

## Utility of Cardiac Monitoring in Fetuses at Risk for Congenital Heart Block

### The PR Interval and Dexamethasone Evaluation (PRIDE) Prospective Study

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**Background**—Anti-SSA/Ro-associated third-degree congenital heart block is irreversible, prompting a search for early markers and effective therapy.

**Methods and Results**—One hundred twenty-seven pregnant women with anti-SSA/Ro antibodies were enrolled; 95 completed an evaluable course in 98 pregnancies. The protocol included fetal echocardiograms performed weekly from 16 to 26 weeks' gestation and biweekly from 26 to 34 weeks. PR intervals >150 ms were considered prolonged, consistent with first-degree block. Ninety-two fetuses had normal PR intervals. Neonatal lupus developed in 10 cases; 4 were neonatal lupus rash only. Three fetuses had third-degree block; none had a preceding abnormal PR interval, although in 2 fetuses >1 week elapsed between echocardiographic evaluations. Tricuspid regurgitation preceded third-degree block in 1 fetus, and an atrial echodensity preceded block in a second. Two fetuses had PR intervals >150 ms. Both were detected at or before 22 weeks, and each reversed within 1 week with 4 mg dexamethasone. The ECG of 1 additional newborn revealed a prolonged PR interval persistent at 3 years despite normal intervals throughout gestation. No first-degree block developed after a normal ECG at birth. Heart block occurred in 3 of 16 pregnancies (19%) in mothers with a previous child with congenital heart block and in 3 of 74 pregnancies (4%) in mothers without a previous child with congenital heart block or rash ( $P=0.067$ ).

**Conclusions**—Prolongation of the PR interval was uncommon and did not precede more advanced block. There was a trend toward more congenital heart block in fetuses of women with previously affected offspring than those without previously affected offspring. Advanced block and cardiomyopathy can occur within 1 week of a normal echocardiogram without initial first-degree block. Echodensities and moderate/severe tricuspid regurgitation merit attention as early signs of injury. (*Circulation*. 2008;117:485-493.)

**Key Words:** antibodies ■ echocardiography ■ heart block ■ immunology ■ pregnancy ■ atrioventricular node

One of the strongest clinical associations with autoantibodies directed to components of the SSA/Ro-SSB/La ribonucleoprotein complex is the development of congenital heart block (CHB) in an offspring, an alarming prospect facing 2% of primigravid mothers with these reactivities.<sup>1</sup> This risk is 5- to 10-fold higher in women who have had a previously affected child with either CHB or the neonatal lupus rash.<sup>2</sup> Tissue injury in the fetus is presumed to be dependent on the Fc $\gamma$ R-mediated transplacental passage of maternal IgG autoantibodies.<sup>3</sup> CHB carries a significant mortality (20% to 30%, primarily fetal and

neonatal) and morbidity (67% of surviving affected children require permanent pacing before adulthood).<sup>4-8</sup> Evidence is emerging that, in addition to conduction disease, 10% to 15% of affected offspring will have a life-threatening cardiomyopathy.<sup>9-13</sup> This more extensive injury can occur in utero or postnatally, even as late as 9 years of age.<sup>11</sup>

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Because CHB is identified most often between 18 and 24 weeks of gestation,<sup>4,5</sup> intrauterine therapy may be possible.

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Consideration has been given to prophylaxis with prednisone, dexamethasone, and/or plasmapheresis. Although 1 limited retrospective study from Japan suggested the efficacy of prednisone in preventing block,<sup>14</sup> this therapy (at least in low and moderate doses) early in pregnancy did not prevent block in several cases previously reported.<sup>5</sup> Prednisone would not be expected to be efficacious because maternal administration does not decrease levels of anti-SSA/Ro-SSB/La antibodies,<sup>15</sup> and placental 11 $\beta$ -dehydrogenase prevents active drug from reaching the fetal circulation.<sup>16,17</sup> Fluorinated glucocorticoids that are resistant to placental enzymes have been studied more extensively in the treatment of established block. Unfortunately, to date, this approach has not been successful in reducing the degree of block once complete atrioventricular (AV) dissociation has been documented.<sup>18</sup> On the basis of immunohistology of several hearts from fetuses dying of CHB,<sup>19</sup> this is not surprising because fibrosis is extensive and replaces the AV node, even in the 2 youngest hearts studied (gestational age, 20 and 22 weeks). However, it has been reported that less advanced degrees of block have reverted to normal sinus rhythm after maternal glucocorticoid therapy.<sup>18,20</sup> The concern regarding exposure of both mother and fetus to steroids may outweigh potential benefit, given that even among pregnancies in mothers of previous affected children, 80% are expected to result in a healthy child.

Because fetuses in whom third-degree block is the presenting marker of injury may not benefit from treatment, the critical times to intervene would be predicted to be when the PR interval is prolonged but atrial signals continue to reach the ventricles (first- or second-degree block) or when signs of myocardial dysfunction alone are present. From a clinical perspective, there is a clear need to identify an early marker of CHB. From a basic science perspective, the knowledge that antibodies can induce lesser degrees of injury would be important. Accordingly, an observational study of pregnant women known to have anti-SSA/Ro antibodies was initiated to determine the earliest noninvasive echocardiographic marker of AV nodal and/or myocardial injury. The primary outcome measure was the mechanical PR interval. Secondary outcomes included evaluation of myocardial function. The hypothesis is that there is a serial, orderly progression from normal sinus rhythm through first-degree to more advanced block and that a window of opportunity exists to diagnose and treat to prevent complete and irreversible block.

## Methods

### Patient Population

Patients entered this prospective, multicenter, observational study between December 2000 and April 2006. A total of 127 pregnant women with anti-SSA/Ro antibodies (with or without anti-SSB/La antibodies) were enrolled from 33 centers across the United States by participating clinicians, including rheumatologists, pediatric cardiologists, and obstetricians. The institutional review boards of all participating sites approved the protocol and consent forms before initiation of the study, and written informed consent was obtained from all subjects before enrollment.

At study entry, all patients fulfilled the following entry criteria: presence of anti-SSA/Ro and/or anti-SSB/La antibodies documented by a commercial laboratory or in the research laboratory of the New York University School of Medicine before the 16th week of a current pregnancy (and within the preceding 5 years) and a pregnancy of <18 weeks in which the fetus had a normal heartbeat

documented before the 18th week of gestation and a structurally normal heart. Mothers were excluded if they were taking >10 mg/d prednisone or the equivalent. Mothers could be clinically asymptomatic or have symptoms of a rheumatic disease. Rheumatologic disease was assigned on the basis of case report forms filled out by the participating obstetricians and cardiologists performing the echocardiograms and verified by telephone interviews and review of medical records when available (by J.P.B.). The following categories were assigned in most cases: (1) asymptomatic if a patient denied any clinical symptoms that would be consistent with systemic lupus erythematosus (SLE) or Sjogren's syndrome (SS); (2) undifferentiated autoimmune disease if insufficient criteria for SLE or SS; (3) SLE if 4 criteria of the American College of Rheumatology<sup>21</sup> were satisfied; (4) possible, probable, or definite SS if patients had at least dry eyes and dry mouth or only 1 symptom plus evidence of objective criteria in addition to autoantibodies as per the European Classification<sup>22</sup>; or (5) SLE and SS if criteria for both were met.

### Enrollment and Follow-Up Visits

The protocol called for fetal echocardiography to be performed weekly from 16 to 26 weeks and then biweekly until 34 weeks, followed by an ECG and echocardiogram at birth. In addition, an ECG was performed up to 3 years postnatally when available. The fetal echocardiographic parameters were limited to essential measurements; to be included in the analysis, a case required at least 2 fetal echocardiograms plus postnatal outcome. Ninety-five percent of cases provided at least 50% of the requested data points.

Fetal echocardiographic scans were performed according to standard methods.<sup>23–29</sup> The studies were recorded on VHS videotape or DVD/optical disk by the pediatric cardiologist or obstetrician caring for the patient. The videotapes were then sent to the core fetal echocardiographic laboratory where the studies were read and quantified as recorded on the fetal echocardiographic data abstraction forms (by D.M.F.). A complete 2-dimensional echocardiographic and color Doppler study of the fetal heart included all standard views to rule out the presence of any structural abnormalities of the fetal heart that could cause CHB, ie, L-transposition of the great arteries, AV septal defect, or heterotaxias. The 2-dimensional echocardiogram was reviewed for the presence of pericardial effusions, pleural effusions, ascites, or scalp edema. The M-mode study included views of both ventricles obtained by a perpendicular M mode at the level of the AV valve leaflets. The measurements taken from these M-mode recordings included the atrial cycle length, ventricular cycle length, and a deduced diagnosis of the heart rhythm. The M-mode study assessed the diameters on the standard views of the left ventricular end-diastolic and end-systolic diameters.<sup>23</sup> Derived M-mode values included the left ventricular shortening fraction, defined as the left ventricular end-diastolic diameter minus the left ventricular end-systolic diameter divided by the left ventricular end-diastolic diameter. The lower limit of normal shortening fraction was set at 28%.<sup>23</sup>

Doppler study using a pulsed wave of the fetal heart was used to obtain the mechanical Doppler PR interval measurements.<sup>30</sup> The 2-dimensional directed pulsed Doppler gate was placed distal to the mitral valve within 20° of parallel to the left ventricular outflow tract. By obtaining the pulsed Doppler signal in this location, we determined the mitral valve Doppler flow pattern (specifically the E/A ratio), as well as the aortic Doppler pattern on the same simultaneous tracing. The tracing was frozen, and the interval between the onset of the mitral valve A wave and the upstroke of the aortic valve flow was measured. The time interval (in milliseconds) between these 2 Doppler samples represents the delay from the onset of atrial contraction to the onset of ventricular contraction, which is representative of the mechanical PR interval. Three measurements per subject were taken and averaged. The fetal heart rate also was determined from sequential Doppler aortic outputs on the same tracing. From the identical tracing, the Tei index, or myocardial performance index, was calculated as the ratio of isovolumic contraction time plus isovolumic relaxation time divided by the ejection time. This index is an estimate of global left ventricular function in normal sinus rhythm, as previously described.<sup>31</sup>

Previously reported normal values were used for comparison. Specifically, in 56 normal pregnancies, 2 SD above the upper limit of normal for the PR interval (pulsed Doppler echocardiographic assessment of the fetus, validated at birth by simultaneous ECG of the neonate) was 140 ms; 3 SD above the upper limit of normal (>99% CI) was 150 ms.<sup>30</sup> The method, which is independent of heart rate and gestational age, was subsequently validated by site investigators.<sup>32</sup>

The definition of “abnormal” fetal Doppler mechanical PR interval was set a priori at 3 SD, rather than 2 SD, above the normal mean.<sup>30</sup> A more stringent criterion for defining abnormal was used because we envisioned this threshold to represent a clinical trigger for labeling the fetus with a serious disease (20% mortality) and potentially treating the maternal-fetal dyad with a drug associated with serious toxicity (maternal dexamethasone). In the present study and in a study by Sonesson et al,<sup>33</sup> several fetuses with PR intervals in the range of 135 to 140 ms spontaneously reverted and were not associated with clinical pathology. Furthermore, our more stringent threshold did not prevent the study investigators from recalling for a rapid repeat study those women whose fetuses had PR intervals 2 SD above the mean (140 ms).

The normal fetal left ventricular Tei index was  $0.53 \pm 0.13$ .<sup>31</sup> The presence or absence of tricuspid valve regurgitation was noted and graded as mild if the regurgitant jet filled <25% of the right atrial area or moderate to severe if it exceeded this value.<sup>23</sup>

ECG measurements obtained at birth and 1 year were descriptively compared with normal values for ECGs,<sup>34</sup> including heart rate, PR interval, QRS duration, and QT and QTc intervals.

## End Points

The primary outcome for the study was the degree of cardiac injury, classified into one of the following categories: (1) normal fetal echocardiogram throughout the study; (2) prolonged mechanical PR interval (>150 ms) that did not progress to more advanced degrees of AV block; (3) prolonged mechanical PR interval that progressed to second- or third-degree block; (4) second- or third-degree AV nodal block not preceded by a prolonged mechanical PR interval; (5) any sign of myocardial injury without change in cardiac rate or rhythm such as shortening fraction <28% (ie, 2 SD below normal mean), hydropic changes, or moderate/severe tricuspid regurgitation; or (6) death. In fetuses identified with first-degree block, the decision to treat with dexamethasone was agreed on by the subject and her treating physician, often after consultation (with J.P.B. and D.M.F.) but in the absence of a formal protocol.

## Laboratory Studies

All sera were 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 ELISA (Diamedix Corp, Miami, Fla). In this commercial test, the cutoff for normal has been established at 19 EU for both SSA/Ro and SSB/La. However, patients with titers <30 EU were not included in the study because review of previous cases of CHB in the Research Registry for Neonatal Lupus revealed none with levels in this range. In addition to evaluation by commercial ELISA, sera were evaluated by ELISA using the recombinant proteins 48-kDa SSB/La, 52-kDa SSA/Ro, and 60-kDa SSA/Ro, which were synthesized and purified as previously described.<sup>35,36</sup>

## Statistical Analysis

Fisher’s exact test was used to compare the rate of CHB in pregnancies of women who had a prior child with CHB with the rate of CHB in pregnancies of women who previously had only healthy children or who had no previous pregnancies. The titers of anti-SSA/Ro antibodies in the pregnancies complicated by CHB were compared with titers in pregnancies in which fetuses had no conduction abnormalities using the Mann-Whitney test (Instat3, GraphPad Software, San Diego, Calif).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

### Study Population

One hundred twenty-seven women signed informed consent for the study. Five mothers had a spontaneous miscarriage before the first echocardiogram at 16 weeks; in none of these was there any suspicion of a cardiac disorder in the fetus. Two mothers were subsequently identified to be taking >10 mg prednisone. In 7 mothers, evaluation of anti-SSA/Ro-SSB/La antibodies in the clinical immunology laboratory at New York University Hospital for Joint Diseases and in the research laboratory (J.P.B.) did not confirm previously positive results, and these women were not included in further analysis. Fifteen mothers voluntarily dropped out during the course of evaluation. Ninety-eight pregnancies in 95 mothers were included in the subsequent evaluations. The ethnic backgrounds of these 95 mothers were as follows: white, 54 (57%); black, 12 (13%); Asian American, 13 (14%); Hispanic, 10 (11%); other, 5 (5%); and Pacific Islander 1, (1%).

### Incidence of Neonatal Lupus

Table 1 summarizes the overall incidence of neonatal lupus in its various manifestations for different categories of mothers’ pregnancy histories. For 44 mothers, this pregnancy was their first or there was a history of miscarriage before 20 weeks. Thirty mothers had previously healthy children. Eight mothers had a previous child with rash, and 16 had a previous child with CHB.

Six fetuses developed a cardiac conduction abnormality. Three developed third-degree block (Figure 1). The first (patient 1-2-27) had normal PR intervals from 16 to 22 weeks of gestation (16 weeks, 116 ms; 17 weeks, 117 ms; 18 weeks, missed; 19, weeks, 110 ms; 20 weeks, 138 ms; 21 weeks, 120 ms; and 22 weeks, 129 ms). Transient mild tricuspid regurgitation was detected at 17 weeks, and an unexplained but persistent atrial echodensity was first observed at 22 weeks’ gestation. At 23 weeks, third-degree block was noted. Despite initiation of maternal treatment with 4 mg dexamethasone orally per day, the pregnancy was terminated at 24 weeks because of severe hydrops. The second fetus (patient 1-30-1) had normal PR intervals from 16 to 19 weeks (16 weeks, 110 ms; 17 weeks, 111 ms; 18 weeks, missed; and 19 weeks, 100 ms). Moderate/severe tricuspid regurgitation was observed at 19 weeks. The mother did not return until 21 weeks, when third-degree block was diagnosed. Despite 4 mg dexamethasone, third-degree block has persisted through follow-up at 8 months of age; the child received a pacemaker at birth. In the third fetus with third-degree block (patient 1-23-30), the PR interval was normal at 18 weeks, and 10 days later, third-degree block with severe hydrops was noted. There was a globular poorly functioning right ventricle with an echodense endocardium. The pregnancy was terminated at 20.5 weeks for severe hydrops unresponsive to 4 mg/d maternal dexamethasone.

Three fetuses had first-degree block based on prolongation of the PR interval (>150 ms) (Figure 2). One fetus (patient 1-3-1) had a normal PR interval from 17 to 19 weeks (17 weeks, 104 ms; 18 weeks, 116 ms; and 19 weeks, 107 ms). At 20 weeks, the PR interval was 165 ms, and the mother elected to take 4 mg/d dexamethasone. The subsequent PR interval, 7 days later, was

**Table 1. Outcomes in 98 Prospectively Followed Pregnancies in 95 Women With Anti-SSA/Ro-SSB/La Antibodies Correlated With the Mothers' Pregnancy Histories\***

PRIDE Outcome	Previous Pregnancy History (n=98)			
	No Previous Affected Child (n=74), n			
	First Pregnancy (n=44)	Previous Children Healthy (n=30)	Previous Child With Rash (n=8), n	Previous Child With CHB (n=16), n
Normal sinus rhythm	38	27	8	13
First-degree block	0	1	0	2
Second-degree block	0	0	0	0
Third-degree block	2	0	0	1
Rash/normal sinus rhythm	3	1	0	0
Isolated cardiomyopathy	0	0	0	0
Died (non-CHB)	1	1	0	0
Poor outcome unrelated to neonatal lupus	0	0	0	0

\*Three of the 95 mothers had 2 evaluable pregnancies during the course of the study; all 3 appear in the First Pregnancy column. The second pregnancies of 2 are tabulated in the Previous Children Healthy column, and the second pregnancy of the third subject is tabulated in the Previous Child With Rash column.

135 ms. The mother continued 4 mg/d dexamethasone for the remainder of the pregnancy, with all PR intervals ranging from 110 to 133 ms. ECG at birth was normal with a PR interval of 116 ms; ECG at 9 months of age revealed normal sinus rhythm with a PR interval of 124 ms. A second fetus (patient 1-23-9) had a normal PR interval of 135 ms at 19 weeks, missed the 20- and 21-week echocardiograms, and had a PR interval of 160 ms at 22 weeks, which decreased to 126 ms after 2 days of 4 mg dexamethasone. Dexamethasone was continued until 26 weeks when oligohydramnios was detected. The PR interval was 143 ms and remained between 108 and 135 ms until birth, when the ECG confirmed normal sinus rhythm with a normal PR interval of 110 ms. The third fetus (patient 1-2-8) had serial echocardiograms with normal PR intervals between 20 and 30 weeks (20 weeks, 136 ms; 22 weeks, 119 ms; 23 weeks, 108 ms; 24 weeks, 125 ms; 26 weeks, 107 ms; 29 weeks, 129 ms; and 30 weeks, 103 ms). The child was born prematurely at 32 weeks. The ECG at birth revealed first-degree heart block with a PR of 170 ms, which has persisted through the most recent ECG at 3 years of age (192 ms). Notably, none of the 6 affected fetuses displayed any discernible pattern of progressive PR prolongation before the primary outcome of block.

Overall, the frequency of any degree of heart block at birth in neonates of mothers who had no previously affected child (CHB or rash) was 3 of 74 pregnancies (4%) compared with 3 of 16 pregnancies (19%) in mothers with a previous child with CHB ( $P=0.067$ ).

Data on the PR interval were evaluated with the 6 affected fetuses excluded, as well as secondary outcomes in the remaining 92 fetuses. All 92 fetuses displayed longitudinal PR intervals within the previously validated normal values obtained between 16 weeks and term, which were  $<150$  ms (mean $\pm$ 3 SD) (Figures 1A and 2A). Secondary outcomes included measures of myocardial function. The Tei index, an assessment of global myocardial function, remained normal throughout gestation in these unaffected fetuses (data not shown). It should be noted that, in the 1 fetus with a measurable Tei index at the time of PR prolongation, the Tei

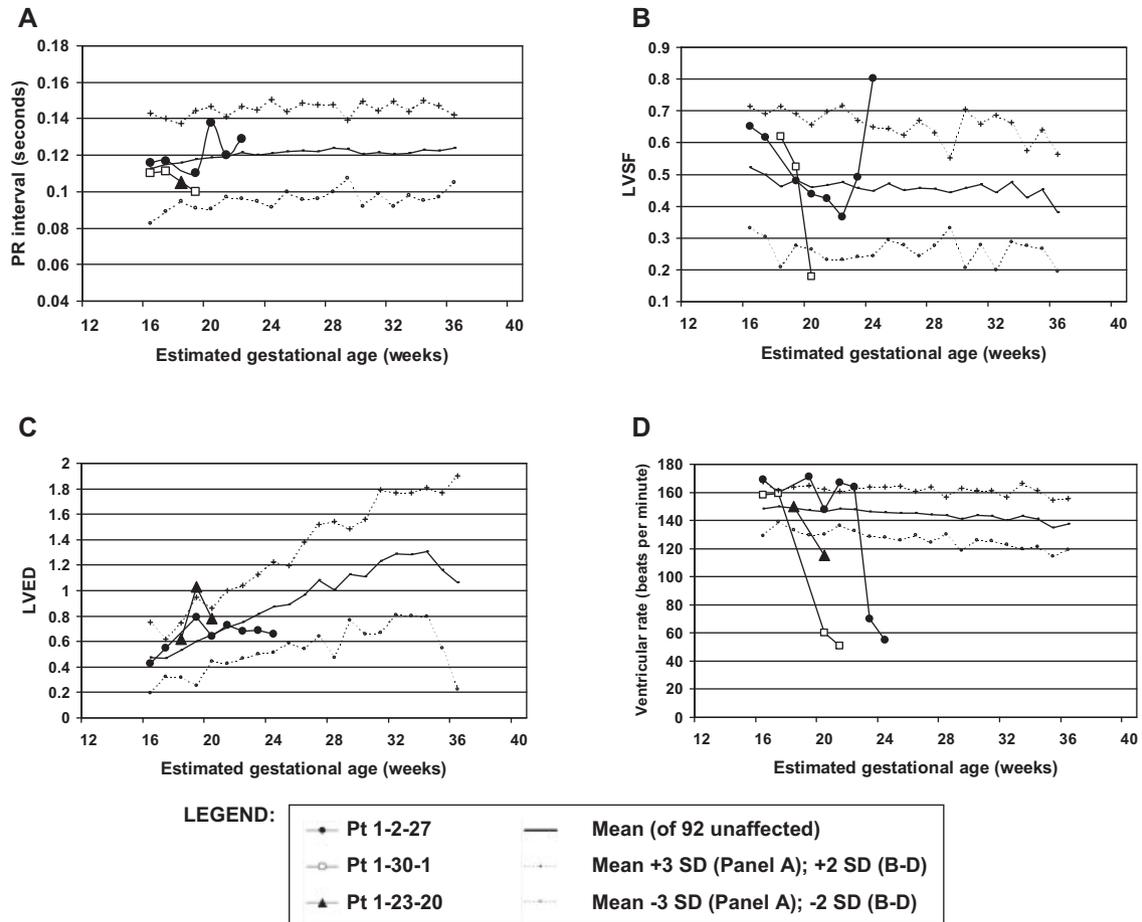
index was prolonged as a result of the PR interval being a component of the isovolumic contraction time. The left ventricular shortening fraction was transiently  $<28\%$  in 10 of the 92 unaffected fetuses (Figures 1B and 2B), but in each case, the ECGs and subsequent echocardiograms were normal. No transient effusions or left ventricular enlargements were detected (Figures 1C and 2C). In the unaffected fetuses, there were neither tachyarrhythmias nor bradyarrhythmias (Figures 1D and 2D). However, 5 fetuses had sinus rates between 113 and 117 bpm. Mild/transient tricuspid regurgitation was noted in 17 of the 92 unaffected fetuses, with 1 additional case described as moderate/severe.

For 82 of 94 live births (87%), ECGs were available at birth and/or by 1 year of age (66 at birth, 56 at 1 year). With the exceptions of the single postnatal case of first-degree block and the survivor with third-degree block, all neonates whose PR intervals were normal throughout the in utero evaluation had normal PR intervals on ECG. Additional ECG time intervals are detailed in Table 2.

Four rashes consistent with neonatal lupus were documented in the cohort. In 2 neonates, the rash was present at birth. In 2 neonates, the rash developed at 2 weeks of age. Each of these neonates had a normal birth ECG, and none developed any cardiac disorders through 1 year of follow-up.

### Maternal Diagnoses

Of the 95 mothers, 36 (38%) fulfilled American College of Rheumatology criteria for SLE, 21 (22%) were classified as probable or definite SS, 5 (5%) had SLE with secondary SS, 14 (15%) were classified as having an undifferentiated autoimmune syndrome, 1 (1%) had rheumatoid arthritis, 1 (1%) had primary antiphospholipid syndrome, 1 (1%) had scleroderma, and 12 (13%) were completely asymptomatic; in 4 (4%), the diagnosis was unknown. Specifically, the maternal diagnosis of the 6 mothers whose children had heart block was SLE for 3 and undifferentiated autoimmune syndrome for 1; 2 were asymptomatic.



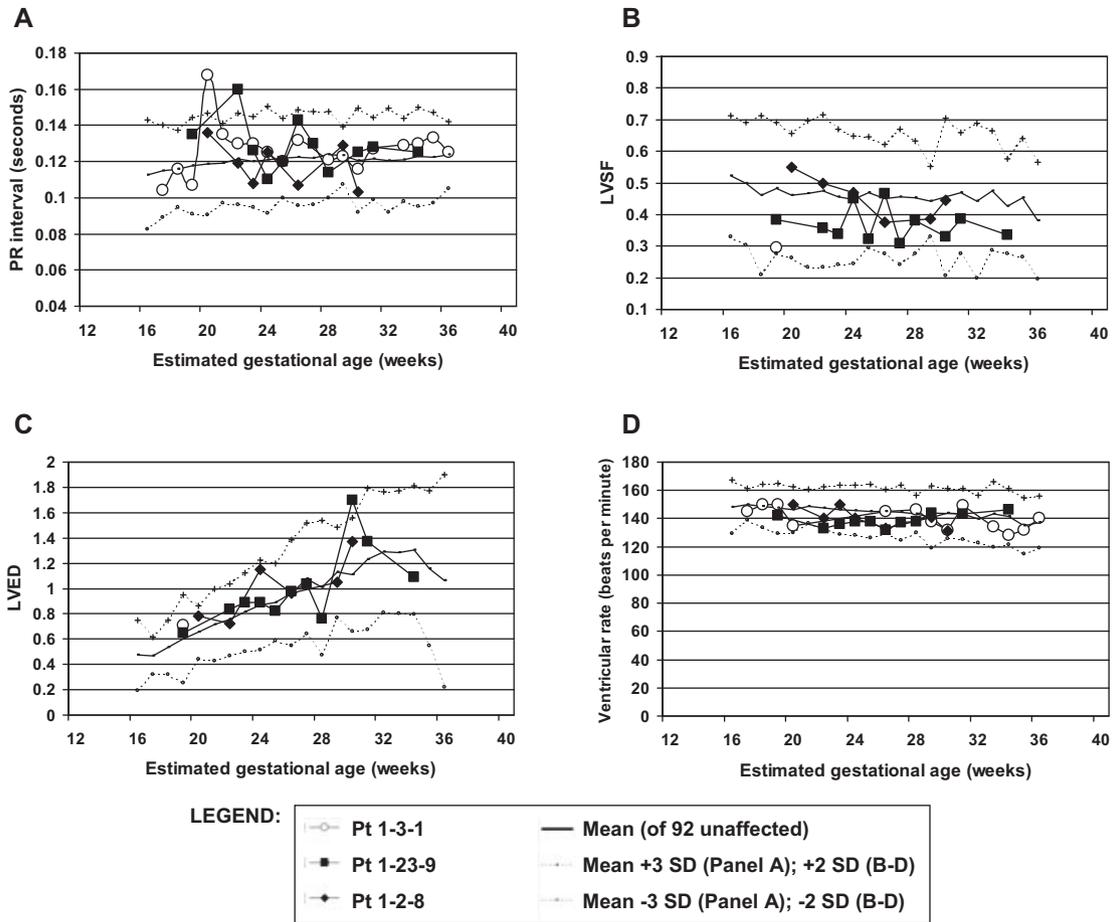
**Figure 1.** Cases of third-degree heart block. Fetal echocardiographic findings in affected vs unaffected fetuses. Means and SD were calculated by dividing the data into gestational subgroups. A, Doppler mechanical PR intervals are displayed as mean  $\pm$  3 SD for the 92 unaffected fetuses in the PRIDE study according to estimated gestational age (EGA). There is no change over EGA. The available cases of third-degree block are displayed when available before onset. None were preceded by a prolonged PR interval. B, Left ventricular shortening fraction (LVSF) is displayed as mean  $\pm$  2 SD for the unaffected fetuses in the PRIDE study according to EGA. There is no change over EGA. The available cases of third-degree block are displayed individually; all are normal before disease onset. C, Left ventricular end-diastolic dimension (LVED) is displayed as mean  $\pm$  2 SD for the unaffected fetuses in the PRIDE study according to EGA. There is an expected increase in dimension over EGA. There was no persistent cardiomegaly in the affected cases. D, Ventricular contraction rate is displayed as mean  $\pm$  2 SD for the unaffected fetuses in the PRIDE study according to EGA. There is no change over EGA. The cases of third-degree block produced significant bradycardia.

**Maternal Antibodies**

Maternal sera obtained during the 98 pregnancies contained anti-SSA/Ro antibodies. For the group as a whole, in 4 pregnancies, the antibody titer was between 30 and 50 EU; in 14, it was between 51 and 100 EU; and in the remainder, it exceeded 150 EU. In an analysis that included only 1 antibody titer measurement per mother, the median titer of anti-SSA/Ro antibodies in the 89 pregnancies that did not result in CHB was 3008 compared with a median titer of 16 128 in the 6 CHB pregnancies ( $P=0.026$ ). Maternal samples from 93 pregnancies were available for evaluation of the fine specificity of the anti-SSA/Ro profile; 80% had antibodies to Ro52, and 65% had antibodies to Ro60. In all 6 pregnancies complicated by heart block, antibodies to both Ro52 and Ro60 were present, which also was the case in 50 of the unaffected pregnancies (57%). In 44 pregnancies, antibodies to SSB/La were detected, 4 of which were complicated by heart block. Although the median titer of anti-SSB/La antibodies was higher in mothers carrying affected fetuses, 732 EU compared with 90 EU in the unaffected pregnancies, this difference did not reach statistical significance.

**Discussion**

Large cohorts of patients are needed to address clinically whether cardiac injury progresses through potentially reversible stages, thereby justifying interventions that may prevent or forestall fibrosis of the node and irreversible third-degree block. The primary outcome of this study, a mechanical PR interval that exceeded 3 SD above the normal mean, was observed in 3% of cases. Two of these fetuses were identified during the middle of the second trimester, the predicted period of cardiac vulnerability. In both, dexamethasone was associated with rapid reversal of the PR interval to normal ranges. Whether dexamethasone was curative or incidental cannot be assigned. A third case first developed first-degree block at 32 weeks after normal PR intervals in utero, as demonstrated on the ECG performed at birth; the block persists at 3 years of age. Three cases of third-degree block were identified, none of which were preceded by a less advanced degree of block, and none were reversed by dexamethasone. Isolated neonatal lupus rash occurred in 4 cases.



**Figure 2.** Cases of prolonged mechanical Doppler PR interval or first-degree heart block. Fetal echocardiographic findings for affected vs unaffected fetuses. Means and SD were calculated by dividing the data into gestational subgroups. A, Doppler mechanical PR intervals are displayed as mean  $\pm$  3 SD for the 92 unaffected fetuses in the PRIDE study according to estimated gestational age (EGA). There is no change over EGA. The 2 cases of isolated PR interval prolongation are displayed. The postnatally diagnosed case showed normal PR intervals throughout gestation. B, Left ventricular shortening fraction (LVSF) is displayed as mean  $\pm$  2 SD for the unaffected fetuses in the PRIDE study according to EGA. There is no change over EGA. The available cases of prolonged PR interval show no decrease in LVSF. C, Left ventricular end-diastolic dimension (LVED) is displayed as mean  $\pm$  2 SD for the unaffected fetuses in the PRIDE study according to EGA. There is an expected increase in dimension over EGA. The available case of prolonged PR interval did not show LV dilatation. D, Ventricular contraction rate is displayed as mean  $\pm$  2 SD for the unaffected fetuses in the PRIDE study according to EGA. There is no change over EGA. The available cases of prolonged PR interval did not show bradycardia.

**Previous Prospective Evaluation of the PR Interval**  
 Sonesson et al<sup>33</sup> reported the first prospective study in which the mechanical PR interval was used to identify early conduction disease in 24 pregnancies of mothers with anti-SSA/Ro antibodies. In contrast to the low percentage of fetuses affected in the data reported here, one third of the

fetuses in that study had signs of a prolonged PR interval. Although one explanation for this high frequency might have been the inclusion requirement for antibodies reactive against the 52-kDa SSA/Ro antigen in all patients, resulting in an “enriched” cohort, this seroreactivity was observed in 80% of the mothers in the PR Interval and Dexamethasone Evalua-

**Table 2. Additional ECG Time Intervals at Birth and 1-Year Follow-Up**

Parameter	At Birth	At 1-y Follow-Up
QRS duration	Normal (98th percentile) <70 ms 3 of 65 (5%) abnormal	Normal (98th percentile) <80 ms 2 of 45 (4%) abnormal
QTc	Normal <480 ms 2 of 46 (4%) abnormal (1 with follow-up normal at 1 y)	Normal <480 ms None of 44 abnormal
Sinus bradycardia	Normal rate >90 bpm None of 65 abnormal	Normal rate >89 bpm 2 of 45 (4%) abnormal (85 and 87 bpm; both were normal at birth)

QTc indicates QT interval corrected for heart rate.

tion (PRIDE). Because information on previous pregnancies was not provided, no inference can be drawn with regard to an increased incidence of injury expected on the basis of the recurrence rate of 20%. Perhaps most important is the definition of a prolonged PR interval, which was set at 135 ms (2 SD above their mean, derived from their previous studies in nearly 300 pregnancies<sup>37</sup>). Reevaluation of the PRIDE study using this lower threshold revealed a consistency between the 2 studies, with about one third of the fetuses in PRIDE having a prolonged PR interval by the Sonesson et al criterion. However, in all PRIDE fetuses, a PR interval between 135 and 150 ms spontaneously reversed by the next echocardiogram. In the Sonesson et al study,<sup>33</sup> only 2 fetuses had a prolonged PR interval as defined by the PRIDE criterion. One fetus had a PR approaching 150 ms at 24 weeks, which decreased to 145 ms by 26 weeks. No information regarding treatment was provided. The other fetus had second-degree block, which reversed to first-degree block after treatment, but it was not clear whether there was an initial progression through first-degree before second-degree block. The 1 fetus said to progress from a prolonged PR interval to third-degree block within 6 days had a PR of 140 ms. The plasticity of the PR interval prolongation was further supported by the return of all abnormal values obtained on the newborn ECG to normal values several weeks later.

The 2 critical issues raised by both the PRIDE and the Sonesson et al<sup>33</sup> studies are the clinical significance of a prolonged PR interval and the biological implication with regard to tissue injury. An isolated prolongation of the PR interval may be transient (spontaneously reversible), related to vagal tone, medication use, or reversible injury, or it may be permanent or progress to more marked delay as a result of physical injury to the specialized electrical pathway, eg, as a result of inflammation or scarring. It may be that PR prolongation represents a variant of normal, and only in retrospect does it have clinical significance if it either is sustained after birth or progresses to more advanced block. A PR interval that exceeds the expected 95% CI of a normal population can be transient, sustained, or progressive. Perhaps the final outcome depends on the influence of fetal and environmental factors. These putative permissive factors might be present in certain fetuses and not others, thus accounting for the rarity of clinical disease. If prolongation of the PR interval does represent tissue injury, regardless of how minimal, it might be so rapid as to go unnoticed.

Accurate identification of the fetus in whom first-degree block unambiguously represents a warning sign would be a major advance because early disease may be reversible. This identification requires a definition that is acceptable to the managing physicians and that has a reasonable prediction of being sustained or progressive if left untreated. This task is particularly challenging because dexamethasone and beta-methasone have both maternal and fetal risks. Maternal risks include hypertension, glucose intolerance, infections, and possibly bone density loss or cataracts. Fetal risks include oligohydramnios; growth retardation, including the head; and possibly central nervous system injury.<sup>38,39</sup>

### Other Possible Early Markers of Injury

This study did not reveal any systematic changes in the appearance of transient pericardial effusions or other fluid

collections, any left ventricular enlargement or reduction in shortening fraction or Tei index, nor any marginal decrease in the overall heart rate. However, tricuspid regurgitation and atrial echodensities preceded hydrops fetalis and heart block on >1 occasion. Perhaps these findings represent signs of cardiac inflammation, including myocarditis, preceding congestive heart failure. The atrial echodensity is suspected to represent endocardial fibroelastosis. This observation may allow another window of therapeutic opportunity.

Previous investigators have suggested that sinus bradycardia may be a specific finding in autoimmune-associated cardiac disease both in animal models<sup>40</sup> and in humans.<sup>41</sup> The PRIDE study detected no sinus bradycardia at birth in otherwise unaffected newborns.

Other investigators have found QT interval prolongation in anti-SSA/Ro-exposed infants without CHB,<sup>42</sup> which apparently disappeared during the first year of life.<sup>43</sup> Of 46 evaluable cases in the PRIDE study, only 2 (4%) exhibited prolonged QT intervals on birth ECG, not significantly increased above the baseline incidence of 2%. None persisted at 1 year. Similarly, only 3 of 65 (5%) had QRS duration above the 98th percentile on ECG at birth, with persistence at the 1-year follow-up in 1; of 45 evaluable at the 1-year follow-up, 2 (4%) who were normal at birth had QRS duration >98th percentile. These findings were not clinically significant.

The PRIDE study also provides a second cohort to compare the epidemiology with the previous report of Brucato et al,<sup>1</sup> in which third-degree block occurred in 2 of 112 infants born to 100 women with anti-SSA/Ro antibodies. Our overall results were similar, with third-degree block developing in 3 of 98 pregnancies in 95 women. Brucato et al did not comment on lesser degrees of block or on previous pregnancy history but highlighted the absence of third-degree block in pregnancies of the 53 women who had SLE in their cohort. Notably, in PRIDE, 1 of the 3 women whose fetuses had third-degree block had an established diagnosis of SLE. As more data accumulate, the early observation<sup>5</sup> that maternal disease status is independent of fetal outcome is being confirmed. Anti-SSA/Ro antibody titers were higher in the mothers whose pregnancies were complicated by CHB than in those whose pregnancies were unaffected. However, high-titer anti-Ro antibodies and the presence of reactivity to Ro52 were not sufficient to cause CHB because this profile also was characteristic of most of the unaffected pregnancies. Although 18% of the mothers in this study had anti-SSA/Ro titers in a relatively low range (30 to 100 EU), it is important to emphasize that clinical testing would have identified these mothers as having anti-SSA/Ro antibodies, prompting their counseling regarding the risk of CHB.

### Additional Measurement Technique

Gardiner et al<sup>44</sup> reported a new technique of real-time fetal ECG measurement of fetal heart rate, electric PR interval, and analysis of various other waveforms and time intervals. Both electric PR interval recordings and Doppler mechanical PR intervals had good predictive values, although electric PR intervals detected 2 additional cases of abnormality compared with mechanical PR intervals. However, these authors' method of measuring mechanical PR intervals was not directly comparable to that used in the PRIDE protocol. Their

normal values were different, whereas the PRIDE method was independently validated by Andelfinger et al.<sup>37</sup> Nevertheless, electric PR intervals derived from fetal ECG may prove to be a useful research tool in the future. At present, fetal ECG is not readily available, whereas mechanical PR intervals by fetal Doppler is readily available, simple, independent of gestational age, obtainable in essentially all cases with minimal training, and widely accepted in practice.

### Study Limitations

Several limitations of PRIDE are acknowledged. The presence of incomplete data acquisition in this multicenter prospective observational study raises the issue as to whether this may have affected the ability to detect all cases of transient prolongation of the fetal mechanical Doppler PR interval. This is considered unlikely to have occurred systematically because first-degree block is completely asymptomatic and could be detected only by measuring fetal mechanical Doppler PR interval. Therefore, missing scans in asymptomatics can be considered to be missing at random. Thus, the percentage of transient PR interval >150 ms should be independent of sampling frequency and unbiased by randomly missing data points in asymptomatic gestations. The utility of the mechanical PR interval as a biomarker of potentially reversible injury is not fully addressed because weekly fetal echocardiograms may not be frequent enough to detect transient changes. This largest study to date confirms that autoimmune-associated heart block is a rare disease and that identification of biomarkers is difficult because of the limited numbers of expected events.

### Conclusions

Given the identification of irreversible block within 1 to 2 weeks of normal sinus rhythm and its occurrence before 24 weeks of gestation, it would seem appropriate to perform intense monitoring between 16 and 24 weeks. The goal of this monitoring would be to identify a biomarker of reversible injury such as a PR interval prolongation >150 ms, moderate/severe tricuspid regurgitation, and/or an atrial echodensity. However, the necessary frequency of such monitoring has not been determined, although our data suggest greater-than-weekly intervals. Prolongation of the fetal Doppler mechanical PR interval is not a definitive tool to detect early signs of anti-SSA/Ro-associated cardiac disease. The efficacy of dexamethasone is unproved, and safety remains a concern. The morbidity and mortality of third-degree block suggest the need for the development of a new prophylactic therapy other than dexamethasone to be given early in pregnancy before the onset of disease and perhaps targeted to the highest-risk pregnancies such as in women with prior affected offspring.

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### Disclosures

Dr Friedman is a member of the speakers' bureau of MedImmune. The other authors report no conflicts.

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### CLINICAL PERSPECTIVE

Anti-SSA/Ro-SSB/La antibody-associated congenital heart block is identified most often between 18 and 24 weeks of gestation, and to date, third-degree congenital heart block is irreversible. Intrauterine therapy should be possible, prompting a search for early markers and effective therapy. Fetal echocardiograms were performed serially in 98 pregnancies in antibody-positive women. Fetal Doppler mechanical PR intervals >150 ms were considered prolonged. Three fetuses had third-degree block before 24 weeks, none with preceding abnormal PR intervals, although 1 had preceding tricuspid regurgitation and another had unexplained atrial echodensities. Thus, advanced block and cardiomyopathy can occur within 1 week of a normal echocardiogram without initial first-degree block. Three fetuses had prolonged PR intervals, 2 of which reversed with dexamethasone. Congenital heart block occurred in 19% of pregnancies in mothers of previous congenital heart block children and in 4% of pregnancies in women without a previously affected child. Prolongation of the fetal Doppler mechanical PR interval may be a useful, albeit not a definitive, tool to detect early signs of anti-SSA/Ro-associated cardiac disease. However, spontaneous reversal of a prolonged PR interval is as yet unaddressed. The goal of this monitoring would be to identify a biomarker of reversible injury such as a PR interval prolongation >150 ms, moderate/severe tricuspid regurgitation, and/or an atrial echodensity, each of which might prompt repeat evaluation within 48 hours and/or consideration of a short course of dexamethasone. The morbidity and mortality of third-degree block suggest the need for a prophylactic therapy early in pregnancy before disease onset, targeted at pregnancies in women with prior affected offspring.