Immune-Mediated Fetal Complete Atrioventricular Block: Can Dexamethasone Therapy Revert the Process?

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ABSTRACT Fetal complete atrioventricular block (CAVB) is usually autoimmune mediated. The risk of developing CAVB is 2% to 3% in anti-Ro/SS-A seropositive pregnancies and it increases 10 times after previous CAVB in siblings. Despite being a rare complication, CAVB carries a 20% mortality rate and substantial morbidity, as about 65% of newborns will eventually need life-long pacing. Once found, fetal CAVB is almost always irreversible, despite aggressive immunotherapy. This poor outcome prompted some research groups to address this situation. All groups followed anti-Ro/SS-A seropositive pregnancies on a weekly basis during the second trimester of pregnancy and tried to detect first degree atrioventricular block (AVB) using accurate echocardiographic tools, assuming they may characterize the initiation of the immune damage to the A-V conduction system, at which point the process might still be reversible. Some of the groups treated fetuses with first degree AVB with maternal oral fluorinated steroids. We summarized the results of all groups, including our group. We describe a case of a fetus that developed CAVB 6 days after normal sinus rhythm (NSR), who under aggressive dexamethasone therapy gradually reverted to NSR. This fetus had a previous sibling with CAVB. We assumed the immune damage to the conduction system in this small group of fetuses with a previous CAVB sibling may have occurred more quickly than usual. We therefore recommend a twice-weekly follow-up with these fetuses.

IMAJ 2020; 22: 711–716

KEY WORDS: dexamethasone, complete atrioventricular block, fetal echocardiography, prenatal therapy, systemic lupus erythematosus (SLE)

Fetal complete atrioventricular block (CAVB) is usually autoimmune-mediated. Deterioration to CAVB is considered an irreversible process. It is generally agreed that passage of anti-Ro/SS-A and anti-La/SS-B autoantibodies through the placenta is the main reason for fetal CAVB, as they start an inflammatory process in which infiltration of macrophages and giant cells into the atrioventricular (AV) node cause fibrosis and calcification [1]. However, the exact pathological mechanism is still being debated. There are two main hypotheses that may explain these mechanisms:

- **Apoptosis hypothesis:** a two-phase model in the development of fetal autoimmune atrioventricular block (AVB). This hypothesis postulates a first step, in which anti-Ro52 antibodies may cross-react with a fetal cardiac molecule involved in calcium regulation and initiate cardiac conduction disturbances, producing a still reversible first-degree AV block. A second step then occurs with prolonged disruption of calcium homeostasis, which may result in increased apoptosis in the fetal heart associated with further exposure of the Ro and La autoantigens to circulating maternal anti-Ro/La antibodies. This opsonization may then lead to engulfment by macrophages and subsequent generation of a sustained inflammatory reaction in the fetal heart, eventually leading to permanent damage and complete AV block.
- **Cross-reactivity hypothesis:** Suggests that maternal anti-Ro/La antibodies bind, perhaps initially reversibly, to cardiac membrane proteins involved in the control of electric signal generation or conduction or both, and interfere with their function [2].

The risk of developing CAVB is 2% [3] to 3% [4] in anti-Ro/SS-A seropositive pregnancies and it increases 10 times after previous CAVB in siblings [5]. In fetuses affected by immune CAVB the chance of reversion, or even regression to a lower degree of AVB, is negligible. Despite being a rare complication, CAVB carries 20% mortality and substantial morbidity as about 65% of newborns will eventually need life-long pacing. A recent meta-analysis investigated the role of antenatal fluorinated steroids administration in fetuses affected by immune-mediated CAVB. Ciardulli and colleagues [6] included studies in which fetuses with normal cardiac anatomy and immune mediated CAVB were followed. The group compared fetal outcome between fetuses treated with maternal dexamethasone 4 mg once per day and untreated fetuses. Eight studies (162 fetuses) were included. The rate of regression from CAVB to a lower grade AVB was 3.0%/4.3% between treated and untreated fetuses respectively; odds ratio (OR) 0.9. A pacemaker at birth was required in 71.5%/57.8% of the treated/untreated fetuses. There was no difference in the overall mortality rate in the two groups. These grave results of treatment in the already affected group of fetuses emphasize the need for accurate tools, which can detect

Table 1. Previous literature on detection and treatment results of fetal AVB

Group, year	Cohort size	Method	Weekly/ biweekly F/U	Indication for therapy	Therapy	Number of high grade AVB (%)	Ability to revert AVB by first AVB Dx	Reference
PRIDE, 2008	127	Doppler LV in/out	16–26, 26–34	> 150 ms	Po Dex 4mg qd	3 CAVB	no	Friedman
Jaeggi, 2011	165	Rt TVI, Doppler SVC/ Ao	19–24*	≥ Mobitz II or progression		1 CAVB	no	Jaeggi
Jaeggi, 2017	127**	Doppler SVC/ Ao	18–24***	≥ 6 z scores	Po Dex 8mg qd ± IvIG#	4 CAVB, 2 second AVB	no##	Kan
Sonesson, 2019	212	Doppler LV in/out + SVC/ Ao	18–24		Betamethasone	5 CAVB, 2 second AVB	no	Sonesson
Rein, 2020	> 350	Rt TVI	16–26, 26–36 qm	> 2 *z*-scores	Po Dex 4 mg once per day		yes	Perles

*Until about 35 weeks if a previous child had CAVB
**62/189 were excluded due to low anti Ro titers
***16–28 w sometimes biweekly if prior history of sibling with AVB. More frequent exams were performed at the detection of possible signs of cardiac SLE including heart block, EFE, effusions, ventricular dysfunction and valvar regurgitation
#After 2w down to 4 mg qd until 28w, then 2 mg qd until birth. 70g q3w until birth added when IAVB, EFE, AVVR were present
##According to author description, serial echocardiography allowed for the detection of reversible cardiac abnormalities in several cases with normal baseline echocardiogram, although not explicated in the text
AVB = atrioventricular block, CAVB = complete atrioventricular block, qm= every month

the initiation of the immune damage to the A-V conduction system, at which time the process might still be reversible.

A few research groups used this approach over the last years [Table 1] hoping to revert the immune damage to the AV conduction system if detected early enough. The PRIDE (PR Interval and Dexamethasone Evaluation) study was conducted by Friedman and colleagues [7]. They published their preliminary results in 2008. These investigators raised the hypothesis that there is a serial, orderly progression from normal sinus rhythm through first-degree to more advanced AV block and that only a short window of opportunity exists between diagnosis of first degree AVB and deterioration into CAVB. They followed 127 anti-Ro/SS-A seropositive pregnancies. Fetal echocardiograms were performed weekly from 16 to 26 weeks of gestation and biweekly from 26 to 34 weeks. PR intervals above 150 ms were considered prolonged, consistent with first-degree block. The mechanical equivalent to the electric PR interval was measured using pulsed wave Doppler left ventricular inflow/outflow (LV I/O) view, which is the time interval between the initiation of the mitral valve A wave and the initiation of the left ventricular outflow ejection wave. They failed in their attempt, and despite maternal dexamethasone treatment to fetuses with first degree AVB, three fetuses developed complete AVB. None of the three had a preceding abnormal PR interval, although in two fetuses more than one week elapsed between echocardiographic evaluations. They concluded that advanced block can occur within one week of a normal echocardiogram without initial first-degree block and therefore the policy of early detection of first degree AVB is doomed to fail.

Mechanical atrioventricular time interval measurement using tissue velocity imaging of the right heart is superior to other methods in detecting normal and prolonged intervals

In 2011 Jaeggi and colleagues [8] published their follow-up study on 165 anti-Ro/La antibody-positive fetuses using a protocol that was more meticulous in its interval measurements than the PRIDE group. In contrast to the PRIDE group, this group claimed that fetal AV prolongation did not predict progressive heart block at birth. The same research team [9] did agree that prenatal dexamethasone therapy might prevent cardiac damage in a selected high risk cohort. At least one fetus with high grade AVB reverted to 1:1 AV conduction after dexamethasone therapy.

Krishnan and colleagues [10] tried to prevent high grade AVB with maternal dexamethasone therapy. However, they did not measure AV conduction.

Recently Sonesson and colleagues [11] published their results of 212 anti-Ro52 antibody-exposed pregnancies that were prospectively followed. Their rationale, diagnostic methods, and intervention plan were similar to the PRIDE group, except for measuring also Doppler SVC/Ao intervals and using betamethasone instead of dexamethasone as an anti-inflammatory agent. Seven fetuses (> 3%) developed second to third AVB. Three of the five cases with AVB III and one of two cases with 2:1 AVB

II developed within one week of AV. Interval z-score was either normal or mildly increased (1,1.9,1.9,2.8). Two of the second AVB fetuses responded to therapy with normal sinus rhythm (NSR) restoration. None of the third AVB fetuses reverted in response to steroids. The researchers concluded that fetal AV interval was a poor predictor of congenital heart block (CHB) progression, but that CHB surveillance still detected fetuses with AVB II or III shortly after development, which allowed for timely treatment initiation and potentially better outcome.

In accordance with the PRIDE group hypotheses, in 2000 we established our institutional intervention program for AVB detection and prevention in fetuses of mothers with autoimmune disorders, which required a strict weekly study from 14 to 26 weeks of gestation [12]. In the last 20 years, we have examined over 350 fetuses of mothers with autoimmune disorders, and measured their AV conduction by right ventricular AV interval measurement using tissue velocity imaging (TVI) technique. We applied a strict weekly follow-up protocol [13]. All 19 fetuses that developed first degree AVB were immediately treated with standard doses of dexamethasone administered to the mother. They all reverted to NSR [14].

During our thorough review of the literature, we were not able to find even one well-documented case of a fetus with immune-mediated CAVB who successfully reverted to NSR. There was one case described of fetal CAVB, which was discovered 11 days after documented NSR. The fetus was treated with high dose dexamethasone and reverted to sinus rhythm [15]. However, it only lasted for a short period, and the fetus deteriorated back to CAVB, which necessitated permanent pacemaker implantation after delivery.

With regard to reversibility of the pathophysiologic process, all previously quoted research teams agreed that CAVB is never reversible. Conversely, we encountered a fetus with CAVB, which seems to cast doubt on this statement:

A 34-year-old female in her fourth pregnancy was referred to our laboratory for fetal AV conduction assessment. She had anti-Ro, anti-La, and ANA antibodies but was clinically asymptomatic and taking no medication. Her first pregnancy had been uneventful. Her second pregnancy ended with spontaneous abortion. She had bichorionic twins in her third pregnancy. During her 21st gestational week, one of the twins was incidentally found with CAVB and remained so, despite initiation of dexamethasone 4 mg daily treatment. A female baby was born with CAVB who underwent permanent pacemaker implantation on her first day of life. During this pregnancy, the mother was initially referred to our facility at 15 weeks of gestation. She was followed weekly according to our laboratory protocol [12]. During the 22nd week of gestation, 6 days after the previous study had showed normal AV conduction, the fetus was in CAVB, with an atrial rhythm of 150 bpm and ventricular rate of 60 bpm. The left ventricle was dilated with reduced global systolic function. Hydrops fetalis was evolving, with pericardial, pleural, and peritoneal effusion and skin edema. Assuming the fetus was at the hyper-acute phase of AV conduction damage related to lupus carditis, we decided to initiate high dose oral dexamethasone therapy to the mother giving her 6 mg twice in the first 24 hours. We gradually decreased dexamethasone dose to 4 mg daily over the next 9 days [Figure 1]. For the first 24 hours of high dose therapy, the fetus remained in CAVB; however, after 48 hours, we started recording long episodes of second-degree AVB with 2:1 conduction and ventricular rate of 70 bpm. At 72 hours, the fetus was in stable second-degree AVB. One week after initiation of the high dose therapy, the fetal rhythm was alternating between second degree Wenkebach AVB with a drop of every third beat and first degree AVB resulting in a heart rate of 75–105 bpm [Figure 2]. On the eighth day of therapy, the fetus reverted into sinus rhythm of 160 bpm with borderline prolongation of AV conduction, as the AV interval measured by TVI was 104-106 ms (normal < 106 ms) [12]. This sinus rhythm with first AVB continued under dexamethasone 4 mg daily regimen, until 35 weeks of gestation when cesarean section was performed. A 2.5 kg male newborn was delivered with a

Fetuses with a previous sibling with CAVB should be followed biweekly from the second trimester of pregnancy until labor

Figure 1. Timeline of heart rate and treatment from 6 days before appearance of complete atrioventricular block (CAVB) until 35 days after it. Day 0 relates to diagnosis of CAVB.
1st = first AVB, 3rd = CAVB, M1 = Mobitz type I AVB, M2 = Mobitz type II AVB, N = normal conduction

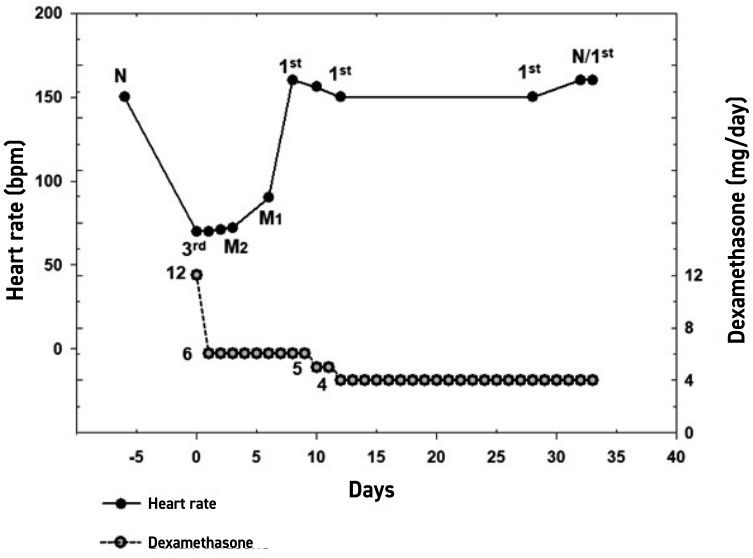
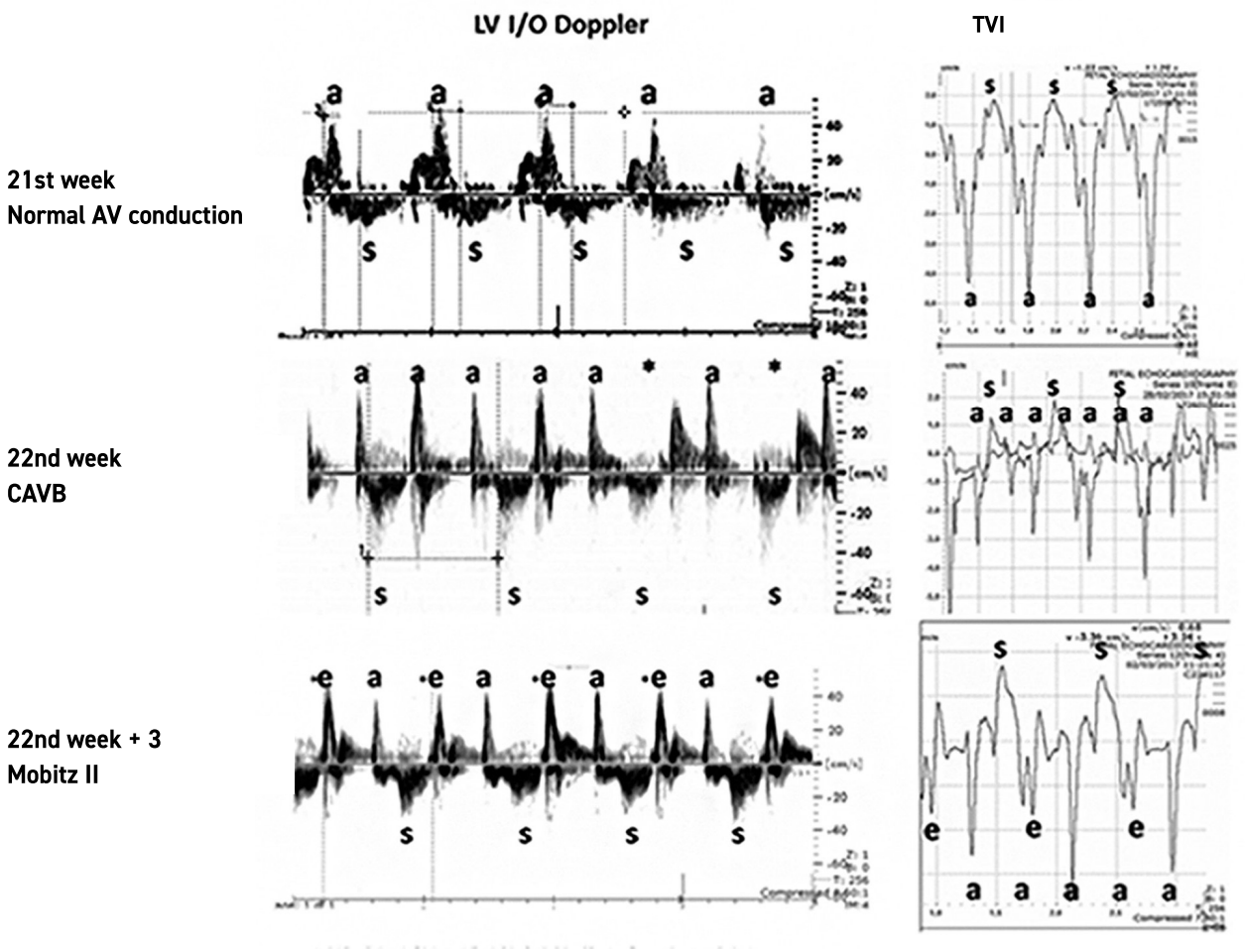


Figure 2. Side by side charts of fetal cardiac activity: on the left, pulse-wave Doppler of left ventricle inflow-outflow. On the right, tissue-velocity tracings of right heart
BPM = beats per minutes, CAVB = complete atrioventricular block, HR = heart rate, NSR = normal sinus rhythm, TVI = tissue velocity imaging



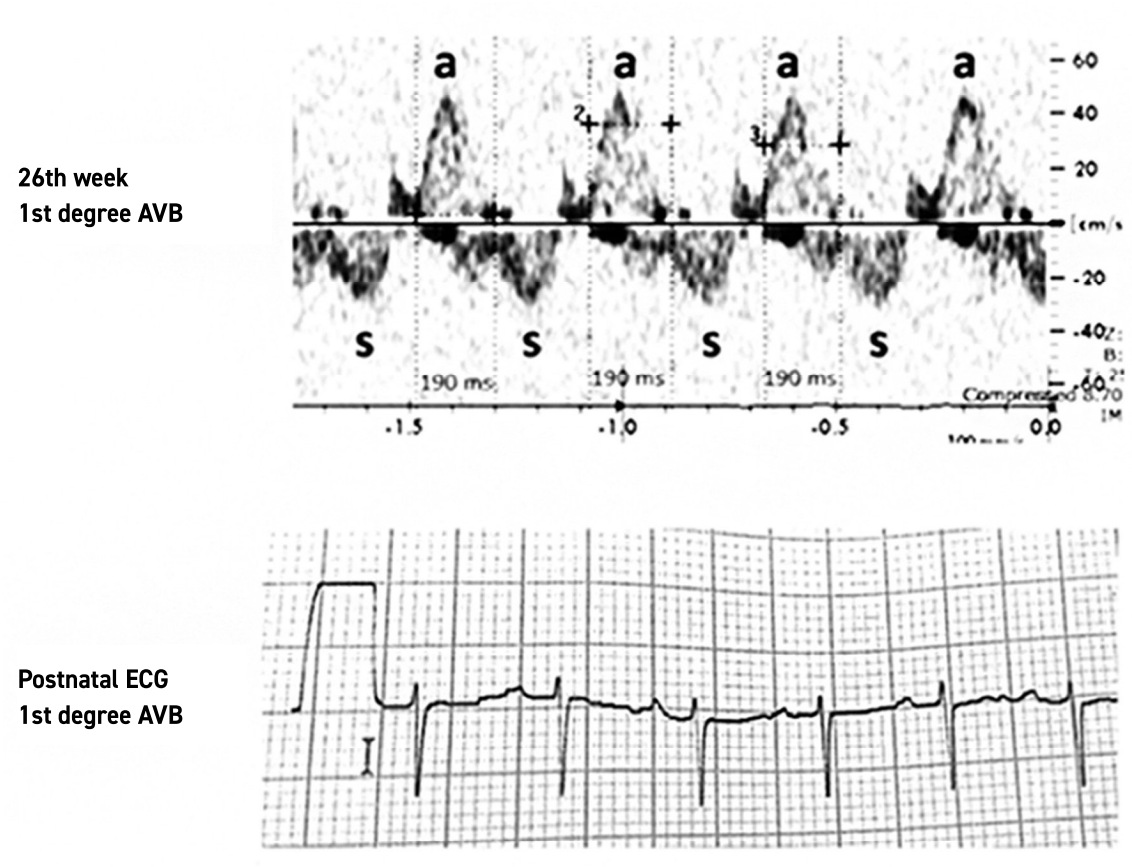
Up-left: Left sided PW Doppler on day -6 (21st week):	NSR with 1:1 atrio-ventricular conduction. HR ~120 BPM
Up-right: Right sided TVI on day -6:	NSR with 1:1 atrio-ventricular conduction. HR ~120 BPM
Mid-left: Left sided PW Doppler on day 0:	CAVB with AV dissociation. Atrial (a) rate of ~120 BPM and ventricular (s) rate of ~70 BPM
Mid-right: Right sided TVI on day 0:	CAVB with AV dissociation. Atrial (a) rate of ~120 BPM and ventricular (s) rate of ~70 BPM
Low-left: Left sided PW Doppler on day 10:	Second degree Mobitz I (Wenkebach) AVB with 2:1 AV conduction: a is followed by s The next a (*) is concealed in the e wave and is non-conducted with no subsequent s
Low-right: Right sided TVI on day 10:	Second degree Mobitz I (Wenkebach) AVB with 2:1 AV conduction: First a is followed by s. The next a is clearly noted preceding the e wave and is non-conducted with no subsequent s

heart rate of 130–160 bpm. His electrocardiogram (ECG) ECG showed NSR of 140 bpm with prolonged PR interval of 180 ms [Figure 3]. He continued to be treated with for 4 more weeks. Twenty-four months later, the child showed normal growth and development. His ECG exhibited NSR of 120 bpm with normal PR interval.

To the best of our knowledge, this case is the first documented case of autoantibody-associated fetal CAVB that reverted to sustained NSR in the newborn.

High dose dexamethasone treatment elicited a gradual reversed process from high grade to low grade AVB up to normal conduction. This might corroborate better with the above-men-

Figure 3. Tracings showing recovery from high grade AVB
AVB = atrioventricular block, BPM = beats per minutes, ECG = electrocardiogram



Up: Left sided PW Doppler on day: First degree AVB with 190 ms a-s interval and 1:1 AV conduction giving ventricular rate of ~130 BPM
Down: Postpartum ECG strip with first degree AVB and HR of ~ 140 BPM

tioned cross-reactivity hypothesis, with reversible antigen-antibody binding rather than the irreversible cell-death process involved in the apoptosis model.

Other groups failed to restore sinus rhythm from CAVB even with aggressive immunomodulation therapy. Ruffatti and colleagues [16] described six fetuses with either second degree AVB or CAVB in which a combination therapy of plasmapheresis, IV immunoglobulins and oral steroids was used. All fetuses remained in CAVB, despite this aggressive therapy. Reviewing the literature, they found 10 fetuses with CAVB treated with steroids, either died prenatally or were born with CAVB. Indeed, the fetus we describe here was followed every week from the 13th week of gestation. However, at the 22nd week of gestation, it was unexpectedly in CAVB whereas his AV conduction had been normal 6 days earlier. We thought that we were facing a hyper-acute, ongoing, hence still reversible process of damage to the AV conduction. Therefore, we immediately initiated very high dose dexamethasone treatment.

Maternal dexamethasone therapy in all fetuses with first degree AVB will prevent most fetuses from deteriorating to CAVB in a setup of frequent and accurate AV interval measurements during the second trimester

Regarding the failure to detect first or second degree AVB in our fetus, one could theoretically argue that high grade AVB could develop abruptly from preceding NSR, without intermediate phases. However, first degree AVB is universally accepted as a transitional stage before CAVB development [17]. Moreover the recovery of our fetus from CAVB via an intermediate stage of second degree AVB and, through first AVB to NSR, does suggest that deterioration from NSR to CAVB is

gradual and organized in a mirror-image pattern. Perhaps, it could have been a timing issue, when rapid deterioration of AV conduction could have occurred in less than a week. In such a case, the once-a-week study protocol [18-20] might have been inadequate. It is thus conceivable, that in such a high-risk group of fetuses with previous CAVB in siblings, the time interval for deterioration from NSR to irreversible CAVB might be shorter than the traditionally quoted 6 days [20] implying that follow-up should be more frequent in this group. Twice-weekly follow-up in this small subgroup was also suggested by Kan et al. [9].

CONCLUSIONS

We reviewed the literature reporting on research conducted over the last 2 decades that was focused on diagnosing an early transition phase into high-grade AVB in the anti-Ro exposed fetus. Although controversial, we and others believe that low-grade AVB could be detected in the fetus. Our data suggest that dexamethasone may prevent this deterioration. Regarding reversibility of CAVB, high dose dexamethasone might revert the process providing the fetus is still at the hyperacute phase of the immune damage. We recommend its administration immediately after the diagnosis of high grade AVB is confirmed. Furthermore, we concur with Jaeggi and co-authors, that a twice-weekly follow-up may be advisable in the high-risk subgroup of fetuses having siblings with CAVB.

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The world is a looking glass and gives back to every man the reflection of his own face.

William Makepeace Thackeray (1811–1863), British novelist, author and illustrator. He is known for his satirical works, particularly *Vanity Fair*, a panoramic portrait of English society