dexamethasone therapy and remains so at 4 years of age, another reverted to normal sinus rhythm with variable first-degree block after dexamethasone but eventually returned to second-degree block at 8 months of age. In one fetus, bradycardia was detected only transiently in utero at 20 weeks, but at birth the infant had borderline first-degree block that then progressed to second-degree block requiring a pacemaker at 18 months of age. These observations suggest that in utero injury can have continued sequelae despite clearance of maternal antibodies from the neonatal circulation. Intervention with glucocorticoids might decrease acute inflammation but not necessarily prevent subsequent fibrosis. These data support serial cardiac monitoring of all fetuses with any bradycardia and our earlier series in which mean follow-up extended into the second decade (12). Indications for placement of pacemakers in children include daytime heart rate averaging <50 beats/min, especially when associated with episodes of junctional exit block or a flat junctional response to exercise (32), a prolonged QT interval (33) and a wide QRS complex (34).

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Acknowledging that there are no controlled trials to refer to, the management of a fetus with heart block, hydrops, dilated cardiomyopathy and the expected maternal serologic profile is based on isolated cases in the Registry and anecdotal cases in the literature. The approach includes administration of long-term oral maternal dexamethasone (20,22–24), oral maternal terbutaline (38), and plasmapheresis in a situation in which it appears that fetal demise is imminent (Epstein A, personal communication, 1995).

Perhaps one of the most pressing issues in CHB is the management of a pregnancy subsequent to the birth of an affected child. In consideration of any prophylactic intervention, several factors need to be weighed, including risk of recurrence and efficacy and toxicity of available treatments. In the present study the recurrence rate for CHB was 16%. In an earlier study reported by our group, 4 pregnancies (18%) of 22 immediately following the birth of a child with CHB resulted in a second affected child (12). In the study by McCune et al. (28),
of 13 pregnancies occurring after the birth of the first child with documented NLS, 2 resulted in offspring with heart block. Collectively these recurrence rates are ~15% to 18%, and they exceed by at least twofold (and perhaps up to 18-fold) the projected estimate of 1% to 7.5% for the development of CHB in a child whose mother has anti-SSA/Ro or anti-SSB/La antibodies, or both, and no previously affected children (9,10). The latter comparison suggests the possibility that not all maternal anti-SSA/Ro or anti-SSB/La responses that they are “pathogenic” and may vary from one pregnancy to another (e.g., specific epitope recognition confers a higher risk of CHB). Alternatively, in utero injury during the midsecond trimester may be more frequent than clinically identified but some fetuses may heal without permanent consequence. This latter speculation could account for discordant disease in monzygotic twins in published reports (see Buyon [1] for review) and confirmed here. Discordance in twins (particularly those that share a common placenta) argues against a change in maternal antibody specificity as a contributor to the relatively low recurrence rate.

Given the available data, prospective management other than serial echocardiograms is probably not justified. It may be reasonable to consider serial fetal echocardiography at 16, 18, 20, 22 and 24 weeks of gestation for all women at risk of a child with CHB. If abnormalities are detected, echocardiograms should be used to follow disease with the goals of reversing a newly diagnosed block and ameliorating an associated myocarditis.

Conclusions. The present study substantiates that in autoantibody-associated CHB, 82% of cases are detected before 30 weeks of gestation, there is a 14% mortality rate before 3 months of age, the cumulative probability of survival at 3 years is 79%, and 63% of live-born children eventually require pacemakers. The recurrence rate of 16% is two- to threefold higher than the rate previously reported for a mother with anti-SSA/Ro-SSB/La antibodies who has never had an affected child (9,10), supporting the recommendation of close echocardiographic monitoring in all subsequent pregnancies of mothers whose children have CHB. Early damage in utero may be progressive, which supports the importance of neonatal ECGs.

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References