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Home Monitoring for Fetal Heart Rhythm During Anti-Ro Pregnancies

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ABSTRACT

BACKGROUND Fetal atrioventricular block (AVB) occurs in 2% to 4% of anti-Ro antibody–positive pregnancies and can develop in <24 h. Only rarely has standard fetal heart rate surveillance detected AVB in time for effective treatment.

OBJECTIVES Outcome of anti-Ro pregnancies was surveilled with twice-daily home fetal heart rate and rhythm monitoring (FHRM) and surveillance echocardiography.

METHODS Anti-Ro pregnant women were recruited from 16 international centers in a prospective observational study. Between 18 and 26 weeks' gestation, mothers checked FHRM twice daily with a commercially available Doppler monitor and underwent weekly or biweekly *surveillance* fetal echocardiograms. If FHRM was abnormal, a *diagnostic* echocardiogram was performed. Cardiac cycle length and atrioventricular interval were measured, and cardiac function was assessed on all echocardiograms. After 26 weeks, home FHRM and echocardiograms were discontinued, and mothers were monitored during routine obstetrical visits. Postnatal electrocardiograms were performed.

RESULTS Most mothers (273 of 315, 87%) completed the monitoring protocol, generating 1,752 fetal echocardiograms. Abnormal FHRM was detected in 21 mothers (6.7%) who sought medical attention >12 h (n = 7), 3 to 12 h (n = 9), or <3 h (n = 5) after abnormal FHRM. Eighteen fetuses had benign rhythms, and 3 had second- or third-degree AVB. Treatment of second-degree AVB <12 h after abnormal FHRM restored sinus rhythm. Four fetuses had first-degree AVB diagnosed by echocardiography; none progressed to second-degree AVB. No AVB was missed by home FHRM or developed after FHRM.

CONCLUSIONS Home FHRM confirms the rapid progression of normal rhythm to AVB and can define a window of time for successful therapy. (Prospective Maternal Surveillance of SSA [Sjögren Syndrome A] Positive Pregnancies Using a Hand-held Fetal Heart Rate Monitor; NCT02920346) (J Am Coll Cardiol 2018;72:1940–51) © 2018 by the American College of Cardiology Foundation.

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Fetal atrioventricular block (AVB) develops in 2% to 4% of mothers with anti-Ro/SSA (Sjögren's) antibodies (1). Although uncommon, fetal AVB has significant morbidity and mortality (2). Complete or third-degree AVB appears to be irreversible, but anecdotal reports suggest that treatment of second-degree AVB can restore sinus rhythm (3–5). Unfortunately, weekly or biweekly fetal echocardiographic surveillance has only rarely detected AVB in time for treatment to be successful (6). One explanation for this failure may be the rapid (<24 h) transition from normal rhythm to third-degree AVB noted in case reports (7). Such a rapid transition would only be serendipitously identified by weekly fetal echocardiograms. Previously, we demonstrated the feasibility of an ambulatory Doppler fetal heart rate and rhythm monitoring (FHRM) program, called "heart sounds at home" (8). In this program, anti-Ro/SSA-positive pregnant women monitored fetal heart rate (FHR) and rhythm twice daily in the ambulatory setting and underwent a fetal echocardiogram if the fetal heart rhythm was irregular (8). In the current report, we summarize the echocardiographic and monitoring results and the outcomes of 273 anti-Ro/SSA positive pregnancies surveilled by both echocardiography and home FHRM.

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METHODS

STUDY GROUP. Sixteen centers participated in this prospective observational case series. At each center, pregnant women positive for anti-Ro/SSA antibodies detected by standard maternal anti-Ro/SSA serum screening were invited to participate in the study. Anti-Ro/SSA serum screening results were not quantitative, but either positive or negative. Mothers were recruited at 16 to 19 weeks of gestation and excluded if: 1) baseline fetal echocardiogram at enrollment (16 to 19 weeks) showed atrioventricular (AV) conduction abnormalities; or 2) they were unable to follow the protocol.

ECHOCARDIOGRAMS. Three types of echocardiograms were performed in this study. First, a *baseline* echocardiogram was performed before enrollment in the study. Second, *surveillance* echocardiograms were performed every week or every other week, depending on local site protocol. Third, *diagnostic* echocardiograms were performed anytime during the study if the mother detected abnormal FHRM. Echocardiograms were performed and reviewed by the site investigator.

The AV interval was assessed on all echocardiograms. Cycle length was measured between the onsets of 2 aortic Doppler waveforms. The AV interval was measured from a 5-chamber view with the pulsed Doppler sample gate positioned between mitral valve inflow and aortic valve outflow, as previously described (9,10). We averaged 5 fetal cycle lengths in milliseconds (ms) and 5 AV intervals (ms) measured by Doppler during fetal quiescence. FHR and AV intervals were excluded from analysis if the fetus had any arrhythmia, including atrial ectopy, or second- or third-degree AVB.

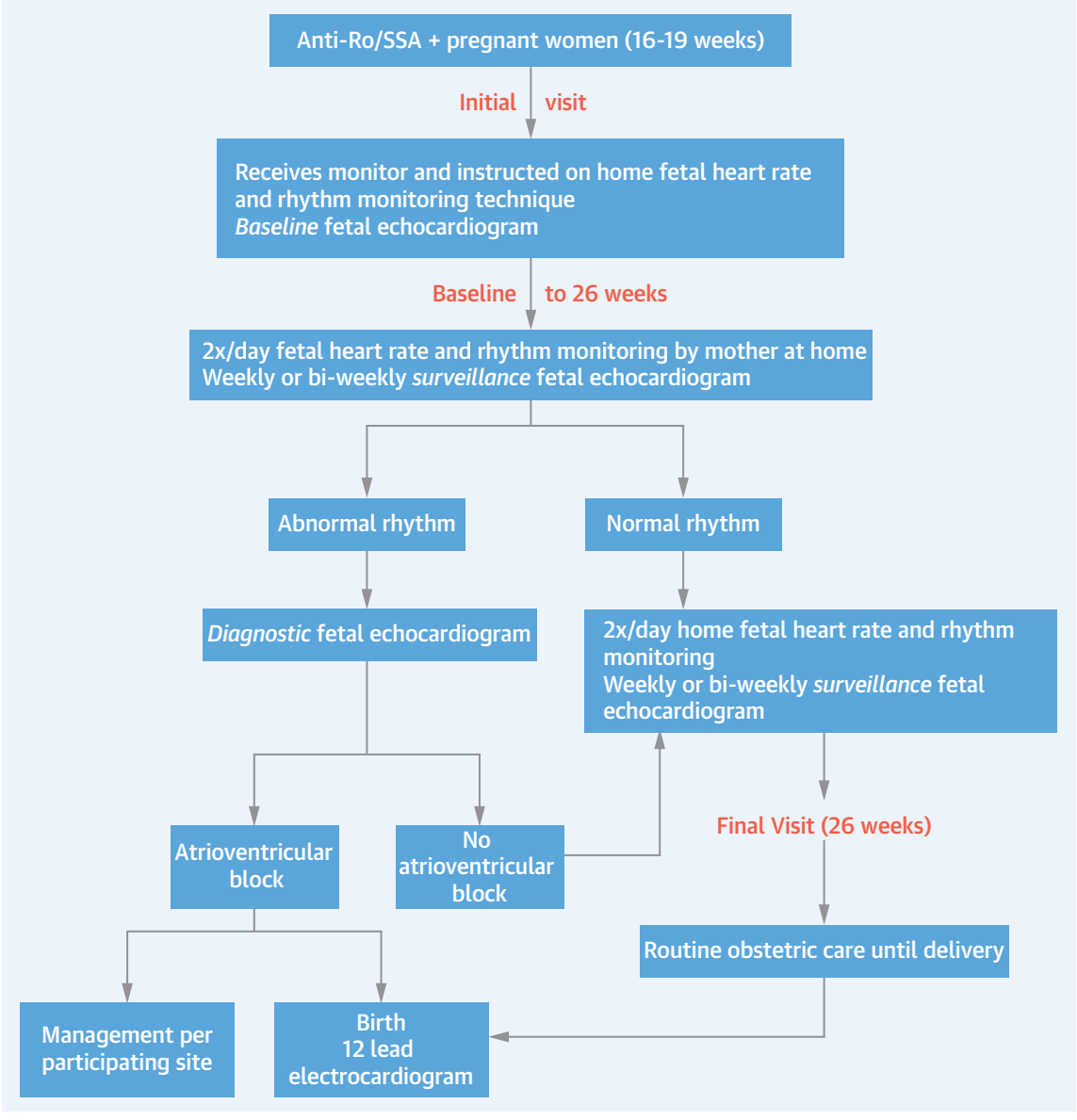
ABBREVIATIONS AND ACRONYMS

AV = atrioventricular
AVB = atrioventricular block
AVVI = atrioventricular valve insufficiency
ECG = electrocardiogram
EFE = endocardial fibroelastosis
FHR = fetal heart rate
FHRM = fetal heart rate and rhythm monitoring
GA = gestational age

In addition to cycle length and AV interval, we sought evidence on fetal echocardiography of anti-Ro/SSA antibody-mediated cardiac disease, including dilated cardiomyopathy, pericardial effusions >5 mm, pleural effusions or ascites, and endocardial fibroelastosis (EFE). Dilated cardiomyopathy was defined as ventricular dysfunction and cardiac dilation (11), and EFE was defined as abnormal echogenicity of the atria, AV valve apparatus, or the ventricles (11). We also evaluated AV valve inflow characteristics: biphasic (normal) or monophasic (fusion of the e and a-waves to create 1 peak), and insufficiency (AVVI). We graded AVVI as trivial (non-holosystolic pulsed Doppler), mild (origin of color Doppler less than one-third the width of the AV valve annulus and holosystolic pulsed Doppler), and moderate to severe (origin of color Doppler one-half to three-fourths of the AV annulus and holosystolic pulsed Doppler). No interobservability or intraobservability measurements were made.

RESEARCH PROTOCOL. At the first (baseline) visit, a detailed past medical, family, and obstetrical history was obtained from eligible participants (**Central Illustration**). A *baseline* fetal echocardiogram was performed to evaluate cardiac structure and function and AV conduction. The mothers were taught to use a hand-held, Food and Drug Administration–approved, commercially available home Doppler device to monitor FHR and rhythm twice daily at home. They were instructed to call the site investigator immediately if: 1) fetal heart rhythm was irregular; 2) FHR was <100 or >180 beats/min; or 3) fetal heartbeat could not be detected. Site investigators had previously agreed to evaluate mothers with a *diagnostic* echocardiogram within 8 h after receiving the mother's call. If second- or third-degree AVB was diagnosed by the echocardiogram, transplacental treatment was offered. The type and duration of

CENTRAL ILLUSTRATION **Surveillance of Anti-Ro/SSA Antibody Positive Pregnancies**



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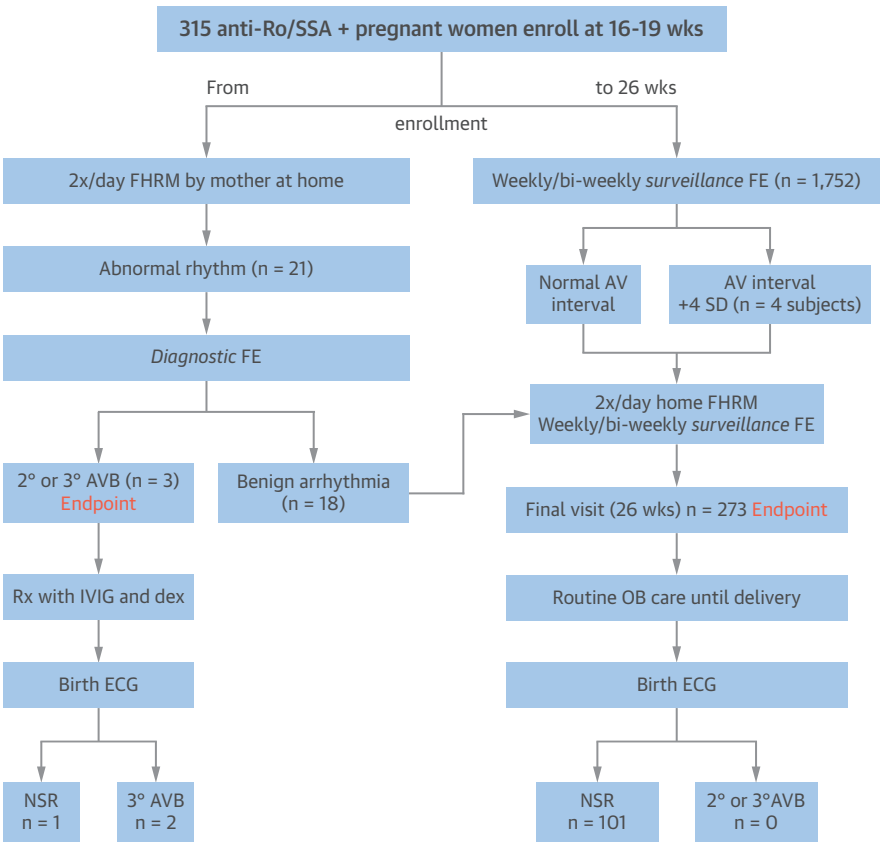
treatment were determined according to the participating site's protocol. If, conversely, the arrhythmia was benign (e.g., premature atrial contractions) or the rhythm and the *diagnostic* echocardiogram were normal, mothers resumed FHRM at home and *surveillance* echocardiograms.

All mothers participated in follow-up (*surveillance*) echocardiograms each week or every other week, depending on the local site protocol. The purposes of the surveillance echocardiograms were first, to detect the echocardiographic equivalent of first-degree AVB (defined as >150 ms from the mitral inflow/aortic outflow pulsed Doppler method) (9,10), and second, to assess for myocardial abnormalities, including EFE, more than trivial AVVI, and pericardial effusions. Abnormalities detected on surveillance

FIGURE 1 Study Protocol, Endpoints, and Results



AV = atrioventricular; Dex = dexamethasone; ECG = electrocardiogram; FE = fetal echocardiogram; FHRM = fetal heart rate monitoring; IVIG = intravenous immunoglobulin; NSR = normal sinus rhythm; OB = obstetrical; Rx = treatment; SD = standard deviation; wks = weeks.

or diagnostic echocardiograms were managed according to site practice guidelines. If all echocardiograms and home FHRM results were normal by the end of 26 weeks, both were discontinued, and the obstetrical provider monitored the pregnancy for its duration according to standard obstetrical practice for normal pregnancies. If the obstetrical provider detected an arrhythmia during a routine visit, the site investigator was contacted to evaluate the fetal rhythm. After birth, 12-lead electrocardiograms (ECGs) were performed to assess whether conduction system disease had developed since the end of the monitoring period.

Study data were collected and managed using REDCap electronic data capture tools hosted at The University of Colorado. REDCap is a secure, Web-based application designed to support data capture for research studies (12). We obtained signed consent from all study participants, and the Institutional Review Boards at all centers approved the study protocol (Core site UC-Denver IRB #13-1879). The study was registered on clinicaltrials.gov (NCT02920346).

STATISTICS. Descriptive characteristics were calculated using mean ± SD for continuous variables and N (%) for categorical variables. Regression models examining AV interval with fetal heart beat and gestational age (GA) were completed using generalized estimating equations (13), with an exchangeable working correlation structure to account for correlated observations with robust variance estimation for confidence intervals and p values. Quantile regression models with natural splines estimated the 5th, 50th, and 95th percentiles for AV interval and FHR. Regression analyses and corresponding figures were performed using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). Other

TABLE 1 Maternal Characteristics in 315 Subjects

Race	
American Indian or Alaska Native	04 (01)
Asian	49 (16)
Black or African-American	34 (11)
Native Hawaiian/Pacific Islander	03 (01)
White	188 (60)
More than 1 race	04 (01)
Unknown or not reported	33 (10)
Ethnicity	
Hispanic or Latino	21 (07)
Not Hispanic or Latino	243 (77)
Unknown or not reported	51 (16)
Diagnosis	
Systemic lupus erythematosus	145 (46)
Sjögren syndrome	112 (36)
Mixed connective tissue disease	22 (07)

Values are n (%).

summaries were computed using Microsoft Excel (Office version 365, 2016, Microsoft Corp., Redmond, Washington).

RESULTS

STUDY GROUP. Of the 315 mothers recruited for the study, 273 completed the monitoring portion (retention rate 87%) (Figure 1). Characteristics of the mothers who enrolled in the study are described in Table 1. The majority of mothers were Caucasian with Asians (16%), and African Americans (11%) also represented. Maternal ethnicity was Hispanic or Latino in 7%. The mean maternal age at the time of enrollment was 32.5 ± 4.5 years (range 18 to 43 years). The most common diagnoses were systemic lupus erythematosus (n = 145) and Sjögren's syndrome (n = 112). Twenty-two mothers had mixed connective tissue disease, and 33 had anti-Ro/SSA antibodies but no rheumatologic diagnosis. No data were available in 3 mothers. Hypothyroidism, known to be a risk factor for fetal AVB among anti-Ro/SSA-positive women (14), was present in 47 mothers. Approximately one-half of mothers were treated with Plaquenil (200 to 400 mg/day) during the study. Among those receiving Plaquenil, treatment was started either earlier than 12 weeks of gestation (68%), after 12 weeks (9%), or the starting time was not reported (23%). Of mothers with a child previously affected with AVB, EFE, or cardiomyopathy, 47% were given Plaquenil earlier than 12 weeks. Plaquenil treatment appeared to be site specific because 53% of untreated pregnancies were recruited from 2 sites.

OUTCOME OF PREVIOUS PREGNANCIES. Of the 315 mothers recruited, 305 provided data from 731 previous pregnancies, including live births (562) and fetal losses (169). Nineteen mothers (6.0%) reported 20 previous pregnancies with fetal anti-Ro/SSA-mediated cardiac disease, including conduction system disease, dilated cardiomyopathy, and EFE (Table 2). Among fetuses with evidence of cardiac disease, 6 of 20 died in the fetal or newborn periods, for a perinatal mortality of 30%, which is similar to previously published studies (2).

ECHOCARDIOGRAMS. Complete data were available from 1,752 fetal echocardiograms. The baseline and final surveillance echocardiograms occurred at 17.91 ± 0.99 weeks and 25.94 ± 2.04 weeks, respectively. Diagnostic echocardiograms were performed in 21 mothers with abnormal FHRM at home.

SURVEILLANCE ECHOCARDIOGRAPHIC RESULTS: AV INTERVALS AND FETAL HEART RATES. Mean AV intervals, FHR, and GA from baseline and surveillance echocardiograms are shown in Table 3. The predicted 5th, 50th, and 95th percentile trajectories from quantile regression for AV interval and FHR across GAs are shown in Figures 2A and 2B. When incorporating the correlated structure of the longitudinal data in simple linear regression models, FHR was significantly associated with GA ($p < 0.0013$) such that a GA increase of 7 days was associated with a mean FHR decrease of 0.69 beats/min. Similarly, GA was significantly associated with AV interval ($p < 0.001$) such that a GA increase of 7 days was associated with a mean AV interval increase of 0.95 ms. Finally, FHR was significantly associated

TABLE 2 Outcome of Previous Pregnancies With 20 Affected Fetuses

	First-Degree AVB	Second-Degree AVB	Third-Degree AVB	D-CM	D-CM + Third-Degree AVB	EFE	UK or NR	Total
Liveborn and neonatal survivor	1	2	4	0	1	4	–	14
Liveborn and neonatal death	0	0	1	0	0	0	–	1
Fetal demise	0	0	3	1	1	0	–	5
Total	1	2	8	1	2	4	2	20

Values are n.
AVB = atrioventricular block; CM = cardiomyopathy; EFE = endocardial fibroelastosis; UK or NR = unknown or not recorded.

TABLE 3 GA, Fetal Heart Rate, and AV Intervals From Baseline and Surveillance Echocardiograms

Echoes (n)	GA (weeks)	Heart Rate (beats/min)	AV Interval (ms)*
44	16	151.2 ± 6.8	107.5 ± 6.9
97	17	150.4 ± 6.2	111.0 ± 8.8
204	18	148.7 ± 7.1	111.4 ± 9.4
175	19	148.9 ± 7.0	113.1 ± 9.6
198	20	147.7 ± 7.2	114.8 ± 10.1
186	21	148.5 ± 6.8	115.7 ± 10.5
189	22	148.2 ± 7.8	115.9 ± 9.2
182	23	145.4 ± 7.5	117.7 ± 9.4
165	24	145.9 ± 7.4	117.6 ± 10.7
74	25	143.3 ± 8.3	116.7 ± 10.5
140	26	144.3 ± 7.4	117.5 ± 9.9

Values are mean ± SD unless otherwise specified. *The AV interval was measured using the mitral inflow and aortic outflow Doppler approach.
AV = atrioventricular; GA = gestational age.

with AV interval ($p < 0.001$) such that a FHR increase of 1 beat/min was associated with a mean AV interval decrease of 0.28 ms. Both GA and FHR are significant predictors of AV interval in a multiple regression model ($p < 0.001$ for both), with the predicted AV interval for various FHRs across GAs shown in Figure 2C. All but 4 fetuses had AV intervals <+ 4 *z*-scores.

SURVEILLANCE ECHOCARDIOGRAPHIC RESULTS: CARDIAC FINDINGS. Four fetuses had small muscular ventricular septal defects. No fetus developed cardiomyopathy or cardiac dysfunction. Nineteen fetuses had trivial or mild tricuspid insufficiency, and 1 had moderate tricuspid insufficiency.

DIAGNOSTIC ECHOCARDIOGRAPHIC RESULTS. Diagnostic fetal echocardiograms after abnormal FHRM at home were performed in 21 (6.8%) mothers. The time between mothers hearing abnormal FHRM and site investigators performing diagnostic echocardiograms were as follows: <3 h (n = 5); 3 to 6 h (n = 4); 6-12 h (n = 5); and >12 h (n = 7). Findings of diagnostic echocardiograms were normal (n = 11, false positive 50%), premature atrial contractions (n = 6), frequent sinus pauses (n = 1), and AVB (n = 3). The 3 fetuses with AVB also had tricuspid insufficiency, EFE, and effusions, but the other 18 fetuses did not.

OUTCOMES OF CURRENT PREGNANCY. Detailed delivery data were available in 148 subjects. Most pregnancies were uncomplicated. The mean GA at delivery was 38.07 ± 2.39 weeks. Mean birth weights and lengths of live-born infants were 2.97 ± 0.59 kg and 49.14 ± 3.91 cm, respectively. There were 4 pregnancy losses; 2 pregnancies (1 with anencephaly and 1 with severe growth restriction) were electively interrupted, and 2 stillbirths without a history of cardiac disease occurred at 23 and 37 weeks. Of the 92 infants who had postnatal ECGs, none had developed conduction system disease between the last monitoring and birth.

OUTCOME OF FETUSES WITH FIRST-DEGREE AVB. First-degree AVB, defined as an AV interval ≥+ 3 *z*-scores (150 ms), was observed in 4 fetuses at 19.29 to 26.14 weeks of gestation (Table 4). One fetus with first-degree AVB and EFE was treated with dexamethasone. All mothers continued to monitor at home. No fetus with first-degree AVB developed second-degree AVB.

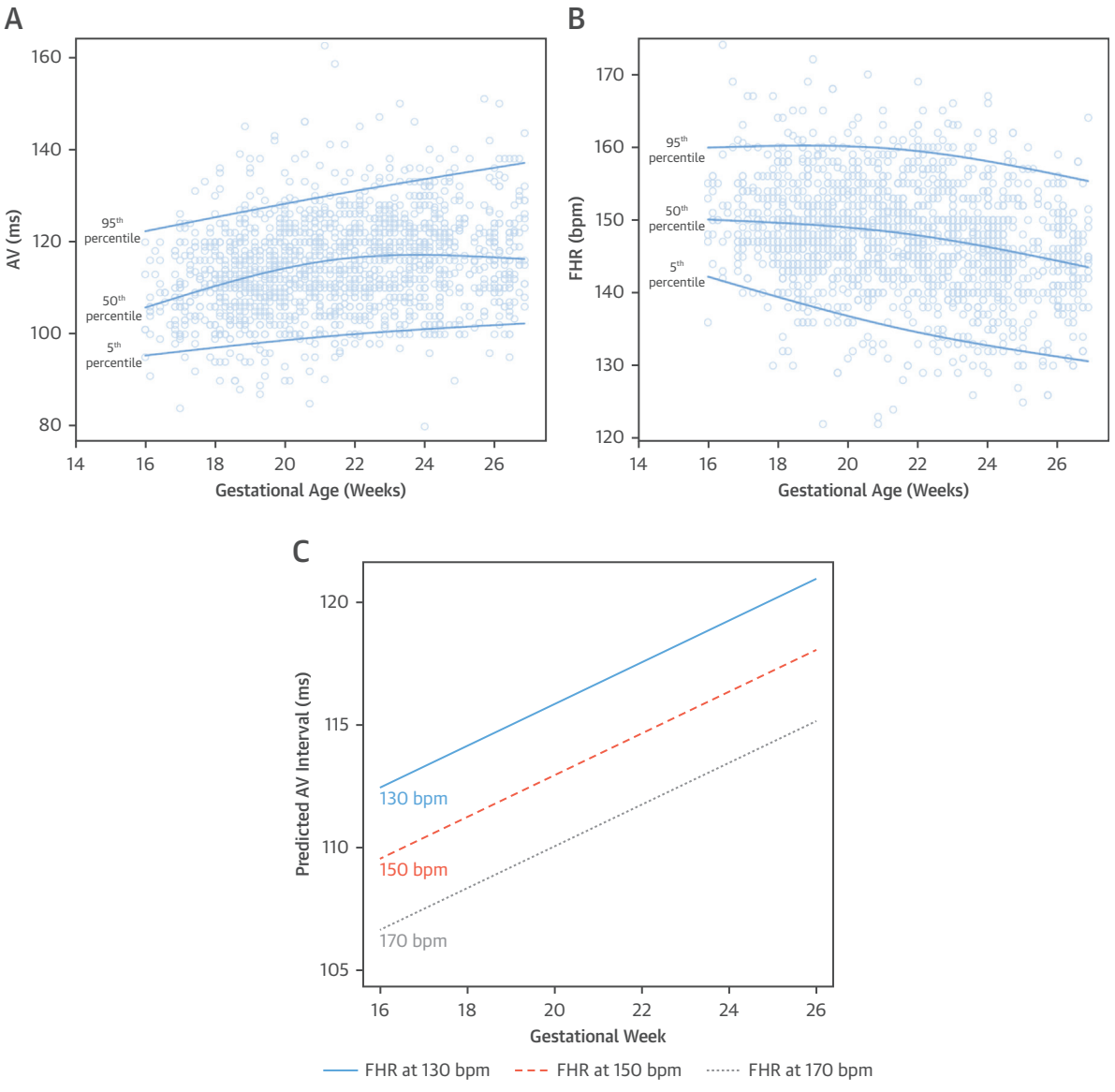
OUTCOME OF FETUSES WITH SECOND- AND THIRD-DEGREE AVB. Three fetuses developed AVB at 18.89, 20.43, and 22.89 weeks of gestation (Table 4). The time course of surveillance echocardiograms, abnormal FHRM, diagnostic echocardiograms, and treatment is shown in Figure 3.

At 20 weeks, Fetus #1 had a normal surveillance echocardiogram, other than a prominent tricuspid valve papillary muscle. Mitral inflow was biphasic, and the AV interval was normal (Figures 4A and 4B). A diagnostic echocardiogram performed 3 days later, the same day the FHRM was abnormal, revealed rare episodes of Mobitz 1, second-degree AVB, a prolonged AV interval (253 ms) during 1:1 conduction, tricuspid insufficiency, and EFE (Figures 4C to 4E). Treatment with dexamethasone (8 mg orally for 7 days, then 4 mg orally, weaning at 28 weeks by 1 mg/week) and intravenous immunoglobulin (IVIG) (given the day of the diagnostic echocardiogram) restored sinus rhythm (Figures 4F and 4G). The infant was delivered in sinus rhythm with an AV interval of 165 ms.

At 22.71 weeks, 4 days after a normal surveillance echocardiogram and 24 h after normal FHRM, the mother of Fetus #2 heard an FHR <100 beats/min. Eight hours after detecting the bradycardia (and 32 h after the last normal rhythm), the diagnostic echocardiogram demonstrated third-degree AVB, EFE, and AVVI. The mother was immediately treated with dexamethasone, 8 mg orally, and IVIG, 70 g. Dexamethasone was continued (8 mg every day for 14 days, then 4 mg/day orally until 28 weeks, and then 2 mg/day until delivery), and IVIG was repeated every 3 weeks. The fetus remained in third-degree AVB, was live born, and received an epicardial pacemaker in the first week of life.

At 18.86 weeks, 2 days after a normal surveillance echocardiogram, and 12 h after normal FHRM, the mother of Fetus #3 detected an irregular cardiac rhythm. She did not contact the site investigator but instead repeated FHRM 12 h later. By that time, the

FIGURE 2 Predicted 5th, 50th, and 95th Percentile Trajectories From Quantile Regression for AV Interval and FHR Across GAs



(A) Fetal echocardiographic atrioventricular (AV) intervals in milliseconds measured by simultaneous mitral inflow and aortic outflow Doppler. Atrioventricular interval versus gestational age (GA) in weeks. Included are the 5th, 50th, and 95th percentiles estimated from quantile regression with natural splines. **(B)** Fetal heart rate (FHR) in beats per minute versus gestational age in weeks. Included are the 5th, 50th, and 95th percentiles estimated from quantile regression with natural splines. **(C)** Predicted mean trajectory of fetal echocardiographic atrioventricular intervals in milliseconds over gestational age in weeks at 3 different fetal heart rates in beats per minute (bpm).

fetus was bradycardic (FHR <100 beats/min), and a diagnostic echocardiogram performed 8 h after the bradycardia was heard was positive for third-degree AVB and EFE. The mother was immediately given dexamethasone and received IVIG 24 h later. Treatment with dexamethasone (8 mg/day for 14 days, 4 mg/day orally until 28 weeks, and then 2 mg/day until delivery), and 1 dose of IVIG (70 g) did not reverse third-degree AVB. This infant was live born and received a pacemaker shortly after birth.

The mothers of Fetuses #2 and #3 had elevated anti-Ro antibody titers of >1,000 U/dl as measured by enzyme-linked immunosorbent assay; Fetus #2 had

anti-La/SSB antibodies, and Fetus #3 did not. The mother of Fetus #1 had elevated anti-Ro antibody levels of 328, but the levels were measured at a different laboratory than for Fetuses #2 and #3. None of the mothers had a previously affected child. Fetus #2's mother had Sjögren's syndrome and was treated with Plaquenil (hydroxychloroquine), 200 mg daily after 12 weeks of gestation. Fetus #3's mother had systemic lupus erythematosus and was treated with prednisone and 400 mg of Plaquenil daily after 12 weeks of gestation. The mother of Fetus #1 had juvenile rheumatoid arthritis and was treated with prednisone and Plaquenil, 200 mg alternating with 400 mg daily, instituted before 12 weeks of gestation.

SUMMARY OF RESULTS. In 3 fetuses, second- or third-degree AVB was detected by FHRM. In all 3 cases, echocardiographic signs of cardiac disease including EFE and AVVI were seen at the time of AVB, but not preceding AVB. When following the twice-daily monitoring protocol, abnormal FHRM signifying second-degree AVB could be detected 12 h after normal FHRM. A prompt diagnostic fetal echocardiogram following within 12 h of abnormal FHRM resulted in successful treatment of second-degree AVB, but a 24-h delay in home monitoring, diagnosis, and treatment resulted in progression to irreversible third-degree AVB. Echocardiography detected 4 fetuses with first-degree AVB, and none had abnormal FHRM or developed second- or third-degree AVB.

No fetal AVB was missed by FHRM. Among subjects receiving postnatal ECGs, no AVB developed between the end of the monitoring period and birth.

TABLE 4 Outcome of Fetuses With AVB

Subject Group	GA (weeks)	Rhythm	EFE	TI	MI	Rx?	Postnatal ECG
Subject							
A	26.14	First-degree AVB		+		N	NSR
	27.0	First-degree AVB					–
B	19.29	First-degree AVB	+	+	+	Y (D)	NSR
	27.0	First-degree AVB					–
C	25.71	First-degree AVB				N	NSR
D	21.14	First-degree AVB				N	NSR
	21.43	First-degree AVB					–
Subject							
1	20.43	First-degree AVB, Mobitz 1, second-degree AVB	+	+		Y (D+IVIG)	NSR
2	22.89	Third-degree AVB	+	+	+	Y (D+IVIG)	Third-degree AVB
3	18.89	Third-degree AVB	+	+	+	Y (D+IVIG)	Third-degree AVB

AVB = atrioventricular block; D = dexamethasone; EFE = endocardial fibroelastosis; ECG = electrocardiogram; GA = gestational age; IVIG = intravenous immunoglobulin; MI = mitral insufficiency; N = no; NSR = normal sinus rhythm; Rx = treatment; TI = tricuspid insufficiency; Y = yes.

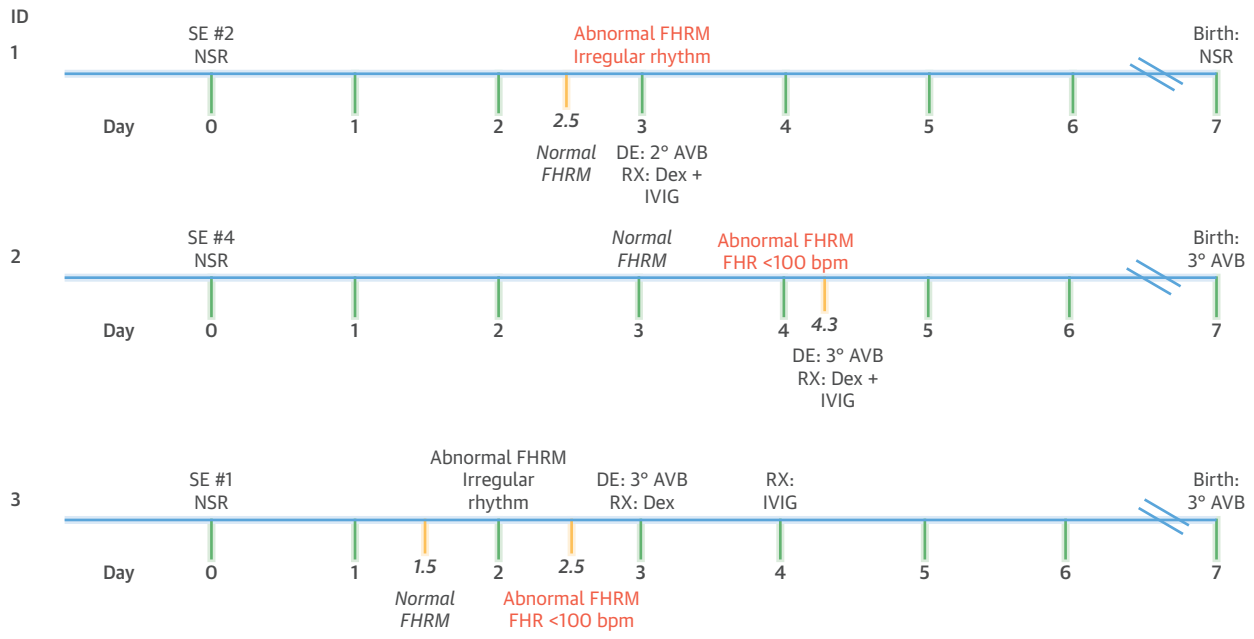
DISCUSSION

There are several important findings in this prospective surveillance study of anti-Ro/SSA-positive pregnancies. First, we confirmed previous findings that surveillance of FHR and rhythm by home Doppler monitoring is feasible, reassuring, and empowering to mothers and does not increase anxiety (8). In the current study, 87% of mothers completed the monitoring protocol and successfully detected abnormal FHR and rhythm, including 3 cases of AVB. Second, the window of time for second-degree AVB to progress to irreversible third-degree AVB, which appears also to be the window of time for effective treatment, is <24 h. Surprisingly, we did not observe any instance of first-degree AVB transitioning to second-degree AVB. Together, these findings demonstrate that frequent (twice-daily) home monitoring by mothers can detect second-degree AVB, thereby identifying the therapeutic window for successful treatment to reverse progression to third-degree AVB (Central Illustration, Figure 1).

The home FHRM program had a high retention rate, mothers successfully detected abnormal rhythms, and no AVB was missed. Among 21 mothers who heard an abnormal FHRM, 11 (50%) had a normal diagnostic echocardiogram. These findings suggest that either the mothers heard a rhythm they thought was irregular or the arrhythmia was transient and resolved before the diagnostic echocardiogram. We now ask mothers to send audio recordings of questionable FHRM to site investigators by text for immediate feedback. This has already reduced false positive results and decreased the need for unnecessary diagnostic echocardiograms. Increasing the FHRM sessions to 3 times daily may also decrease the time from detection to confirmation and treatment of second-degree AVB. Although none of our cohort developed AVB following the monitoring period (after 26 weeks' GA), rare AVB has occurred beyond even 30 weeks of gestation (15), a finding suggesting that longer FHRM surveillance may be beneficial in some cases.

Previous surveillance of anti-Ro/SSA positive pregnancies has been founded on the hypotheses that anti-Ro/SSA-mediated AVB progresses over time, and treatment in the early stages (first- or second-degree AVB) could restore normal conduction.

FIGURE 3 Timeline (in Days) for Home Fetal Heart Rate and Rhythm Monitoring and Surveillance Echoes in 3 Fetuses Who Developed AVB



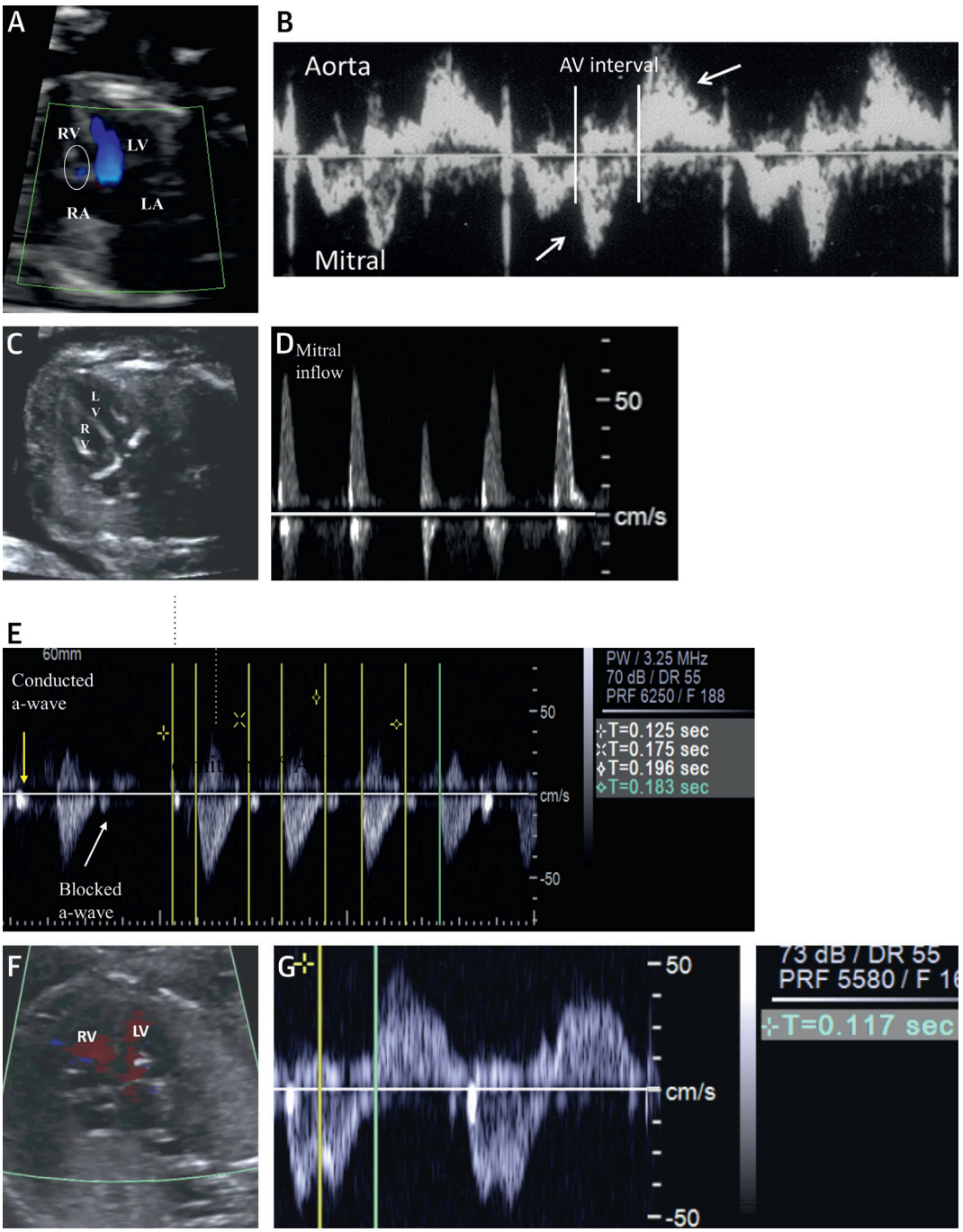
Time 0 is the surveillance echocardiogram before abnormal fetal heart rate monitoring (FHRM). Note that the mother of Fetus #2, did not monitor every 12 h, but every 24 h between day 3 and day 4. AVB = atrioventricular block; DE = diagnostic echocardiogram; Dex = dexamethasone; FHR = fetal heart rate; IVIG = intravenous immunoglobulin; NSR = normal sinus rhythm; Rx = treatment; SE = surveillance echocardiogram.

The barrier to testing this hypothesis has been the absence of a method to detect the transition from normal rhythm to AVB in time for treatment to be effective. The PRIDE (PR Interval and Dexamethasone Evaluation) study (6) demonstrated that third-degree AVB developed between weekly surveillance echocardiograms and did not demonstrate a transition from first- to second-degree or from second- to third-degree AVB. Other studies have also failed to identify a prolonged AV interval (first-degree AVB) that developed in between the echocardiographic monitoring periods. The philosophy of echocardiographic surveillance in these 3 studies was not flawed, but rather surveillance was too infrequent.

The current study does not support or discredit the use of measuring AV intervals during surveillance of anti-Ro/SSA positive pregnancies but raises questions about how to interpret the findings. Our results suggest that the transition from normal rhythm to the echocardiographic equivalent of first-degree AVB is not pathologic and is transient in some cases. One explanation for these findings is because the mechanical AV interval overestimates the electrical PR interval (16), an AV interval $> +3$ z-scores may not be indicative of "first-degree AVB." In other words, true "first-degree AVB" is a much longer AV interval than previously believed (10,16,17). It is well known that the AV interval includes both AV conduction and isovolumic contraction time, and it may be the latter, rather than the former, that is prolonged (18). We speculate that FHRM will, in future studies, provide the opportunity to determine the natural history of a prolonged AV interval because progression to second-degree AVB will be detected within 12 h of a normal rhythm.

In addition to evaluating the AV interval, echocardiographic surveillance in anti-Ro/SSA antibody-positive pregnancies detects myocardial abnormalities such as EFE. In our study, myocardial abnormalities were not seen preceding AVB, but were seen in fetuses with second- and third-degree AVB detected by FHRM. As previously reported (19), trivial to mild non-holosystolic tricuspid valve insufficiency was the most common cardiac finding in ~7% of anti-Ro/SSA-positive pregnancies and did not portend development of conduction system disease or dilated cardiomyopathy.

FIGURE 4 **Fetal Subject #1 at 20, 20.43, and 23 Weeks**



(A) Four-chamber view showing a prominent papillary muscle in the right ventricle (RV) **(circle). (B)** Mitral inflow is biphasic, and the atrioventricular (AV) interval is normal (117 ms). **(C)** Three days later, the endocardial fibroelastosis is obvious and extensive, involving both atrioventricular valves, the proximal portion of the intraventricular septum, and the right atrium (RA). The left atrium (LA) is not clearly seen. **(D)** The mitral inflow Doppler pattern has become monophasic. **(E)** Simultaneous superior vena cava and aorta Doppler image showing that the irregular rhythm heard by fetal heart rate monitoring is type 1, second-degree atrioventricular block. The last conducted atrial beat is shown by the **yellow arrow on the left.** The next atrial contraction is not conducted **(white arrow),** but afterward there is a period of atrioventricular conduction with gradually prolonging atrioventricular intervals. **(F)** After treatment with dexamethasone and intravenous immunoglobulin, at 23 weeks, the tricuspid insufficiency has resolved, and endocardial fibroelastosis has improved, but is still visible. **(G)** The mitral inflow is once again biphasic, and the atrioventricular interval is again normal. LV = left ventricle.

The number of fetuses who developed AVB in this cohort was smaller (~1%) than expected. There are several explanations for these results. First, only 12 mothers (5.6%) had a previous child with conduction system or myocardial anti-Ro/SSA disease. Other series describing echocardiographic surveillance have included only mothers with a previously affected child (20), where the risk of recurrence is known to be 17% to 21% (1). Second, one-half of the mothers were taking Plaquenil, which has been shown to reduce the a priori risk of AVB in this group (21,22). Third, mothers were recruited on the basis of the qualitative, not quantitative findings of anti-Ro/SSA antibodies. Some mothers with a positive antibody screen may have had low antibody levels not previously associated with fetal AVB (23). We speculate these reasons may also explain why isolated EFE and cardiomyopathy did not occur in this cohort.

STUDY LIMITATIONS. First, postnatal ECG data were available only in one-third of the subjects who completed the monitoring protocol. With normal FHRM, most mothers were delivered at their local hospital, which in most cases was not associated with the fetal cardiology center. However, none of the investigators received anecdotal information of abnormal postnatal rhythm. The second limitation is because of the small number of subjects who developed second- or third-degree AVB and because not all mothers followed the protocol, FHRM improved outcome in only 1 subject. Being more selective in our enrollment and recruiting mothers with a high likelihood of developing fetal AVB, including those with a previously affected child or high antibody levels (23), should increase the number of AVB fetuses in future studies. As previously stated, we will also ask mothers to send recordings of suspected abnormal FHRM to the investigator to help mothers determine whether the fetal rhythm is abnormal.

CONCLUSIONS

The use of home surveillance monitoring provides a means in future studies to test the hypothesis that earlier detection of "evolving" AVB will result in earlier treatment, and earlier treatment will restore 1:1 AV conduction.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: AVB in the fetus is a rare but devastating consequence of inflammation and fibrosis caused by maternal anti-Ro/SSA antibodies. Conduction block can develop rapidly, but twice-daily ambulatory fetal heart rhythm monitoring with a commercial Doppler device can successfully detect the irregularity of emerging second-degree AV block before progression to complete block.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether earlier detection of conduction block in fetal hearts can facilitate treatment to restore intact AV conduction and improve the outcomes of pregnancy in women with anti-Ro/SSA antibodies.

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