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Prolongation of the Atrioventricular Conduction in Fetuses Exposed to Maternal Anti-Ro/SSA and Anti-La/SSB Antibodies Did Not Predict Progressive Heart Block

A Prospective Observational Study on the Effects of Maternal Antibodies on 165 Fetuses

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Objectives We prospectively examined the prevalence and outcome of untreated fetal atrioventricular (AV) prolongation in the presence of maternal anti-Ro antibodies.

Background It has been suggested that antibody-mediated congenital complete atrioventricular block (CAVB) may be preventable if detected and treated early when low-grade block is present. With this rationale in mind, dexamethasone has been advocated by others to treat prolonged fetal AV conduction >2 *z*-scores, consistent with first-degree heart block.

Methods Between July 2003 and June 2009, 165 fetuses of 142 anti-Ro/La antibody–positive women were referred to our center for serial echocardiography. Our protocol included weekly evaluation of the fetal AV conduction between 19 (range 17 to 23) and 24 (range 23 to 35) gestational weeks. AV times were compared with institutional reference data and with post-natal electrocardiograms.

Results Of 150 fetuses with persistently normal AV conduction throughout the observation period, a diagnosis of CAVB was subsequently made in 1 at 28 weeks, after the serial evaluation had ended. Of 15 untreated fetuses either with AV prolongation between 2 and 6 *z*-scores or with type 1 second-degree block, progressive heart block developed in none of them. Three of these 15 fetuses (20%) had a neonatal diagnosis of first-degree block that spontaneously resolved (n = 2) or has not progressed (n = 1) on follow-up examinations. No other cardiac complications were detected.

Conclusions Fetal AV prolongation did not predict progressive heart block to birth. Our findings question the rationale of a management strategy that relies on the early identification and treatment of fetal AV prolongation to prevent CAVB. (J Am Coll Cardiol 2011;57:1487–92) © 2011 by the American College of Cardiology Foundation

Irreversible fetal complete atrioventricular block (CAVB) related to maternal anti-Ro/SSA autoantibodies typically develops between 20 and 24 weeks of gestation. The condition may be preventable if the causative disease process is detected and treated with maternally administered dexamethasone at an early stage (1–4). This implies that autoantibody-mediated CAVB does not suddenly develop, but rather represents a progressive condition from first-degree atrioventricular block (AVB1) or second-degree atrioventricular block (AVB2). Serial echocardiography of anti-Ro antibody–exposed fetuses during the period of highest risk of heart block is increasingly offered as a strategy to prevent CAVB. Nevertheless, there is controversy about the relevance of newly discovered, more subtle cardiac manifestations that perhaps relate to antibody-mediated inflammation. AVB1, diagnosed in 3% to 25% of exposed fetuses, resolved in most fetuses with or without steroid treatment (5–7), whereas progression to CAVB has only rarely been reported (7,8). The aims of this prospective study were to evaluate anti-Ro antibody–mediated effects on the fetal heart and develop recommendations that may be used to manage incomplete atrioventricular (AV) block.

Methods

Between July 2003 and June 2009, 142 anti-Ro antibody–positive women with 165 fetuses were prospectively exam-

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Abbreviations and Acronyms

AV = atrioventricular

AVB1 = first-degree atrioventricular block

AVB2 = second-degree atrioventricular block

CAVB = complete atrioventricular block

in/out = left ventricular inflow and outflow pulsed Doppler echocardiography

SVC/aorta = superior vena cava and ascending aorta pulsed Doppler echocardiography

TDI = tissue Doppler imaging

ined by serial fetal echocardiography with GE Vivid-7 (GE Medical Systems, Horten, Norway) and Philips iU22 (Philips ATL, Bothell, Washington) ultrasound systems. Our protocol recommended weekly examinations between 19 and 24 weeks and until about 35 weeks if a previous child had CAVB. AV chronology was evaluated by simultaneous pulsed Doppler of the superior vena cava/aorta (SVC/aorta; N = 165; 737 examinations) and left ventricular inflow/outflow tracts (in/out; n = 165; 737 examinations). AV intervals were measured from the onset of the A-wave to the beginning of the aortic flow wave. Right ventricular tissue Doppler imaging (TDI) (178 examinations) was used for first 39 study fetuses and thereafter to confirm AV block. TDI-derived AV intervals were measured from the onset of late diastolic wall motion (A′) to the onset of the isovolumetric ventricular contraction spike (IV). Averaged AV times from 3 to 5 cardiac cycles were compared with institutional reference data (9). Post-natal examinations at 4 to 6 weeks of age included 12-lead electrocardiography. In accord with other studies, AV/PR intervals >2 *z*-scores were considered prolonged (6,7,10). The study was approved by our ethics board.

Statistical analysis. Results are expressed as median (range), mean ± SD, frequencies, or *z*-scores. Linear regression adjusted for repeated measures was used to evaluate the effect of gestational age on AV duration. One-way analysis of variance was used to compare post-natal PR with fetal AV duration. Analyses were performed using SAS statistical software version 9.2 (SAS Institute, Cary, North Carolina).

Results

A total of 737 echocardiograms were performed with a median of 4 (range 2 to 12) examinations between 19 (range 17 to 23) and 24 (range 23 to 36) weeks. None of the 165 fetuses had bradycardia <120 beats/min, endocardial fibroelastosis, effusions, or cardiac dysfunction. Figure 1 shows the age-adjusted AV durations.

Normal AV times <2 *z*-scores were found in 150 fetuses. One fetus (fetus 1 in Figs. 1D and 1E) had normal findings on 3 echocardiograms to 24 weeks when no further evaluation was planned. CAVB with a ventricular rate of 62 beats/min was diagnosed at 28 weeks. The child is clinically well and without a permanent pacemaker at age 4 years. Electrocardiograms showing sinus rhythm (148 ± 17 beats/min) with normal PR intervals (97 ± 8 ms) were obtained in 116 other fetuses at 49 (range 5 to 309) days of life.

Transient AV prolongation ≤3 *z*-scores was detected in 11 fetuses (7%) by SVC/aorta (10 of 737 examinations), in/out (8 of 737 examinations), and/or TDI (4/178 examinations). Eight of them had AV prolongation by 2 imaging modalities during the same (n = 5) or different (n = 3) visits. Without dexamethasone treatment, 10 of 11 had normal electrocardiographic findings at 56 (range 43 to 87) days of life, showing sinus rhythm (150 ± 20 beats/min) and normal PR durations (102 ± 13 ms). The exception is a now 6-year-old girl with transient AVB1 (PR duration 132 ms) at 1 month.

Persistent AV prolongation >3 *z*-scores to birth was detected in 3 fetuses (2%) (fetuses 2 to 4 in Figs. 1D and 1E) that without dexamethasone did not progress. In fetus 2, there were normal findings on examination at 20 weeks. Two weeks later, the AV intervals were prolonged (SVC/aorta: 150 ms; *z*-score 4.1; in/out: 165 ms; *z*-score 5.4; TDI: 125 ms; *z*-score 4.8). A healthy girl was delivered at 32 weeks for maternal reasons. AVB1 (PR 152 ms) was confirmed by neonatal electrocardiography and persists at age 3 years (PR 190 ms; *z*-score 5.9). Fetus 3 had AV prolongation from 22 weeks to delivery (SVC/aorta: 144 to 162 ms; *z*-scores 3.3 to 4.7; in/out: 150 to 164 ms; *z*-scores 3.5 to 4.6; TDI: 136 ms at 32 weeks; *z*-score 3.6) but normal electrocardiographic findings at birth (PR 118 ms) and 2 months (114 ms). Fetus 4 (Fig. 2), when first seen at 22 weeks, had persistent AV prolongation (SVC/aorta: 144 to 160 ms; *z*-scores 3.4 to 4.8; in/out: 148 to 170 ms; *z*-scores 3.5 to 5.7; TDI: 123 ms at 22 weeks; *z*-score 4.6). PR intervals were borderline prolonged at birth (128 ms) and normal at 6 months (138 ms).

Mobitz type 1 AVB2 was seen in a fetus at the 24-week examination (Fig. 3) but resolved the next day. At day 2 of life, transient 2:1 AV block in association with QTc prolongation (0.49) was detected, but there were normal electrocardiographic findings (PR 128 ms; QTc 0.43) at 3 months.

Figure 4 illustrates the relationship between fetal AV duration and PR duration in early infancy. PR intervals in fetuses with normal or transiently prolonged AV conduction were shorter compared with fetuses with persistent AV prolongation >3 *z*-scores to birth.

In summary, progressive heart block developed in none of 15 untreated fetuses with AV prolongation. This results in 0% sensitivity and 91% specificity in predicting CAVB by serial echocardiography when >2 *z*-scores are used for the abnormal AV interval range.

Discussion

Currently there are no standard guidelines for the surveillance of autoantibody-exposed fetuses nor is there consensus regarding whether/when AV prolongation should be

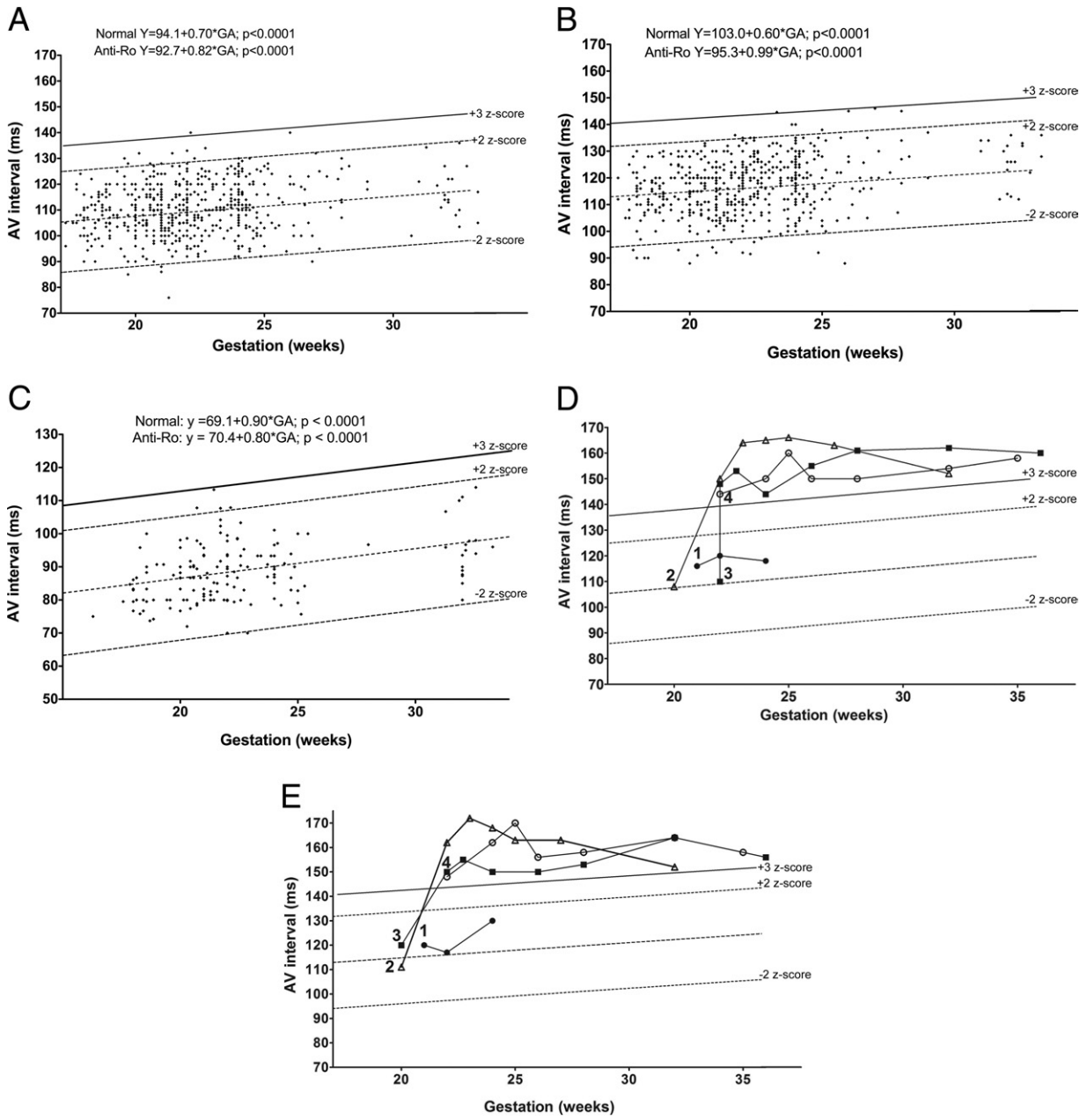

Figure 1 **Fetal AV Time Intervals of the Study Cohort**

The echocardiographic atrioventricular (AV) intervals of 161 fetuses without **(A to C)** and 4 fetuses with **(D and E)** persistent AV prolongation to birth are shown, plotted against normal values (9). The lines denote the ±2 *z*-score (2.5%; 97.5%; **dashed line**) and ±3 *z*-score (99.7%; **solid line**) confidence limits. Regression analyses showed no differences between reference values and AV times of fetuses without persistent AV prolongation by superior vena cava and ascending aorta pulsed Doppler echocardiography (**A**, n = 161), left ventricular inflow and outflow pulsed Doppler echocardiography (**B**, n = 161), and/or tissue Doppler imaging (**C**, n = 39). In the 4 remaining fetuses, persistent AV time abnormalities had developed to birth revealed by superior vena cava and ascending aorta pulsed Doppler echocardiography **(D)** and left ventricular inflow and outflow pulsed Doppler echocardiography **(E).** This includes fetus 1 with normal AV conduction to 24 weeks but congenital AV block after 28 weeks' gestation, fetus 2 with persistent fetal and post-natal first-degree AV block, whereas fetuses 3 and 4 have normal AV conduction despite persistent fetal AV prolongation. GA = gestational age.

treated. A different screening protocol and treatment indication (3,5–7) were used in 4 recent studies. Friedman et al. (5) and Rein et al. (6) treated with maternal steroids if the fetal AV interval exceeded 3 *z*-scores by in/out or 2 *z*-scores by TDI. We were reluctant to use this approach for 2 reasons. First, the 95% limit of observer variability in AV time measurement is ±1 *z*-score (±10 ms) for SVC/aorta, ±1.5 *z*-score (±12 ms) for TDI, and almost ±2 *z*-scores (±17 ms) for in/out (9). It may therefore be possible to diagnose and treat mild AV prolongation when the electrical PR

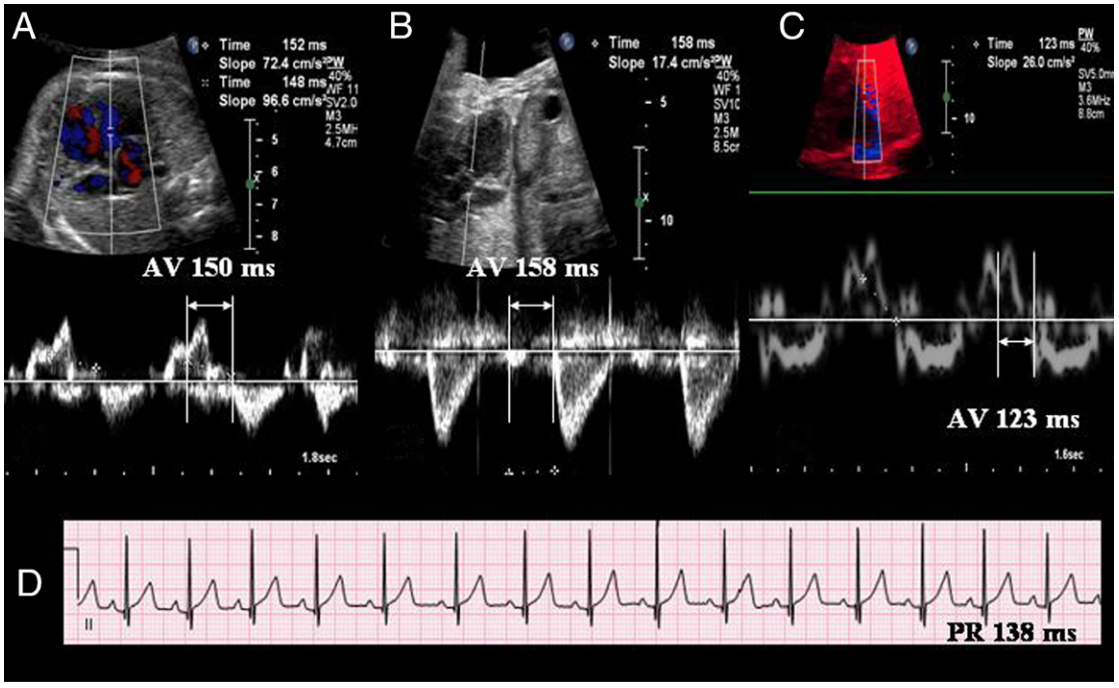

Figure 2 **Fetus With Persistent AV Prolongation**

This untreated fetus (fetus 4) was diagnosed with fetal atrioventricular (AV) prolongation >3 *z*-scores at 22 weeks by left ventricular inflow and outflow pulsed Doppler echocardiography **(A)**, superior vena cava and ascending aorta pulsed Doppler echocardiography **(B)**, and tissue Doppler imaging **(C)** that persisted to birth. At 6 months, the PR duration was normal **(D)**.

duration is normal. Second, progression had been reported in only 2 cases (7,8). The first case had AV prolongation of 3 *z*-score at 19 weeks and CAVB 6 days later. The second case had fetal hydrops when AV prolongation of 3 *z*-score developed at 22 gestational weeks, followed by CAVB and demise despite steroid treatment. In contrast, in 24 similar cases reported in the literature, the fetuses did not progress to CAVB (2,3,5–7,11–14). Four steroid-treated fetuses with AV prolongation ≥190 ms had first or first-to-second degree AVB after birth (2,3,13). Nine other fetuses had shorter AV prolongation (2.3 to 5.5 *z*-scores) that rapidly resolved with dexamethasone (5,6,14). Nonetheless, spontaneous resolution was also seen in 11 untreated fetuses with AV intervals <3 *z*-scores (7,11). These data show that resolution, progression, or nonprogression can occur with and without treatment and highlight the need for a prognostic marker that could reliably distinguish benign or false-positive AV prolongation from true AV nodal disease.

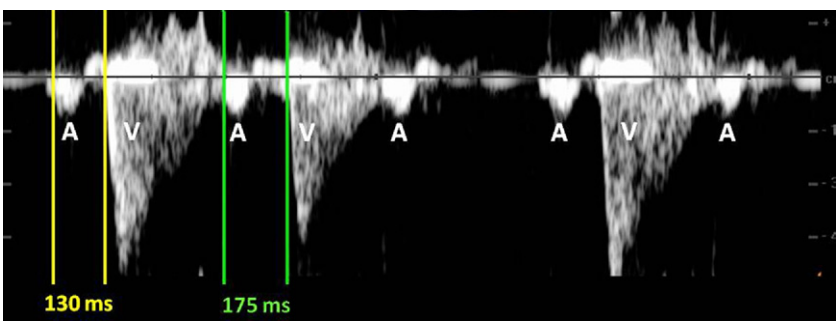

Figure 3 **Fetus With Type 1 AVB2**

Superior vena cava and ascending aorta pulsed Doppler echocardiography of this fetus at 24 gestational weeks shows transient Mobitz type 1 second-degree atrioventricular block (AVB2) with progressive atrioventricular (AV) interval lengthening from 130 ms **(yellow)** to 175 ms **(green)** and normal post-block AV interval. The same child also had brief neonatal 2:1 AV block (not shown).

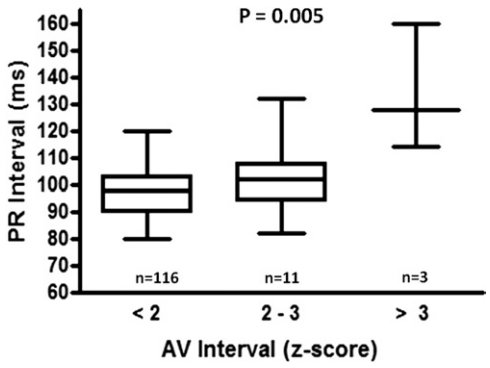

Figure 4 **Box Plots Comparing Fetal AV Intervals With Neonatal PR Durations**

Atrioventricular (AV) prolongation >3 *z*-scores was associated with longer neonatal PR intervals compared with fetuses with no (<2) or mild (2 to 3) AV prolongation.

Prevalence and relevance of AV prolongation. We observed similar proportions of fetuses with AV prolongation to that reported by Rein et al. (6) (>2 *z*-score: 9% vs. 9%) and by Friedman et al. (5) in the PRIDE (PR Interval and Dexamethasone Evaluation Study) (>3 *z*-score: 2% vs. 1.8%) and experienced comparable outcomes, albeit without the use of dexamethasone. The only fetus with a major autoantibody-related complication in this study was not identified because CAVB developed after the usual observation period according to our protocol. Although this case demonstrates that CAVB can develop later in pregnancy, it is uncertain that, in the absence of sensitive and specific early predictors of progressive conduction disease, more extensive surveillance (e.g., to 28 weeks) would have prevented the only case of this condition. Most affected fetuses in other prospective studies had normal AV intervals before the detection of CAVB (5,7,11,12), suggesting that CAVB results from a rapidly evolving inflammatory process that may not initially manifest with incomplete AV block. Conversely, despite significant AV prolongation to 6 *z*-scores in some cases, CAVB did not develop in any of our 15 fetuses, and only 1 child has mild AVB1 beyond infancy. This includes a fetus with Mobitz type 1 AVB2. A similar arrhythmia has been reported only once before in an anti-Ro antibody–exposed fetus with endocardial fibroelastosis and pericardial effusion. After administration of maternal dexamethasone, the child was born with AVB1 (4). In contrast, our patient had isolated, transient fetal and neonatal AVB2, probably related to perinatal QT interval prolongation. Transient QT_c prolongation, although usually less significant, has been reported in otherwise asymptomatic infants born to mothers with anti-Ro antibodies (15). In our case, the finding of neonatal 2:1 AV block prompted the neonatal treatment with a beta-blocker until the genetic workup excluded long QT syndrome.

Study limitations. Thirty-three fetuses (20%) with normal AV conduction were not referred for a post-natal examination. All are reportedly healthy and had normal heart rates at birth and thereafter according to their physicians. This likely precludes undetected CAVB.

Conclusions

Fetal AV prolongation was not predictive of CAVB but spontaneously resolved in all but 1 fetus with persistent mild AVB1. Without severe PR prolongation, AVB1 is considered a benign condition without risk of progressive conduction disease (16). Whether a distinct *z*-score value in AV duration predicts progressive heart block remains an important question. We suggest that transplacental treatment should be restricted to those fetuses with progressive AV block or with additional findings of autoantibody-mediated pathology, such as endocardial fibroelastosis and effusions (4,5,8,13). In contrast, in isolated AV prolongation up to 6 *z*-scores, close monitoring for disease progression without treatment is recommended. The utility of this approach needs confirmation in a large prospective, multicenter study.

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Key Words: echocardiography ■ fetus ■ heart block ■ lupus erythematosus ■ treatment.