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Update on Management of Pregnancies with Sjogren's Antibodies

Bettina F. Cuneo

Update on Management of Pregnancies with Sjogren's Antibodies

Bettina F. Cuneo MD
Clinical Scholar and Professor of Surgery
Adjunct Professor of Pediatrics and Obstetrics
University of Arizona College of Medicine

Disclosures NIHHD100929

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Outline

I. Brief review and background of cardiac neonatal lupus (C-NLE)
II. The natural history and basis of surveillance
III. Ambulatory FHRM: new kid on the BLOQ
IV. Does treatment work?

CARDIAC NEONEONATAL LUPUS

A Model of Passively Acquired Autoimmunity

MATERNAL CIRCULATION

No symptoms, SLE, SS

anti-52kD SSA/Ro

anti-60kD SSA/Ro

anti-48kD SSB/La

PLACENTAL TRANSPORT

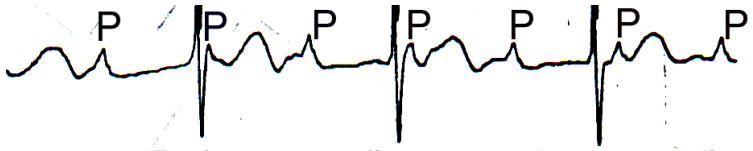
Effective 11 weeks
All IgG subclasses

FcRn

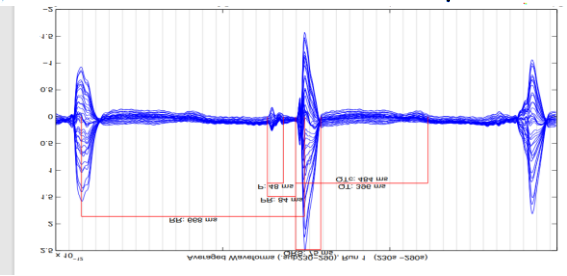
FETAL CIRCULATION

Conduction system disease

1°, 2°, 3° AVB

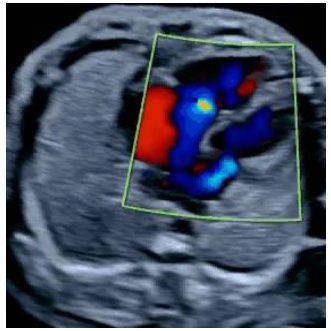


Sinus bradycardia, BBB, JET

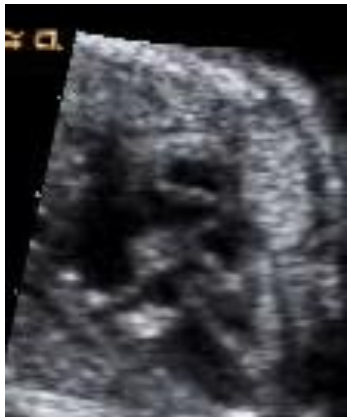


Myocardial disease

Valvulitis



EFE



A Rare Fetal Complication in a Rare Maternal Condition

5000 women

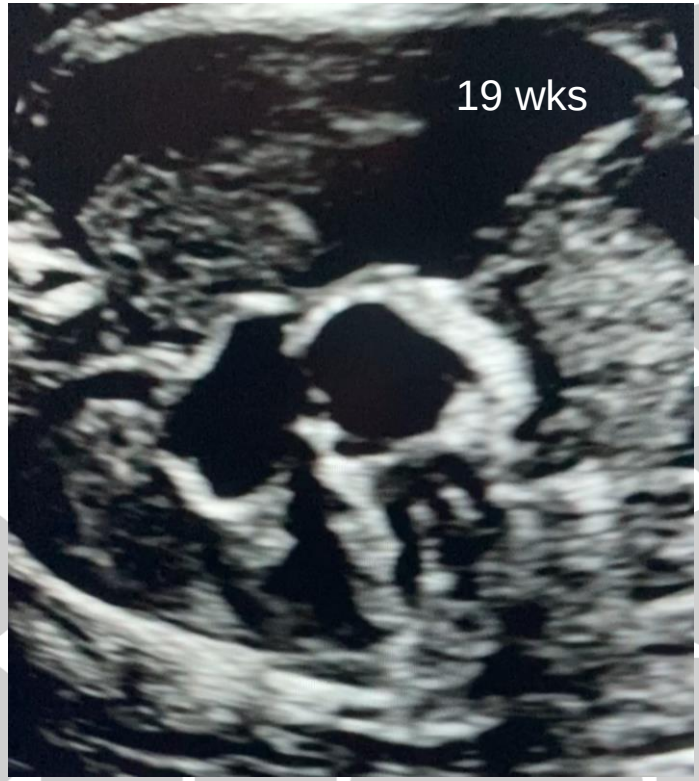
0.86% 50 w. anti-Ro antibodies (Satoh 2012)

50% asymptomatic
25-60% SLE (Choi, 2019)
60-100% SS (Izmirly 2015)

50% of fetal AVB to asymptomatic pregnant subjects

2% One fetus w. AVB

Neonatal lupus registry: 90% 2° or 3° AVB at < 26 weeks
17-30% perinatal mortality (Izmirly, 2012)
85% survivors paced (Mawad, 2022)



Risk Factors for Perinatal Demise:

- Dx ≤ 20 weeks
- Ventricular rate < 45 bpm,
- Atrial rate < 90
- EFE
- Ventricular dysfunction
- Hydrops

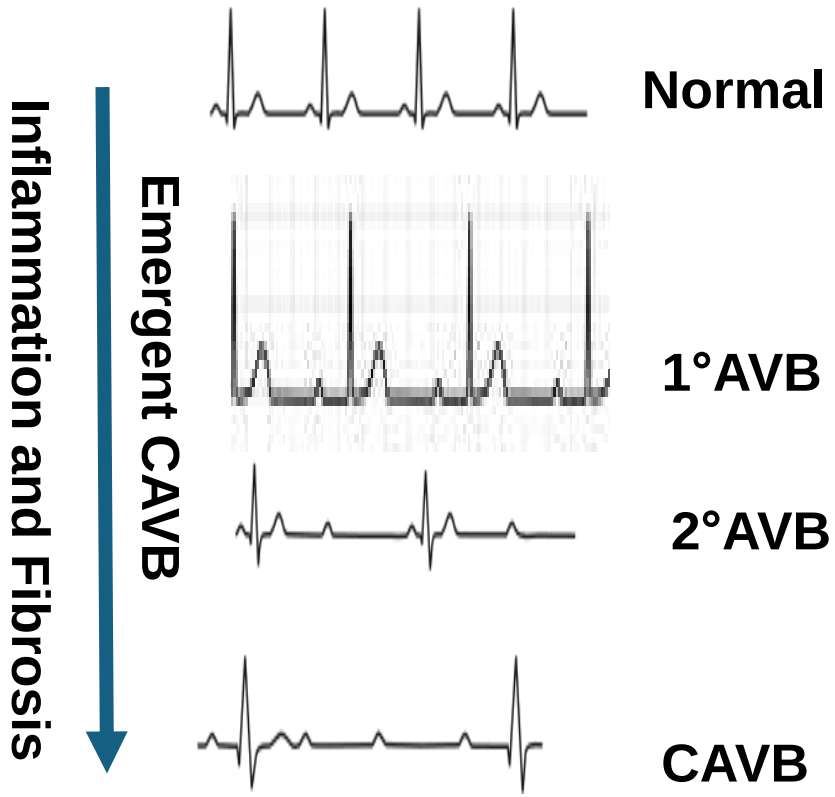
(Mawad, 2022 and Izmirly, 2012)

The Conundrum: How to Manage Anti-Ro + Pregnancies and When to Treat C-NLE

- FHS and NAFTNET Peds cards (70%) and MFM (30%)
- 60% 5-20 referrals/year
- Wide variation, little consensus on any aspect of surveillance or management
  - Surveillance: 94% Echo, 45% office FHRM
  - Majority surveil from 16-28 weeks
  - 58% surveil for anti-LA/SSB alone
  - 34% surveil because of maternal disease (SS, SLE, RA) regardless of antibodies
- 67% treat 3°, 78% treat 2° and 67% treat 1° AVB (but little agreement on definition of 1° AVB

Howley L et. al J. *Mat Fet Neonat Med 2024*

Natural History of AV Conduction System Disease

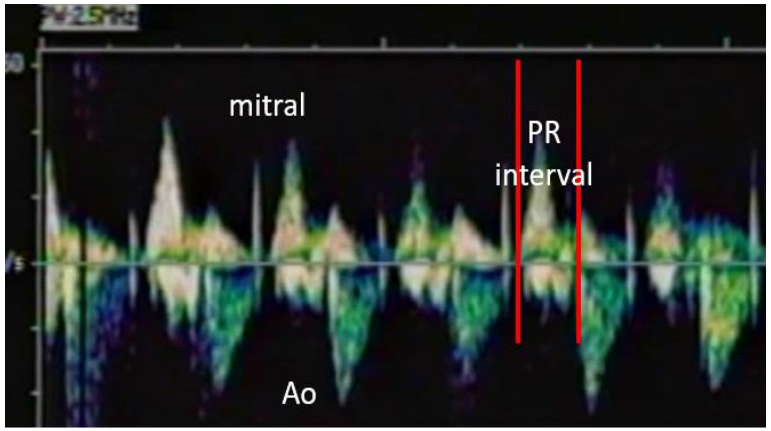


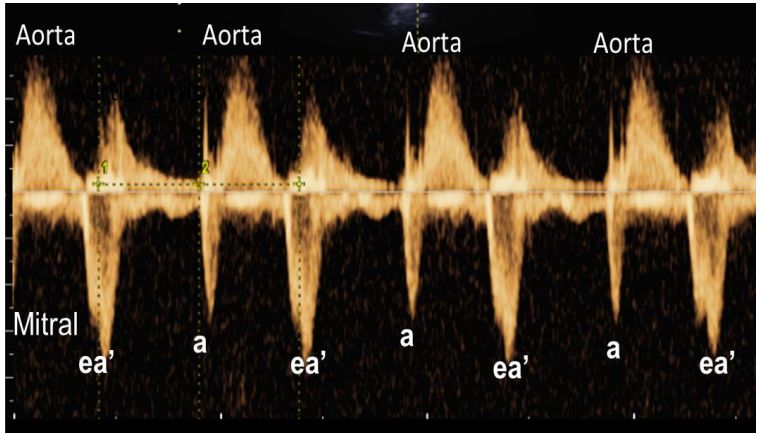
“Emergent CAVB”
(1° and 2°AVB)

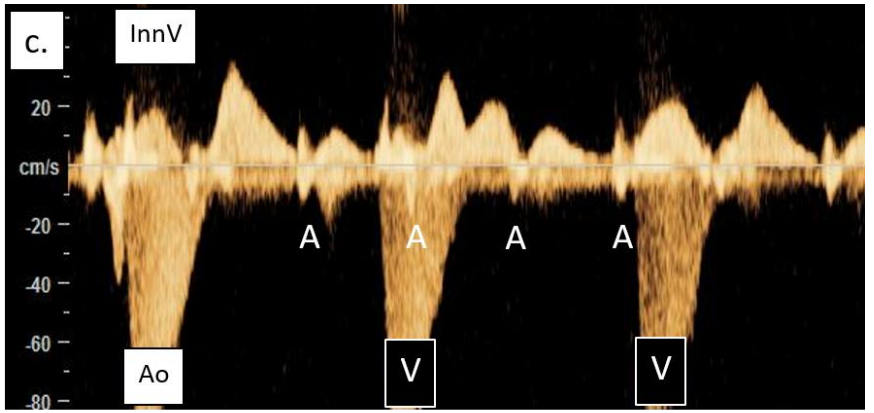
- Vulnerable time when normal cardiac rhythm transitions to CAVB
- Treatment during this time could restore normal rhythm or prevent progression to CAVB

PRIDE Study (PR interval and dexamethasone): Hypothesis

- Fetal 3° AVB result of progression through 1° and 2° AVB
- 1° AVB is a vulnerable time when treatment might prevent progression and even restore sinus rhythm





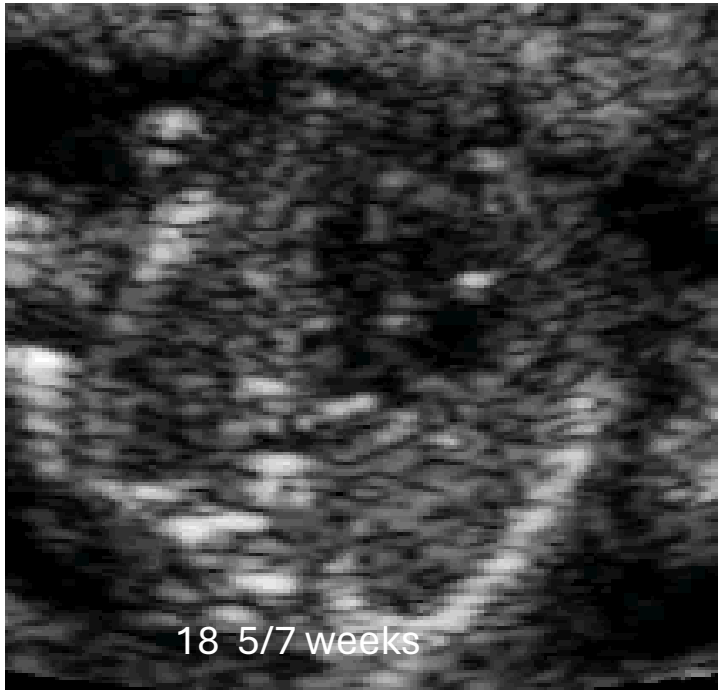


- 3/98 fetuses developed irreversible 3° AVB without prior 1° AVB; 2/3 (hydropic) died (all Rxed w. 4 mg dex)
- 2/3 had extra nodal findings (AVVR, EFE) prior to AVB
- 2 fetuses (unnecessarily) treated for AV intervals 160-165 ms
- Conclusion:

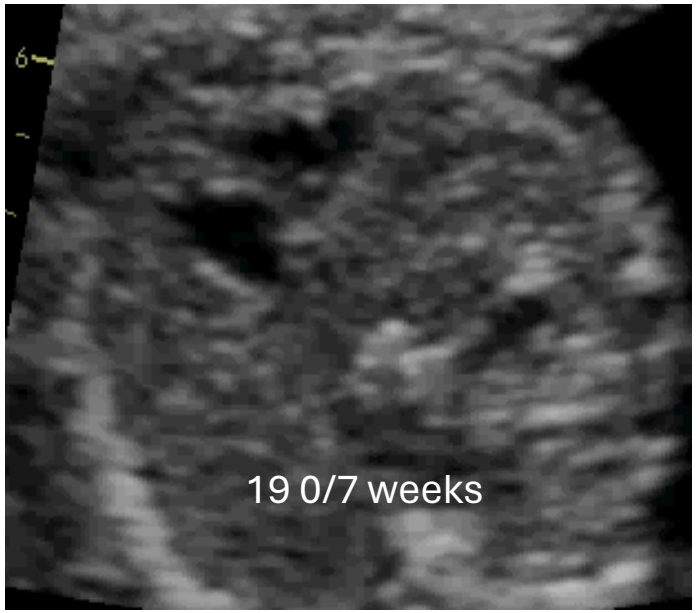
  1. Recognizable harbingers of disease. 2. No transition OR 3. The fetal heart rhythm transitions from normal to 3° AVB in < 1 week

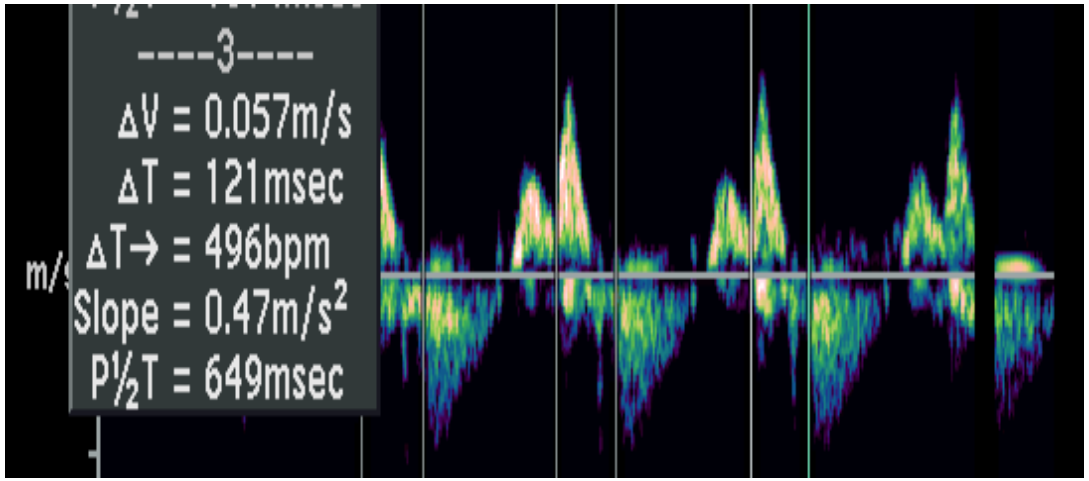
Friedman D. et. al. *Circulation* 2008

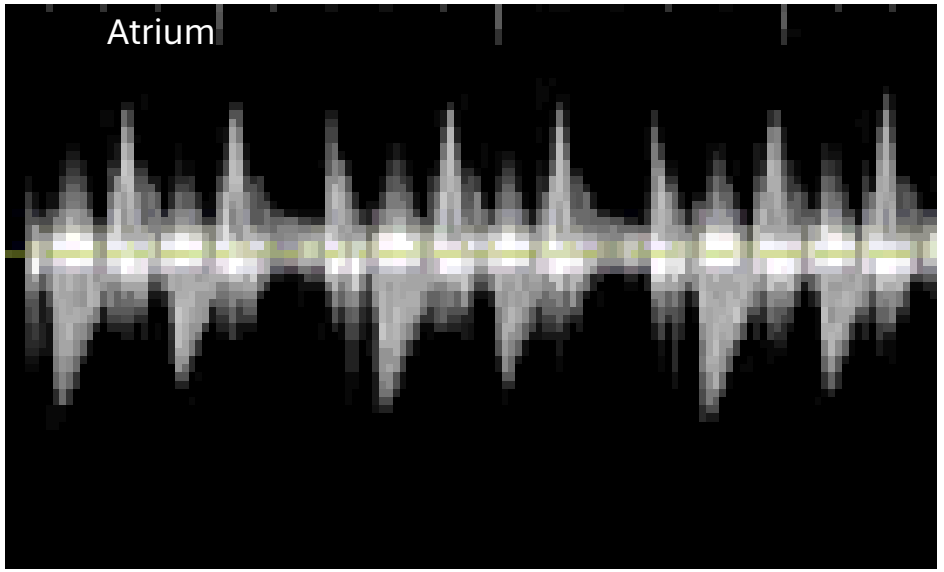
There is a transition period, and it is < 12 hrs



- Normal echo 2 days prior
- Normal FHR/Rhythm at night
- Irregular rhythm the next morning







Cuneo et al *AJOG* 2016

The 4 Questions

- Is every anti-Ro antibody positive pregnant subject at equal risk for fetal AV block?
- How to surveil for a fleeting event (emergent 3° fetal AVB) that occurs rarely?
- Does treatment reverse emergent 3° fetal AVB?
- What is the natural history of extra-nodal disease and an AV interval of 150-170 ms?

Implications of Anti-Ro/SSA Antibody Titer: Not every pregnancy is at the same risk?

Canadian Study
(in house ELISA)

Group 1: (8-49 U/mL) (N = 62)

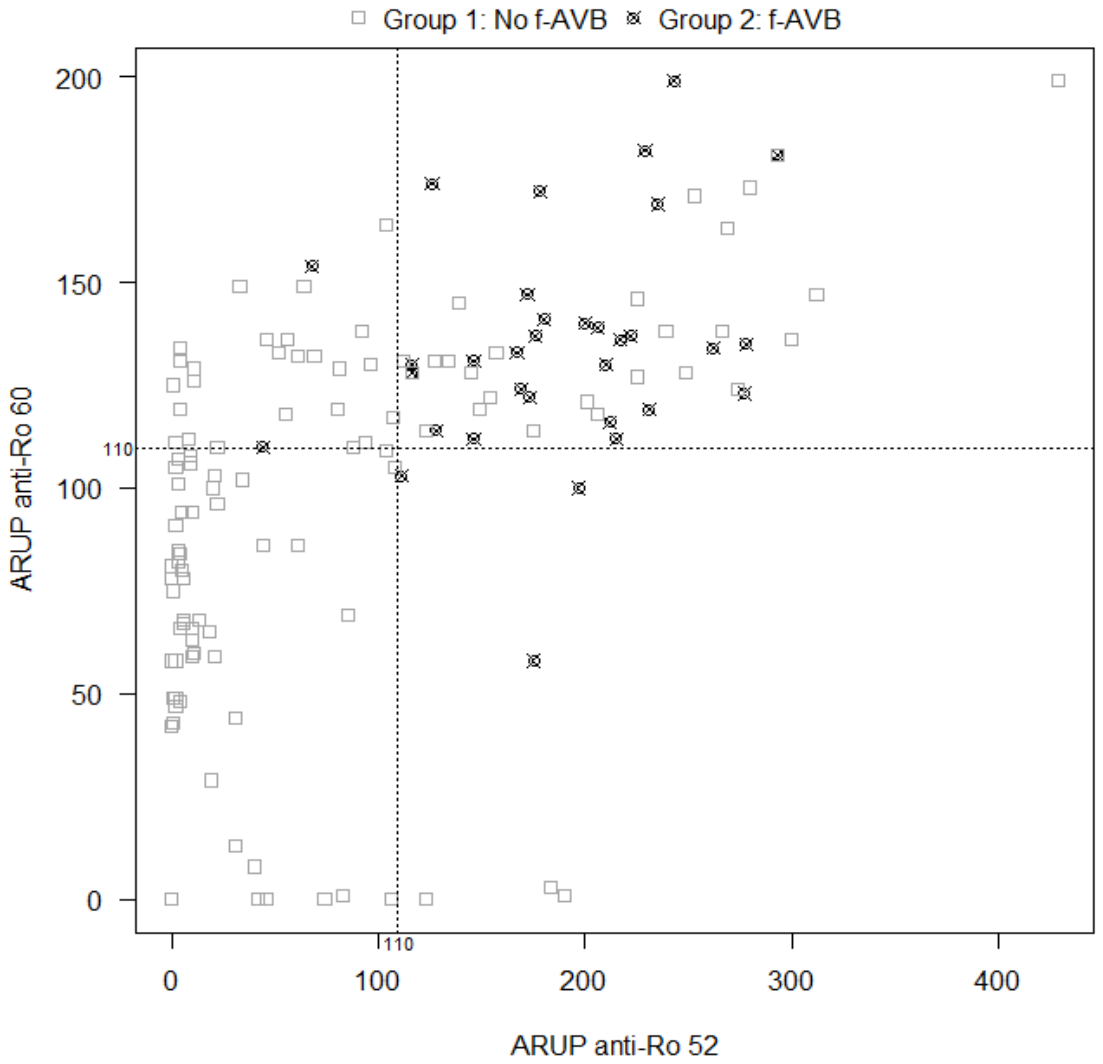
- No cases of anything

Group 2: (50 - >100 U/mL) (N = 127)

- Isolated EFE(n = 1)
- 1˚ or 2° AVB (n = 4)
- 3° AVB (n = 4)

Kan et al, Prenatal Diagnosis, 2017

Colorado/Arizona/New York Study
(In house plus commercial ELISA)



Kaizer A et. al *Am J Obstet Gynecol* 2022

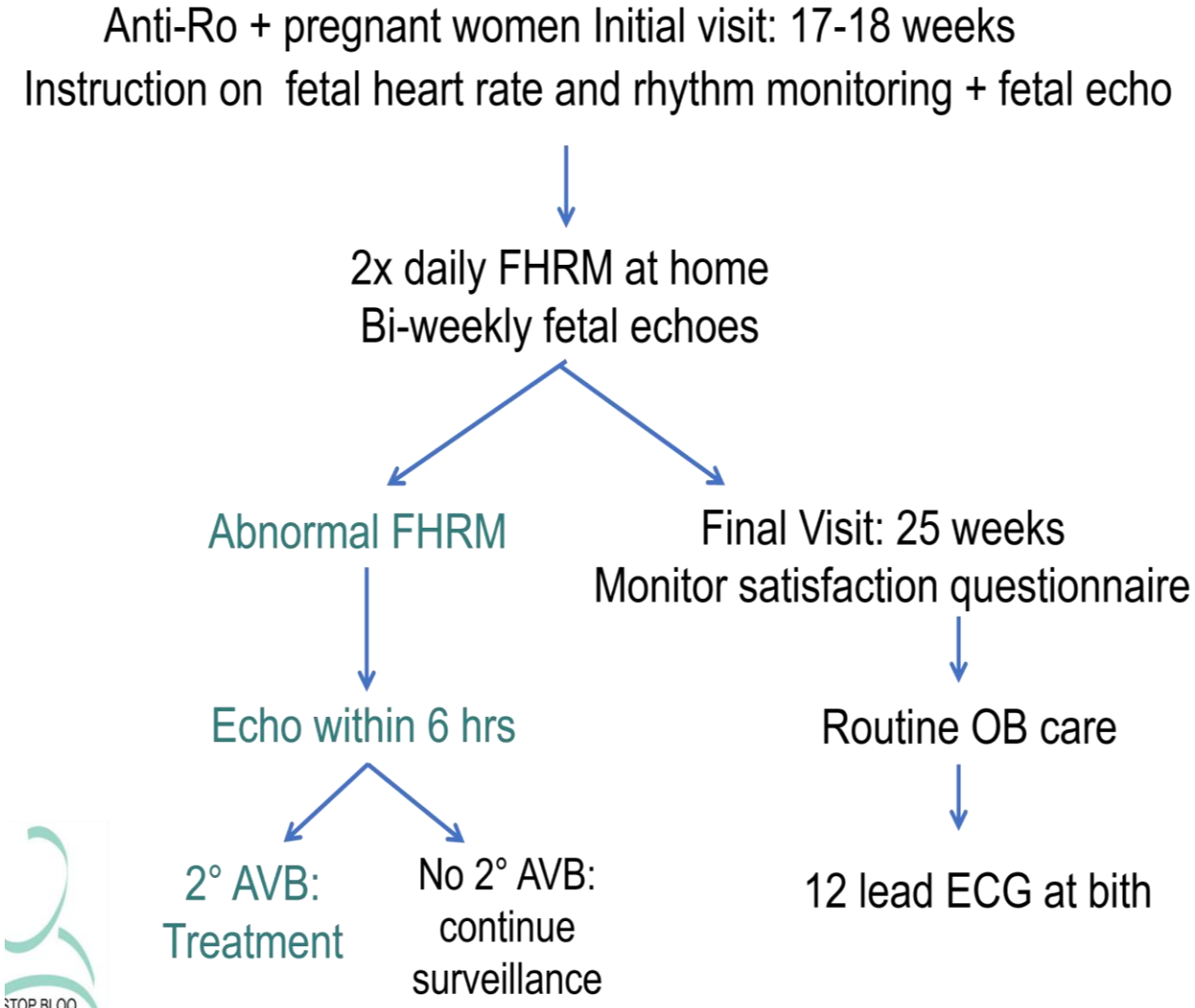
Results of FHRM to 2018: Treatment can reverse emergent CAVB

ID	GA (wks)	Detection to Dx (hrs)	Echo	RX	Birth Rhythm
1	18.9	≥ 24	3° AVB	Dex + IVIG	3° AVB
2	22.9	≥ 24	3° AVB	Dex + IVIG	3° AVB
3	19.5	≥ 24	3° AVB	Dex + IVIG	3° AVB
4	20.4	< 12	2°AVB	Dex + IVIG	1:1 AV
5	19	< 12	2°AVB	Dex + IVIG	1:1 AV
6	19	< 12	2°AVB	Dex	1:1 AV
7	18	< 18	2°/3° AVB	Dex + IVIG	1:1 AV

- Time from detection of 2° AVB to treatment with IVIG and dexamethasone affects outcome
  - >24 hrs, rhythm progresses to irreversible 3° AVB
  - ≤ 12 hrs rhythm improves to 1:1 AV conduction

Cuneo et. al. , *AJOG.* 2016; Cuneo, et. al., *JACC.* 2018; Kan, et. al., *J Perinatol* 2017

Proof of Concept: Surveilling with Ambulatory FHRM is fesible



- High enrollment (94%) and retention (87%)
- Mothers felt empowered and would monitor again
- No AVB was missed (False negatives = 0%)
- False positive = 4%
- 3/273 fetuses developed AVB
  - Subject #1: Did not monitor for 24 hrs: 3° AVB (no change after Rx)
  - Subject #2: Irregular rhythm for 24 hrs: 3° AVB (no change after Rx)
  - Subject #3: Irregular rhythm < 12 hrs: 2° AVB (normal rhythm after Rx)

Cuneo BF et, al. *J Perinatology* 2016 and *JACC* 2019

Surveillance and **T**reatment t**O** **P**revent Fetal AV**B** **L**ikely to **Oc**cur **Q**uickly

The **STOP BLOQ S**tudy

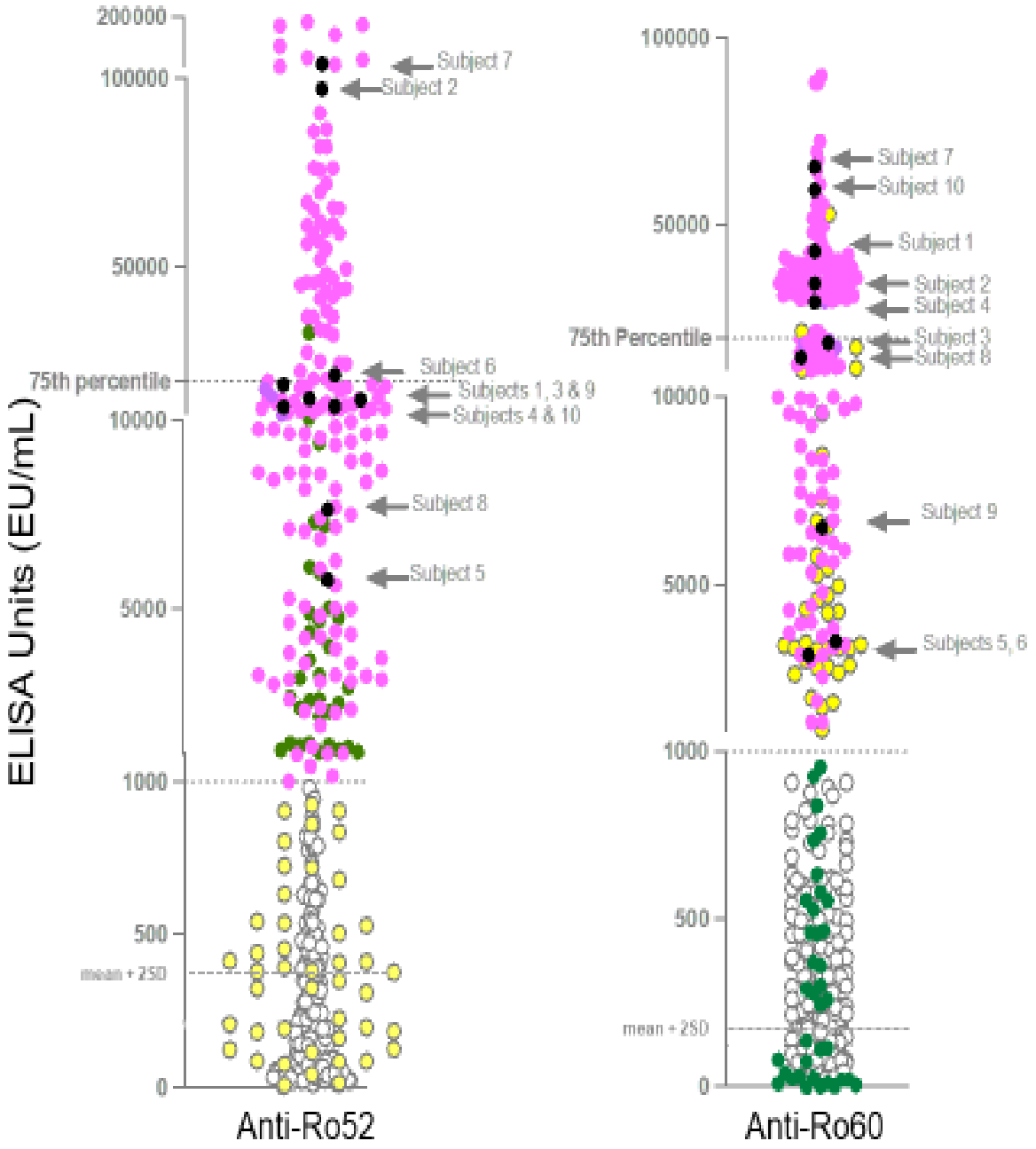
Multicenter (24 sites) 3-step open label one arm clinical trial *leveraging risk stratification by anti-Ro/SSA titer and ambulatory FHRM* and echo to surveil anti-Ro/SSA positive pregnancies

Aim 1**:** Does expeditious treatment of 2° AVB w. Dex and IVIG restore NSR

Aim 2: What is the incidence and natural history of fetal prolonged AV interval ≤170 milliseconds

Aim 3: To assess the incidence and outcome of fetuses with isolated extra-nodal cardiac disease.

NICHD RO1 HD100929



- AVB High anti-Ro52, High Ro anti-Ro60
- High anti-Ro52, High Ro anti-Ro60
- Low anti-Ro52, High Ro anti-Ro60
- High anti-Ro52, Low Ro anti-Ro60
- Low anti-Ro52, Low Ro anti-Ro60

Anti-Ro/SSA Titers and Risk of Fetal AV Block

If both Ro52 and Ro60 are elevated AND previous AVB: 10.7% will have recurrent fetal AVB

If both Ro 52 and Ro60 are elevated WITH NO previous AVB (or primiparous): 4.6% will have fetal AVB

Buyon JP et. al. *A and R* 2023

Anti-Ro/SSA antibody + Pregnant Subjects Recruited for STOP BLOQ

Core Laboratory at NYU performs ELISA for titers to anti-Ro52 and anti-Ro60

261
At high risk for AVB by EITHER anti-Ro52 OR anti-Ro60 >1000 EU or previous child with AVB

17-26 weeks

Weekly or biweekly in clinic

AND

3x/day at home

151
At low risk for AVB by BOTH anti-Ro52 and anti-Ro60 <1000 EU

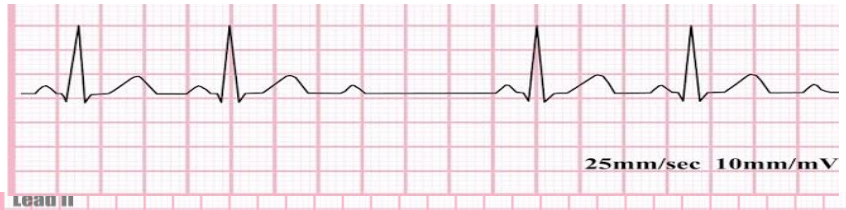
17-26 weeks

Weekly or biweekly in clinic

OR

No Surveillance

10



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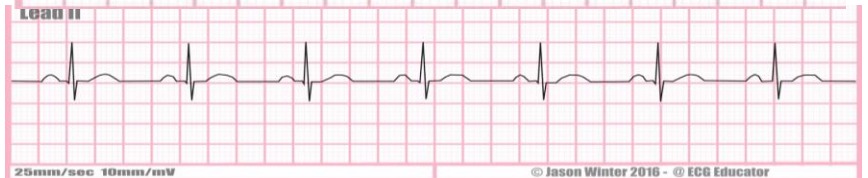

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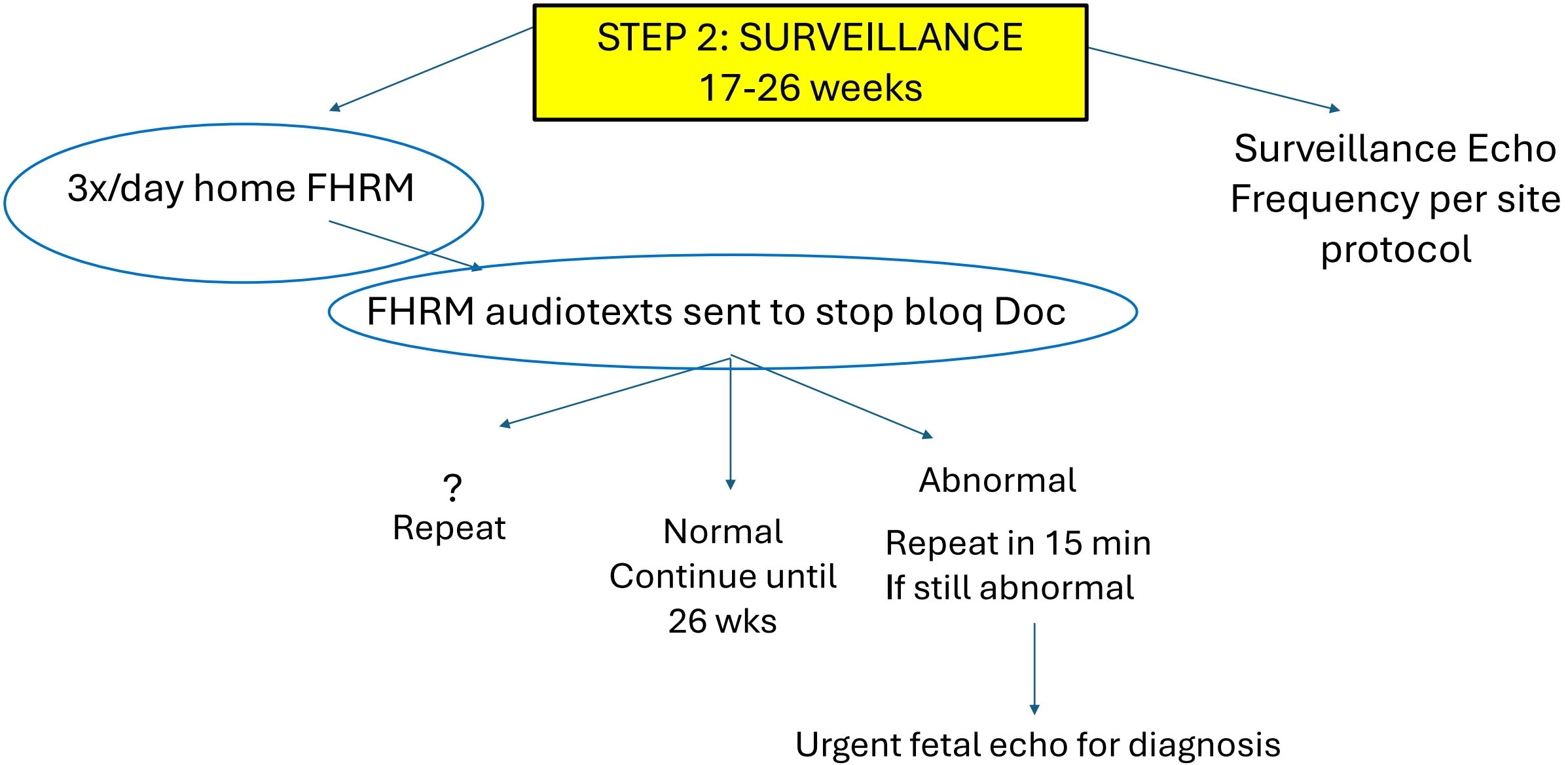
Buyon JP et. al. *A and R*2023


STEP 2: SURVEILLANCE
17-26 weeks
3x/day home FHRM
Surveillance Echo
Frequency per site
protocol
FHRM audiotexts sent to stop bloq Doc
?
Repeat
Normal
Continue until
26 wks
Abnormal
Repeat in 15 min
If still abnormal
Urgent fetal echo for diagnosis

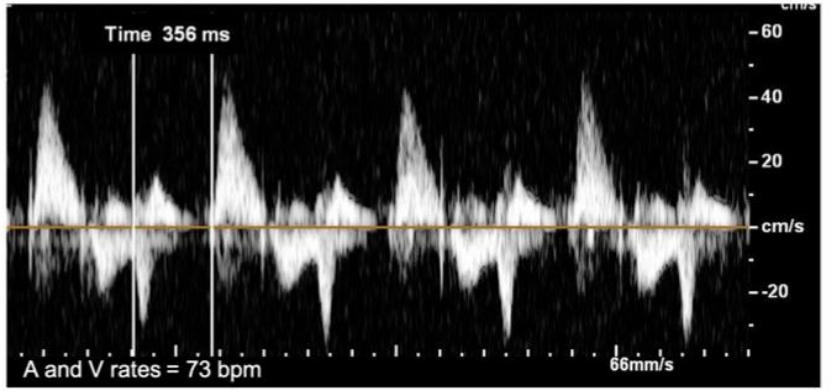
Surveillance by FHRM

- G2P1
- Previously affected child with CAVB (20 weeks), alive, paced
- 300 mg Plaquenil/day since before 2nd pregnancy
- Began monitoring at 17 weeks

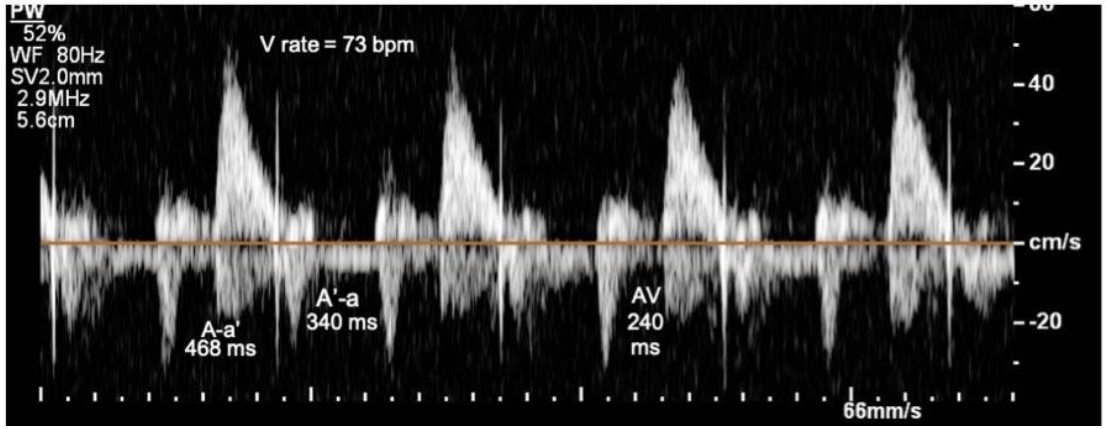
- Abnormal monitoring 17 6/7wks:
- Emergency echo
  - PACs
- Normal surveillance echo 18 4/7 wks
- 19 wks: normal Doppler 5 am
  - Abnormal Doppler 2:00 noon

- Emergency echo 14:00

Figure 1



(A)



Results of Step 2 Surveillance

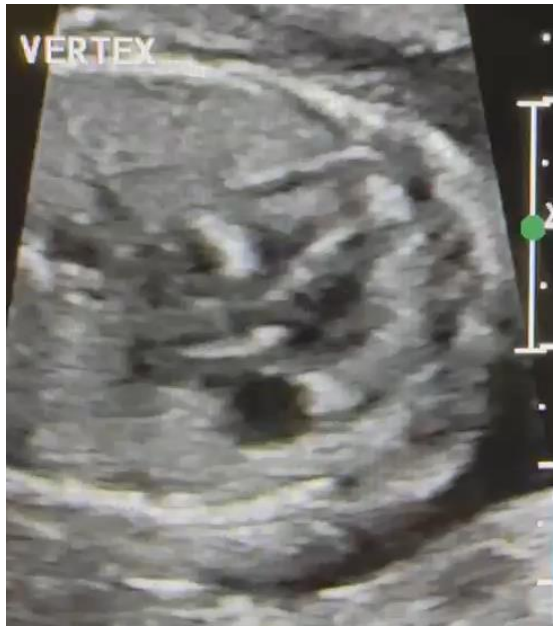
2279 Surveillance echoes

- 3 abnormal
  - 1 PACs
  - 1 moderate AVVR

    16 wks,, treated (off protocol)
  - 1 EFE

    20 wks no Rx

    (continues in study)



53, 823 Doppler recordings

- 42 (0.078%) abnormal
- Emergency echo results
  - 17 normal
  - 16 PACs
  - 7, 2° AVB
  - 3, 3° AVB

60% emergency echoes were abnormal!

What about Treatment?

Clinical Rationale for Treatment with IVIG

- Background:
  - Before 1998
    - 85% with anti-Ro/SSA CM/EFE +CAVB died/transplant
  - Between 1998-2009
    - 20 fetuses with CM/EFE (18 with AVB) Rx IVIG +dex

- Results: Median follow-up 2.9 yrs on 16 patients
  - 3 perinatal deaths
  - 80% alive with normal function
  - 37% not paced

Adding IVIG to dexamethasone therapy changed outcome from 85% dead or transplanted to 80% alive with normal function

Trucco S. et. al. *JACC* 2011

Rationale for Treatment of 2°AVB: Multiple Shortcoming in Published Data

- Small case series non-standard protocols all retrospective
  - Type (Mobitz 1 or 2) of 2° AVB not specified
  - Time from dx to Rx or from NSR to AVB not included
  - Outcomes range from no change to regression or progression with or without Rx
  - Could some of the “spontaneous regressions” without Rx be BAB not 2°AVB??
    - ~40% w. “2° AVB” referred for fMCG had BAB

Outcome	Fetuses Treated	Fetuses Not Treated
Overall *Progression* 2° AVB to CAVB	17/31 (54%)	8/11 (73%)
Overall *Regression* 2° AVB to 1° AVB 2 ° AVB to NSR	9/38 (24%) 6/31 (19%)	4/19 (21%) 1/11 (9%)
Stable rhythm	4/38 (11%)	0/19 (0%)h

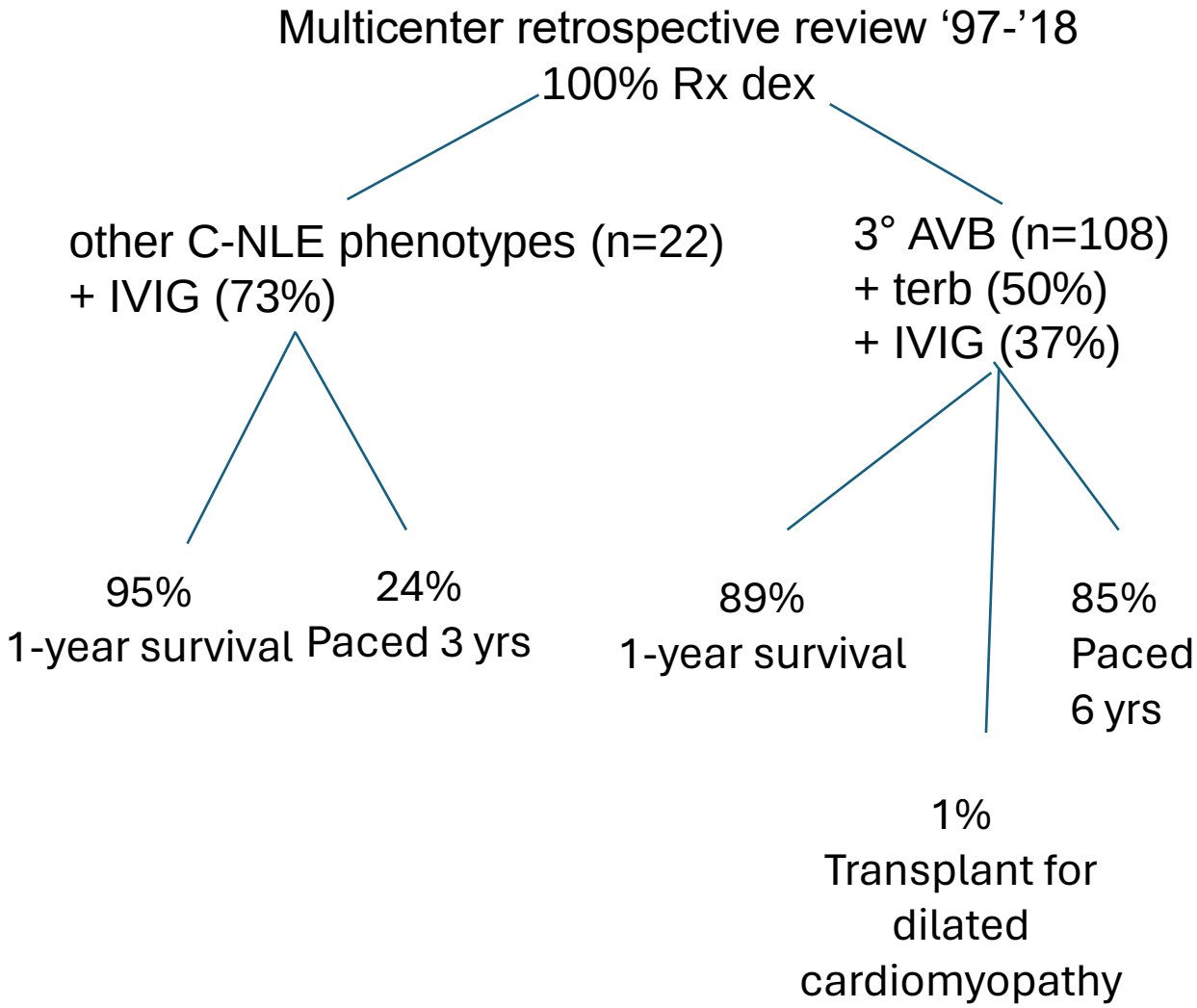
Ciardulli,et. al., *AOGS.* 2018*;* Doti, et. al., *Clin Rheum.* 2016*;* Levesque,*et. al., Autoimmune Rev.* 2015*;* Izmirly…Buyon, *Circulation,* 2011*;* Eliasson, et. al., *Circulation,* 2011

Journal of the American Heart Association

ORIGINAL RESEARCH

Outcome of Antibody-Mediated Fetal Heart Disease With Standardized Anti-Inflammatory Transplacental Treatment

Wadi Mawad, MD; Lisa Hornberger, MD; Bettina Cuneo, MD; Marie-Josée Raboisson, MD; Anita J. Moon-Grady, MD; Jane Lougheed, MD; Karim Diab, MD; Julia Parkman, MD; Earl Silverman, MD; Edgar Jaeggi, MD



Mawad W. et. al. *J Am Heart Assoc.* 2021

Variable	Current	Lopes[13]	Eliasson[9]	Levesque[14]	Van den Berg[15]	Fredi[16]
Prenatal treatment						
Yes	114 (100)	11/57 (19)*	67/175 (38)*	77/198 (39)*	21/51 (41)*	60/84 (71)*
Fluorinated steroids	114 (100)	6 (11)*	67 (38)*	77 (39)*	14 (27)*	60 (71)*
Duration, wk	12.8 (0.3–18)	N/A	10 (1–21)	8 (1.3–18)	N/A	9.5 (4–18)
β-Mimetics	47 (41)	7 (12)*	41 (23)‡	N/A	17 (33)	7 (8)*
Duration, wk	6 (0.3–15.1)	N/A	8 (2–18)	N/A	N/A	N/A
IVIG	46 (40)	0 (0)*	0 (0)*	4 (2)*	0 (0)*	20 (24)†
Outcome						
Fetal survival	109/114 (96)	51/57 (89)	159/175 (91)	175/198 (88)†	43/51 (84)†	68/77 (88)
Gestational age at birth, wk	36.7 (26.6–39.1)	N/A	N/A	37 (28–41)	38±2	35.3±3
Neonatal survival	106/114 (93)	44/57 (77)‡	138/164 (84)†	167/198 (84)†	N/A	63/77 (82)†
Postnatal follow-up, y	4.9 (0–18)	N/A	N/A	7 (0–36)	N/A	N/A
Alive	100/114 (88)			155/198 (78)		
Dilated cardiomyopathy	3/106 (3)			32/174 (18)*		

Values are number (percentage), mean±SD, or median (range). AVB II indicates second-degree atrioventricular block; AVB III, third-degree atrioventricular block; bpm, beats per minute; IVIG, intravenous immune globulins; N/A, information not available; TFTX, transplacental fetal treatment; and TOP, termination of pregnancy.

*$P<0.001$.

†$P<0.05$.

‡$P<0.01$

Comparison of Prenatal Findings and Clinical Outcomes in Fetal AVB II and AVB III Between the Current Cohort With Routine TFTX and Previously Published Cohorts w. Variable TFTX

Variable	Current	Lopes[13]	Eliasson[9]	Levesque[14]	Van den Berg[15]	Fredi[16]
Study years	1997–2018	1988–2006	2000–2007	1976–2014	2003–2013	1969–2017
Fetal cases (AVB II or AVB III)	114	57	175	202	56	84
Included	114	57	175	198	51	77
Excluded (primary TOP)	…	…	…	4	5	7
Anti-Ro antibodies						
Positive	114 (100)	41 (72)*	129 (74)*	197 (99)	48 (86)*	84 (100)
Negative or unknown	0	16	46	1	8	0
Prenatal findings						
Age at diagnosis, wk	22.1 (17–33)	29 (18–40)	24.3±4.3	23 (16–39)	23.4±5	21 (17–38)
Fetal hydrops	9/114 (8)	11/57 (19)†	16/175 (9)	22/175 (13)	5/50 (10)	7/84 (8)
AVB III	108/114 (95)	35/57 (61)*	146/175 (83)‡	167/202 (83)‡	35/56 (63) *	66/84 (79)*
Ventricular rate	61.3±12.2	58.6±13.6	59.8±11.4	N/A	61±14	N/A
Ventricular rate ≤50 bpm (nadir)	38/114 (33)	N/A	36/173 (21)†	44/198 (22)†	N/A	27/73 (37%)
AVB II	6/114 (5)	22/57 (39)	29/175 (17)	35/202 (17)	21/56 (37)	18/84 (21)

Mawad W. et. al. *J Am Heart Assoc.* 2021

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
https://doi.org/10.1080/14767058.2022.2025536

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

NAFTNet retrospective report on the treatment of anti-Ro/SSA mediated fetal heart block with dexamethasone

Sherzana Sunderji[a], Shabnam Peyvandi[b], Edgar Jaeggi[c], Anita Szwast[d], Greg Ryan[e], Francine Tessier[f], Saad Siddiqui[g], Bettina Cuneo[h], Shreya Sheth[i], Marjorie Treadwell[j], Michele Frommelt[k], Shifa Turan[l], Joshua Copel[m], Stephen Emery[n], Larry Rand[b], Anita J. Moon-Grady[b] and for the North American Fetal Therapy Network (NAFTNet)

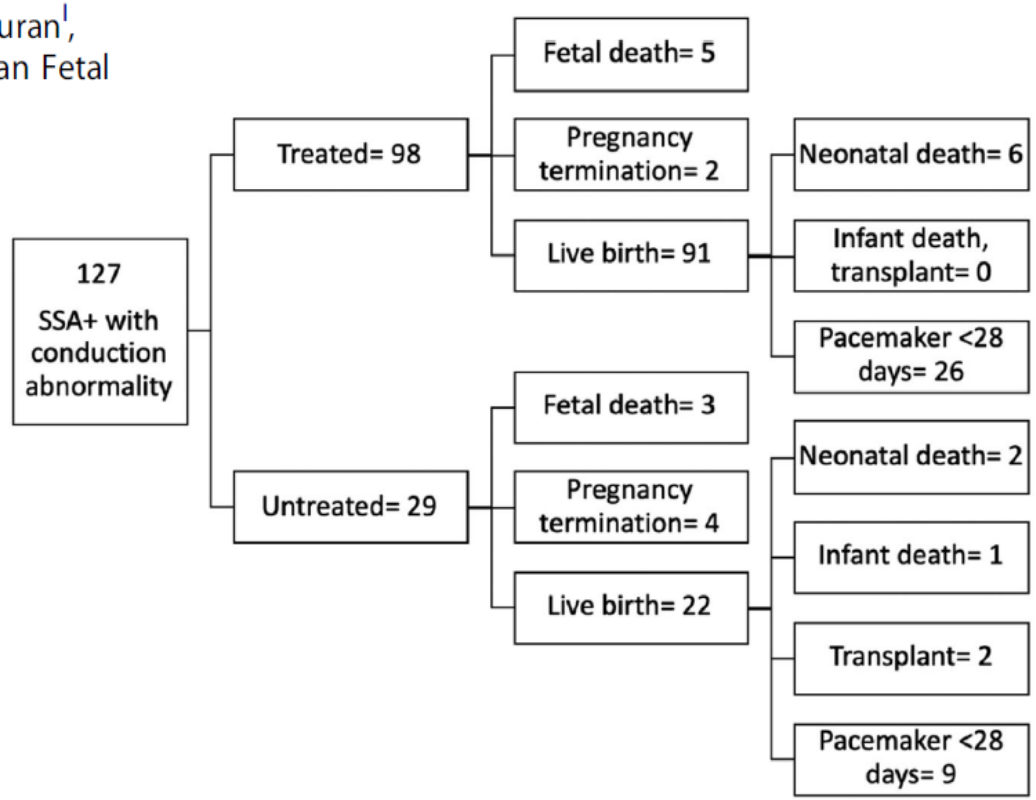


Table 4. Prenatal co-morbidities by study group.

Co-morbidity	Untreated $N = 25$[a]	Treated $N = 96$[a]
Oligohydramnios, *N* (%)	0	14 (13.3%)
Fetal growth restriction, *N* (%)	1	10
Fetal death (not TOP), *N* (%)	3	5
New onset diabetes, *N* (%)	0	2 (2.0%)
New onset maternal HTN, *N* (%)	1	4
Insomnia/mood disturbance, *N* (%)	0	4 (4.1%)
Other (thrush, shingles), *N*	0	2 (2%)
GA birth <37 weeks	11/22 (50%)	45/91 (49.4%)

TOP: termination of pregnancy; HTN: hypertension and hypertensive disorders including pre-eclampsia; GA: gestational age.
[a]TOP excluded from reporting.

Table 5. Primary outcome: percentage of patients in each treatment group that had poor composite outcome defined as having one or more of: oligohydramnios, growth restriction, fetal death, new/worse gestational diabetes or hypertensive disorder, preterm delivery (<37 0/7 weeks).

Met composite outcome	Untreated $N = 25$[a]	Treated $N = 96$[a]	*p* Value
Yes, *N* (%)	15 (60.0%)	61 (63.5%)	.74
No, *N* (%)	10 (40.0%)	35 (36.4%)	

[a]Terminated pregnancies excluded from reporting.

Table 3. Neonatal and postnatal characteristics by treatment group.

Liveborn	Untreated $N = 22$	Treated $N = 91$	p Value*
C-section delivery, *N* (%)	17/21 (80.9%)	80/87 (91.9%)	.22
GA birth, mean (95% CI), weeks	35.6 (34.0–37.3)	36.3 (35.8–36.7)	.27
Birth weight, mean (95% CI), kg	2.7 (2.3–3.0)	2.4 (2.2–2.5)	.1
Pacemaker <28 days, *N* (%)	9/22 (40.9%)	26/91 (28.2%)	.26
30 day survival, *N* (%)	20 (95.2%)	85 (94.4%)	1.0
Transplant, *N* (%)	2 (9.1%)	0	.06
Overall survival, *N* (%)	19 (90.5%)	85 (93.4%)	.46
Overall (excludes TOP)			
Survival after fetal diagnosis	19/25	85/96	.11
Death or transplant after fetal diagnosis	8/25 (32%)	11/96 (11.5%)	<.01

GA: gestational age; TOP: termination of pregnancy.

*Chi-squared or Fisher's exact test for categorical variables and *t*-test or Wilcoxon's rank sum test (non-parametric variables) for continuous variables.

Fetal Diagnosis and Therapy

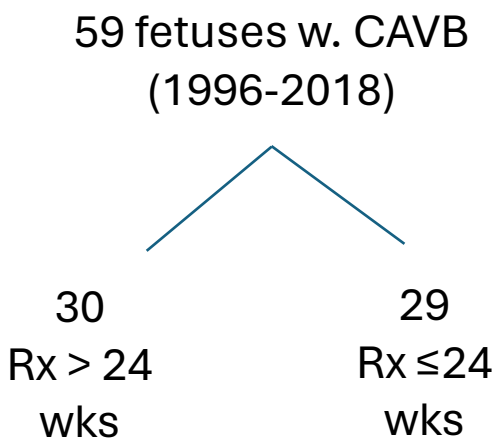
Research Article

Fetal Diagn Ther 2021;48:183–188
DOI: 10.1159/000513202

Effects of Transplacental Dexamethasone Therapy on Fetal Immune-Mediated Complete Heart Block

Mika Saito[a] Earl Silverman[b] Fraser Golding[a] Vitor Guerra[a] Linda Hiraki[b] Varsha Thakur[a] Edgar Jaeggi[a]

[a]Department of Pediatrics, Fetal Cardiac Program, Labatt Family Heart Centre, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada; [b]Division of Rheumatology, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada



- All responders
  - Received 8 mg (not 4 mg) for 2 weeks
  - Treated ≤ 24 weeks
  - Had a faster ventricular rate 80 (60-97 bpm) vs. 60 (38-92 bpm)
- 3° AVB recurred before birth (1) in first year (3) after first year (1).
- F/u ~10 years 40% paced compared to 92% non-responders

Saito M., et. al. *Fetal Diagn Ther* 2021

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

SMFM Consult Series

smfm.org

Society for Maternal-Fetal Medicine Consult Series #64: Systemic lupus erythematosus in pregnancy

Society for Maternal-Fetal Medicine (SMFM); Robert Silver, MD; Sabrina Craigo, MD; Flint Porter, MD, MPH; Sarah S. Osmundson, MD; Jeffrey A. Kuller, MD; Mary E. Norton, MD; Publications Committee

Summary:
Is there a need to perform surveillance if treatment is not effective?

Knowledge is power: regarding SMFM Consult Series #64: Systemic lupus erythematosus in pregnancy

Bettina F. Cuneo, MD; Jill P. Buyon, MD; Lisa Sammaritano, MD; Edgar Jaeggi, MD; Bhawna Arya, MD; Nicholas Behrendt, MD; Julene Carvalho, PhD; Jennifer Cohen, MD; Kristopher Cumbermack, MD; Greggory DeVore, MD; Tam Doan, MD; Mary T. Donofrio, MD; Lindsay Freud, MD; Henry L. Galan, MD; Melanie R. F. Groper, MD; Caitlin Haxel, MD; Lisa K. Hornberger, MD; Lisa W. Howley, MD; Peter Izmirly, MD; Stacy S. Killen, MD; Michelle Kaplinski, MD; Anita Krishnan, MD; Stephanie Lavasseur, MD; Christopher Lindblade, MD; Jyothi Matta, MD; Majd Makhoul, MD; Jena Miller, MD; Shaine Morris, MD; Erin Paul, MD; Erin Perrone, MD; Colin Phoon, MD; Nelangi Pinto, MD; Jack Rychik, MD; Gary Satou, MD; Amit Saxena, MD; Mark Sklansky, MD; James Stranic, MD; Janette F. Strasburger, MD; Shubhika Srivastava, MD; Sharda Srinivasan, MD; Theresa Tacy, MD; Wayne Tworetzky, MD; Orhan Uzun, MD; Simcha Yagel, MD; Michael V. Zaretsky, MD; Anita J. Moon-Grady, MD

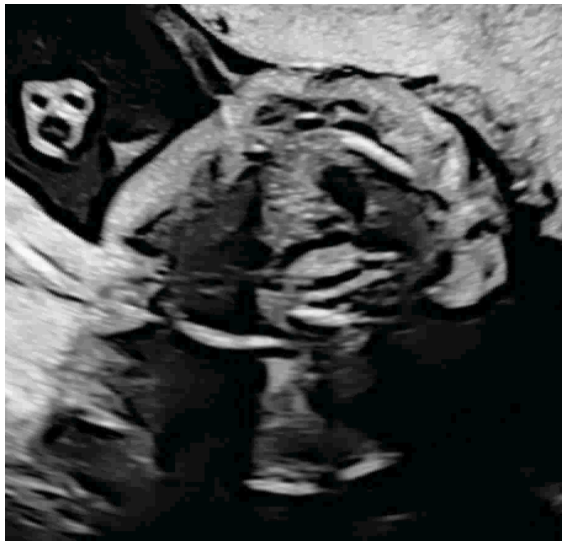
"…A consensus statement on a topic with no consensus requires the equipoise of rheumatologists, pediatric cardiologists, and MFM specialists with experience and expertise in caring for these patients. Presently, the scientific rigor of the data is insufficient for a consensus statement, rendering the current statement premature at best.

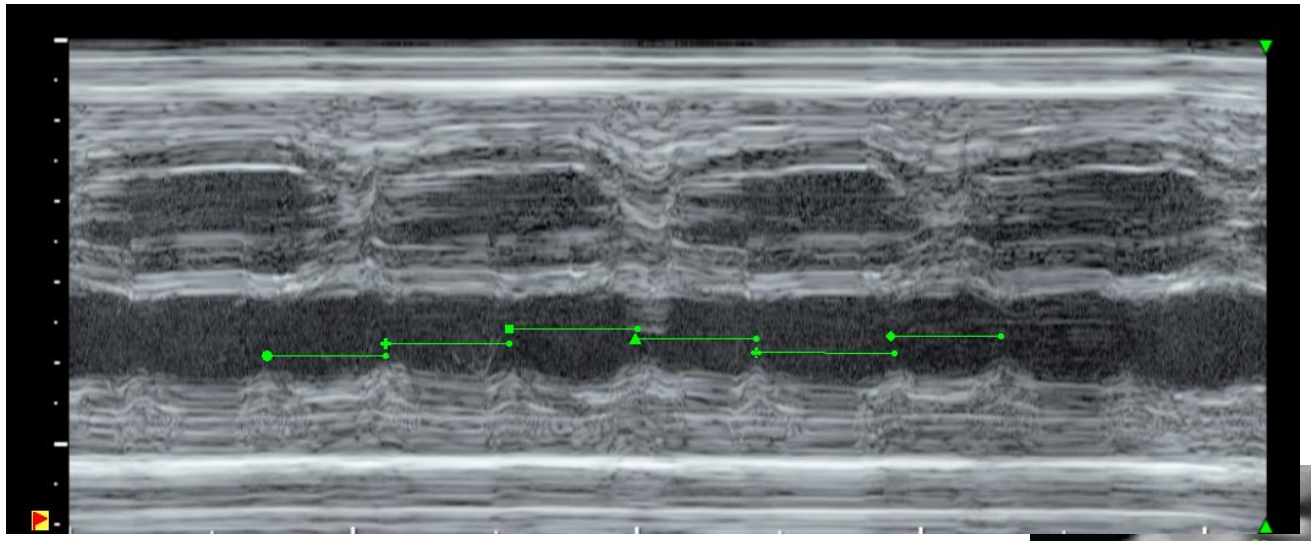
Knowledge should be considered power until unambiguously proven otherwise."

A Recent Experience

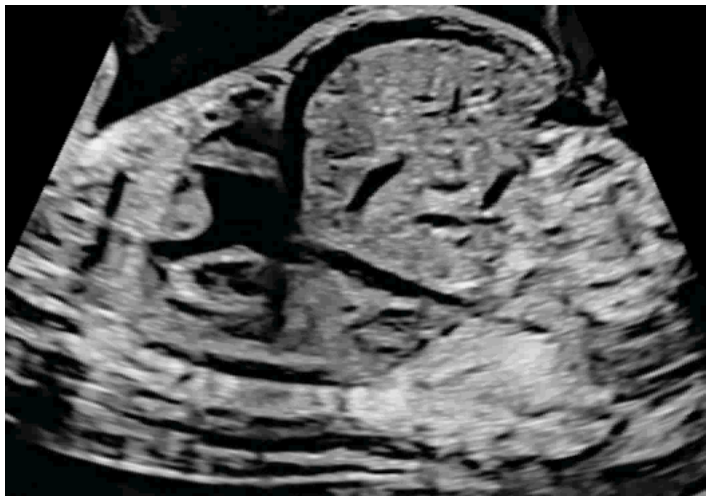
- 24 y.o. G2P0010 presented for 2nd opinion fetal echo at 23 5/7 weeks' gestation
- Pregnancy w. anti-Ro/SSA antibodies and Sjogren's syndrome (diagnosed at 17 years of age)on 200 mg hydroxychloroquine q day.
- Normal screening fetal echocardiogram at 18 weeks' gestation.
- Mother using FHRM since 18 wks: FHRM normal 2 days prior to her 20-wk echo, but she did not do FHRM day before echo.
- 20-week echo demonstrated fetal 3°fetal AVB. No treatment offered
- Re-evaluation at 22 weeks’ gestation demonstrated ascites; parents were told that their baby unlikely to survive. No treatment offered

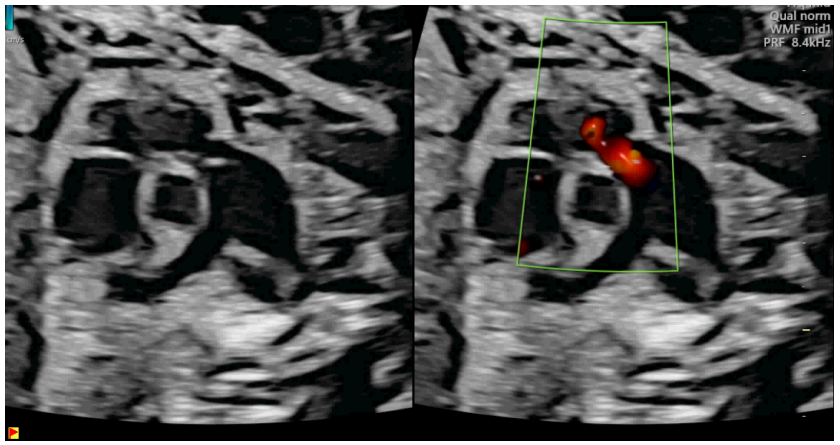
2nd Option Fetal Echo (23 5/7th weeks)

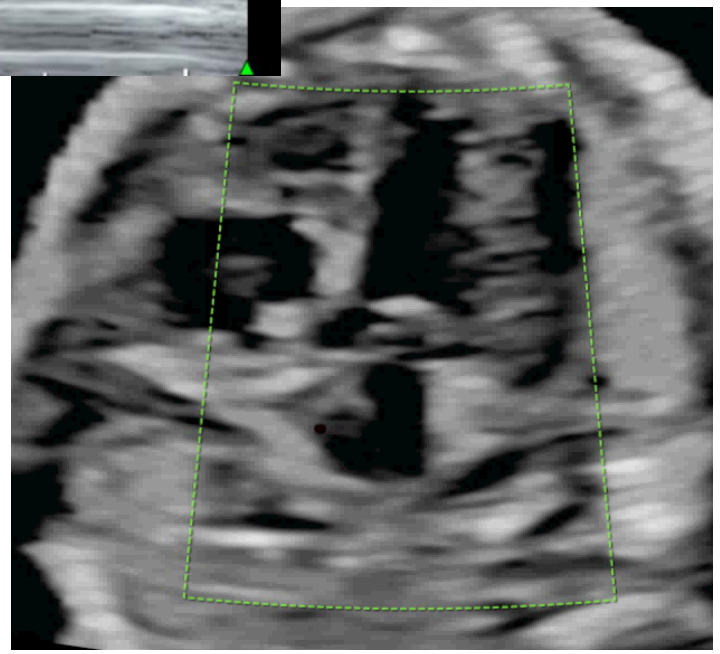


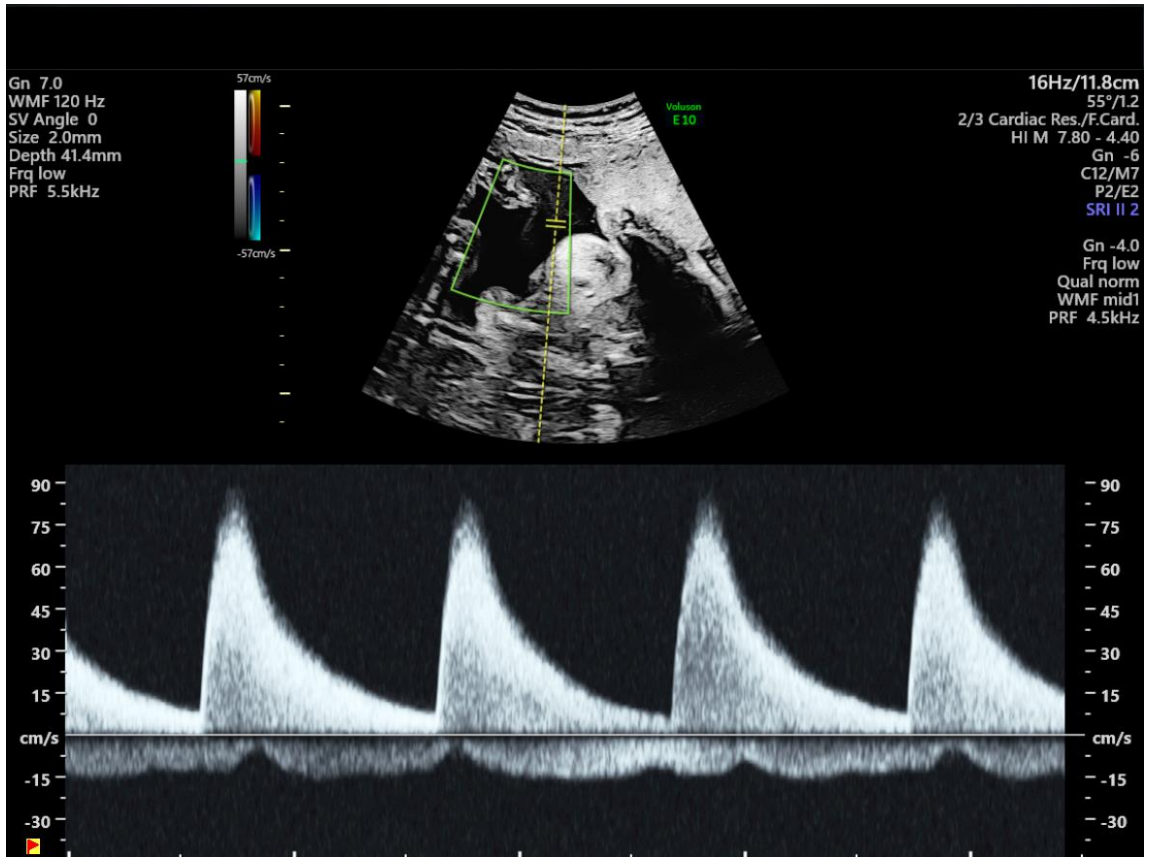


58 bpm
150 bpm





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-57cm/s
Voluson
E10
16Hz/11.8cm
55°/1.2
2/3 Cardiac Res./F.Card.
HI M 7.80 - 4.40
Gn -6
C12/M7
P2/E2
SRI II 2
Gn -4.0
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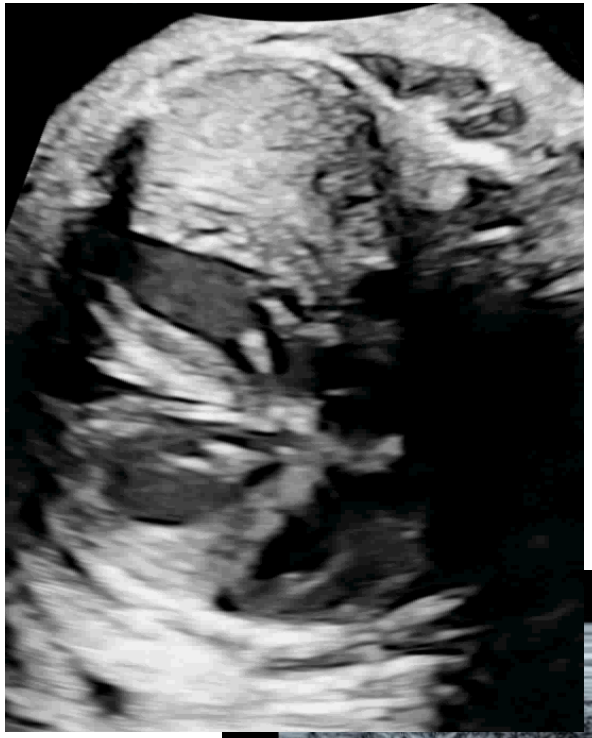

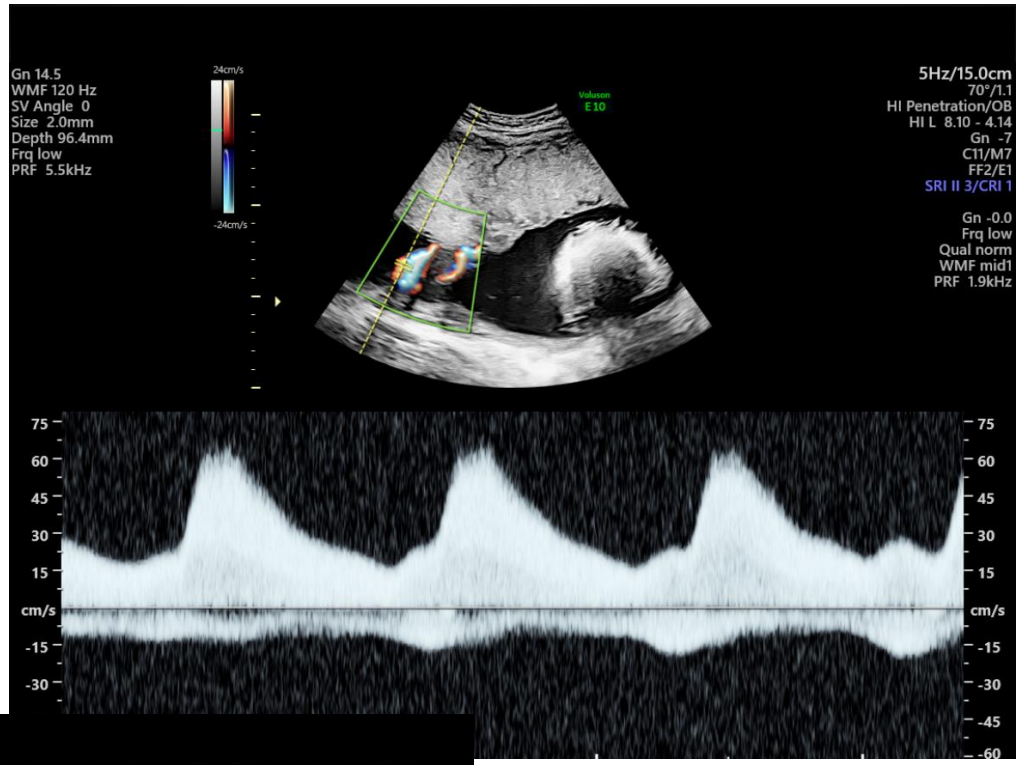
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HI Penetration/OB
HI L 8.10 - 4.14
Gn -7
C11/M7
FF2/E1
SRI II 3/CRI 1
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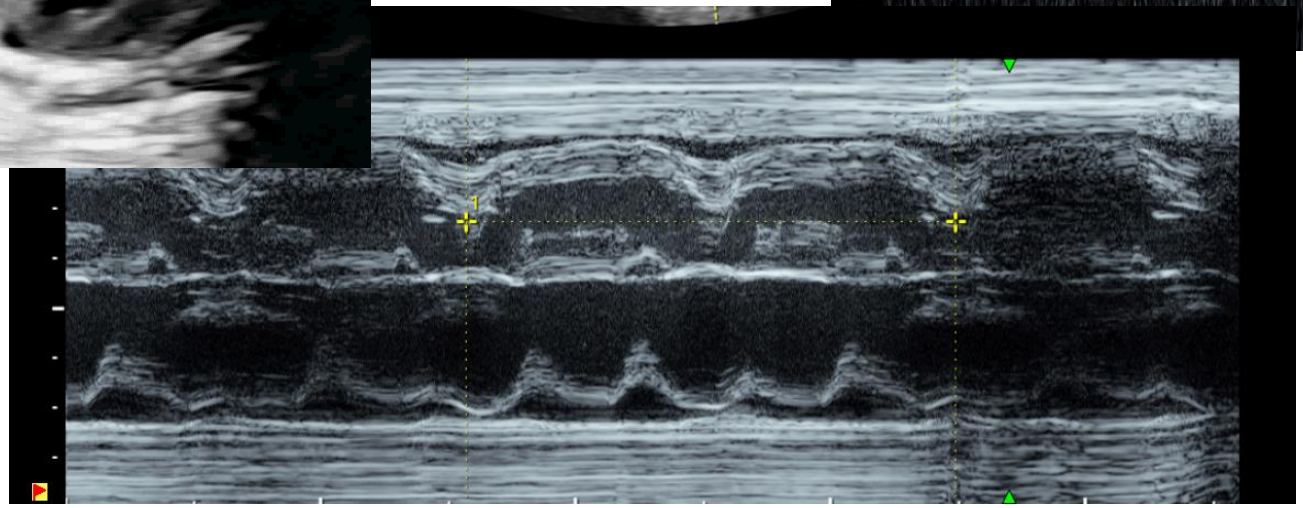


Postnatal course

- Delivered by c-section at 33 3/7 weeks' GA in the setting of PPROM
- Postnatal EKG confirmed 3rd-degree AV block with junctional escape 58-63 bpm; hemodynamically well
- Moderate to severe pulmonary valve stenosis necessitated balloon pulmonary valvuloplasty at 33 days of age
- Pacemaker (dual chamber system) placed at 44 days of age in the setting of feeding and respiratory difficulties
- Now 50 days of age in the NICU recovering from pacemaker placement

Whatever We Go From Here, We Go Together

“The source has manipulated the image” but in good faith!

This picture was photoshopped….

Presentation	STOP BLOQ (n=9)	Clinical (n=62)
Known SSA+	100%	25%
3°AVB	22%	89%
1° or 2°AVB	70%	7%
Extra nodal only	0	5%
Treatment	100%	74% (43/58)*
Outcomes		
Fetal or NND demise	11%(1)	13%*
In Utero	0%	2% (1)
Liveborn	100%	85% (36)
Not paced	50%	33%%
Paced	4/8 (50%)	67%
as neonate (0-1 mo)	3/8 (38%)	89%

*58 excludes VIP and refused Rx

Clinical AVB vs. STOP BLOQ AVB at 13/24 STOP BLOQ sites (9.20-5.23)

Compared to STOP BLOQ

- 75% of mothers did not know they had anti-Ro/SSA antibodies
- Majority presented in 3° AVB
- Extra nodal pathology present
- More were paced and more paced as neonates
- Similar fetal/neonatal loss

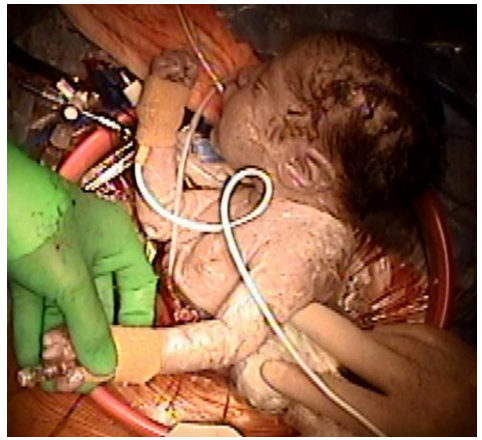
Thanks to those who provided clinical data:
Lisa Hornberger, Lisa Howley, Erin Paul, Stacy Killen, Chris Lindblade, Anita Moon-Grady, Gary Satou, Michelle Kaplinski, Tam Doan, Bhawna Arya, Whitnee Hogan. Mary Donofrio and Anita Krishnan

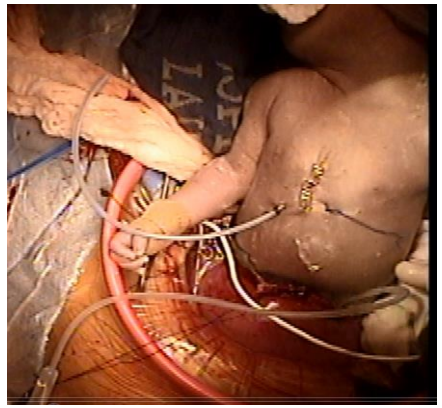
Even if its Bad..There are still options

EXIT to Pacing

Cuneo BF et. al. *Fetal Dx and Ther* 2017

- CAVB at 18 6/7 weeks 2 days after normal rhythm
- FHR 51 bpm at 26 weeks, terbutaline added
- At 36 weeks:
  - FHR 43 bpm
  - CT ratio 74%
  - New pericardial effusion
- EXIT
- Temporary V-lead; paced at 70 bpm
- Delivered 55 minutes after exteriorized
- Permanent epicardial pacemaker 2 days later



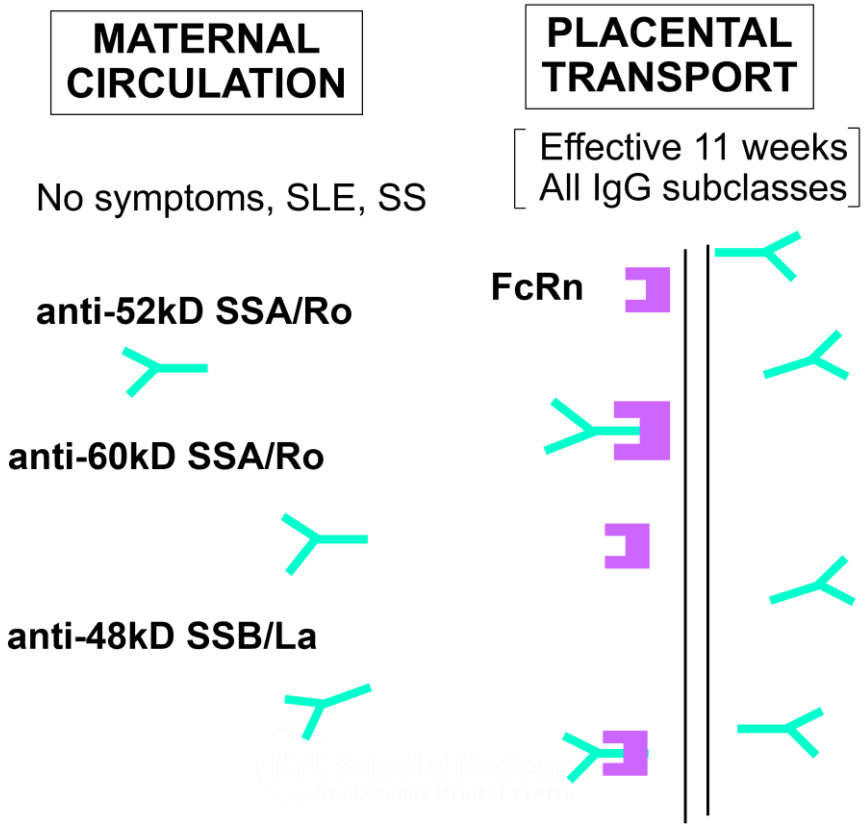


Delayed cord clamping and EPI

- Team effort: neonatology team, peds cardiology, echo tech, MFM and c-section team
- Fetal cocktail (Epi and atropine) given IM after uterine incision
- Exteriorize baby, neo puts in IV
- Code dose epi followed by epi infusion
- Echo to check heart rate and function
- Umbilical cord is clamped and baby delivered, brought to warmer
- Continuous pulse ox and echo
- UV line placed and epi infusion moved from peripheral IV to UV

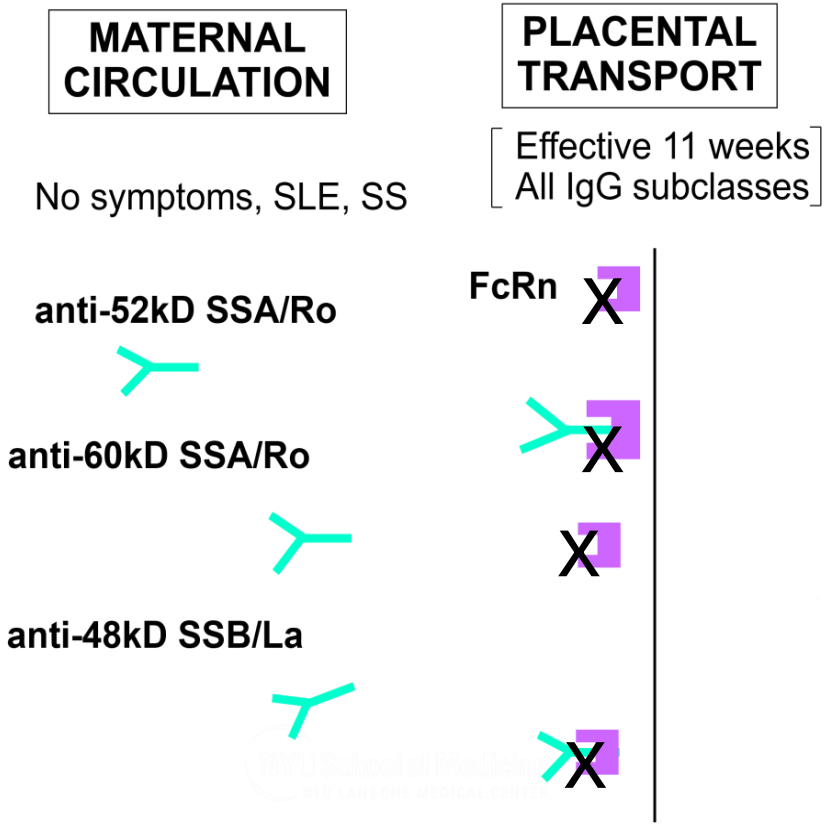
Cuneo BF et. al. *Fetal Dx and Ther* 2017

What next? FcRn –Blocking Agents to Prevent Placental Transport of Anti-SSA/Ro and Reduce Maternal Levels

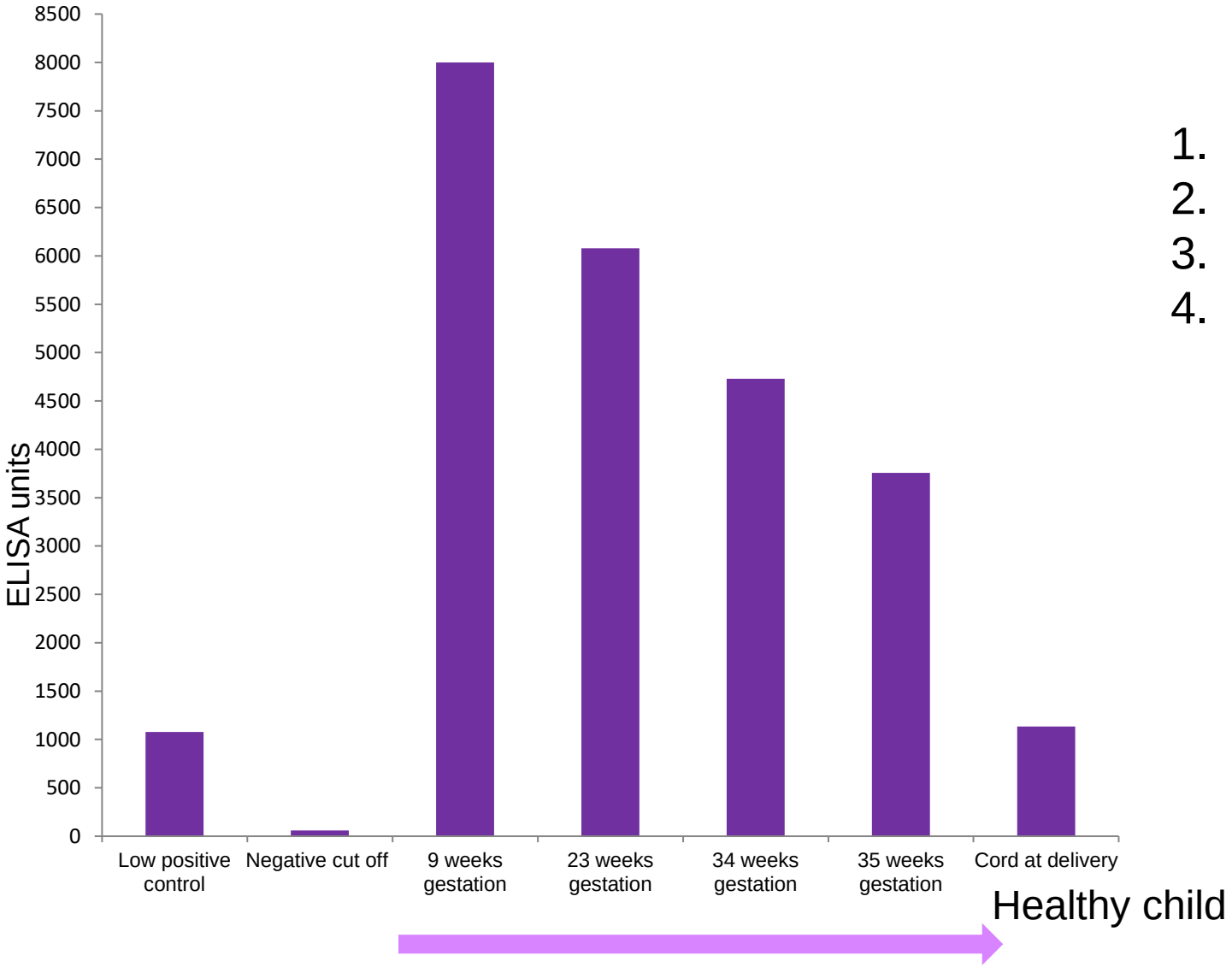


Block FcRn with monoclonal ab

(nipocalimab, rozanolixamab)



Why FcRn Blockade makes sense ……



1. " High Titer" Anti SSA/Ro is required for Dz
2. Defined vulnerable period 18-26 wks
3. Although a proxy, IVIG lowers maternal titers
4. Precedent set: hemolytic disease fetus and newborn UNITY Trial open label Nipocalimab

7/13 (54%) pregnancies with previous early HDFN receiving Nipocalimab achieved a live birth > 32 wks without intrauterine transfusions compared to historic 10%

Moise, K, et al. Safety and Efficacy of Nipocalimab in Pregnant Individuals at High Risk for Early-Onset Severe Hemolytic Disease of the Fetus and Newborn: Results from the Phase 2 UNITY Study. The Fetal Medicine Foundation World Congress, June 25-29. 2023

Thanks to our Site PIs from 25 STOP BLOQ Collaborating Centers

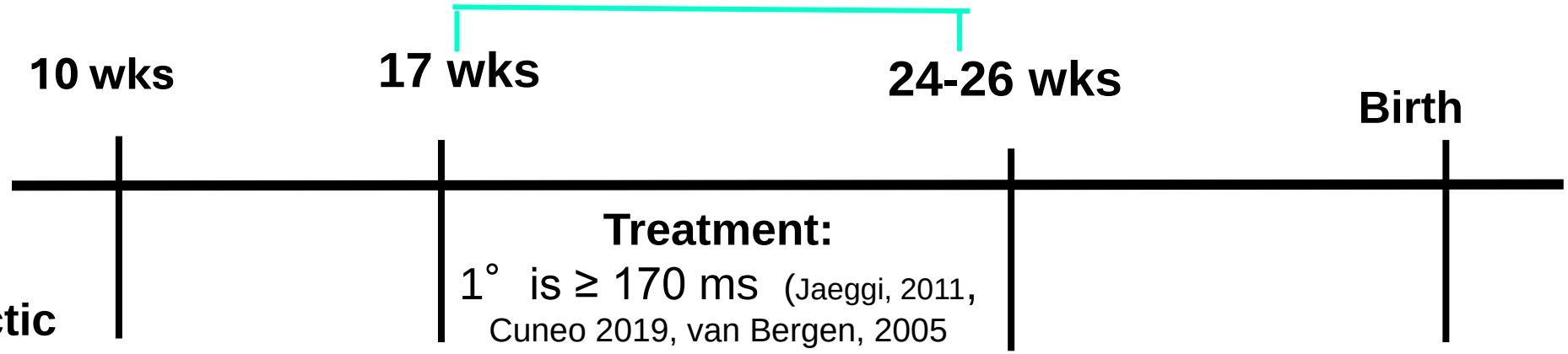
Lisa Howley
Tam Doan and Shreya Sheth
Whitnee Hogan
Gary Joffe
Chris Lindblade
Lisa Hornberger
Gary Satou
Michelle Kaplinski and Terry Taci
Anita Moon-Grady
Whitnee Hogan and Ware Branch
Colin Phoon
Lisa Hoernberger and Angela McBrien
Stephanie Levasseur
Erin Paul and Miwa Geiger
Mary Donofrio and Anita Krishan
Caitlin Haxel
Stacy Killen
A. Abuhamad and E Sinkovskya
Josh Copel and Katherine Kolhari
Sonal Owens
Jyothi Matta
Kristopher Cumbermack
James Stranic
Rukmini Komarlu
Sonal Owens

Cuneo1@arizona.edu

Where to Go From Here

Weekly or biweekly fetal echocardiograms, 3x/day FHRM

Pregnant subject with high titer anti-Ro abs



Treatment:

1° is ≥ 170 ms (Jaeggi, 2011, Cuneo 2019, van Bergen, 2005

Prophylactic Therapy:

Hydroxychloroquine

Vit D to forestall fibrosis

2° 8 mg dex x10-14 days (then taper)
+70g IVIG (once? Q4 wks?)

4 mg-2 mg → Prednisone?

IVIG q 3-4 weeks → IVIG?

3° (?) irreversible but Rx can improve outcome →

Knowledge is power: regarding SMFM Consult Series #64: Systemic lupus erythematosus in pregnancy

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"Lastly, we agree that opinions vary on optimal surveillance and treatment for this disease. But a consensus statement on a topic with no consensus requires the equipoise of rheumatologists, pediatric cardiologists, and MFM specialists with experience and expertise in caring for these patients. Presently, the scientific rigor of the data is insufficient for a consensus statement, rendering the current statement premature at best.

It is anticipated that the medical community and our patients would be better served by waiting for the outcomes of 2 studies hat will lead to the necessary evidence-based guidelines. Although consensus statements are not meant to be rigid directives for all patients, they do serve to guide clinical practice and consequently, the current statement may deter surveillance and treatment that has the potential to be lifesaving.

Knowledge should be considered power until unambiguously proven otherwise."

Cost Comparisons: Proposed and Current Practice

Current practice

6.7 million pregnant women/yr (2006)

0.87% Ro+ 58,290 women/year

Weekly (Biweekly) echoes $2000 x 10 ($2000 x 5)

$116,580,000,000 ($582,900,000) cost for screening

10-fold difference

Proposed study

High titer Ro testing ($50) in all $2,914,500

62% of Ro + High titer 36,140 women/year

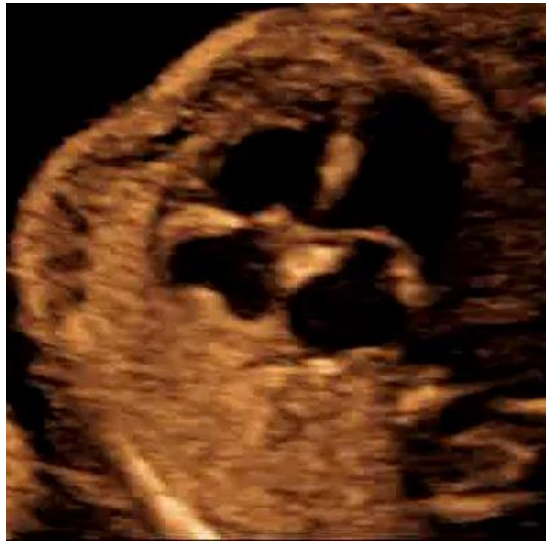
2 fetal echoes $2000 x 2 on high titer $144,560,000

FHRM ($40) $1,445,600

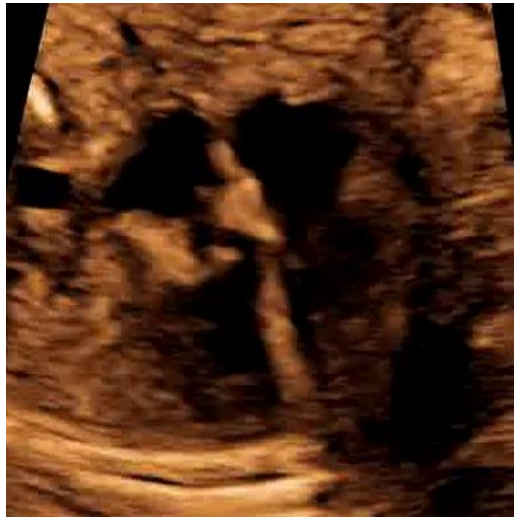
$**146,005,600** cost for screening

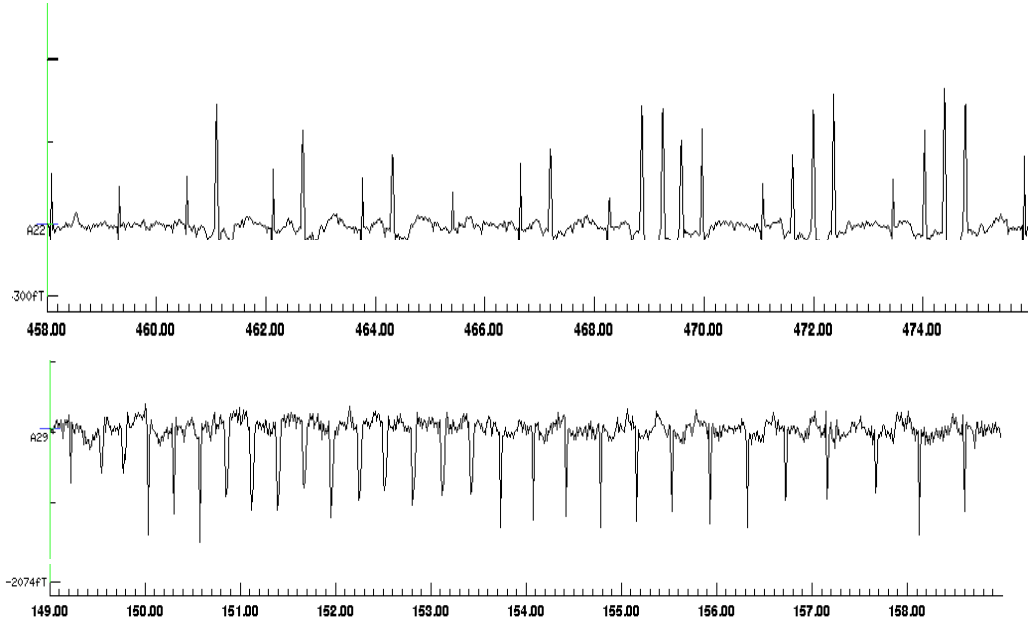
EFE and other rhythms (19 weeks)

19-weeks

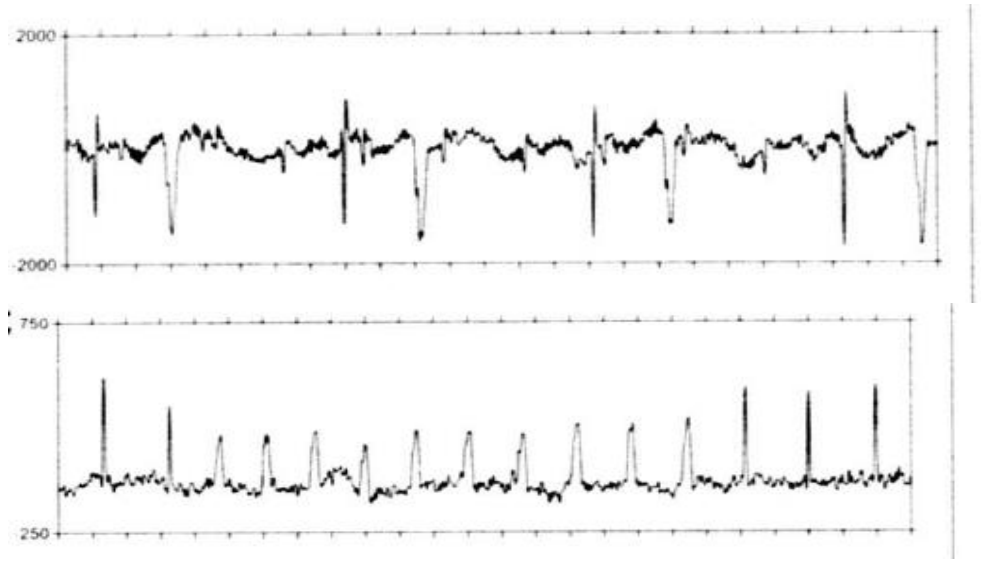


20-weeks





JET: 18% w. AVB

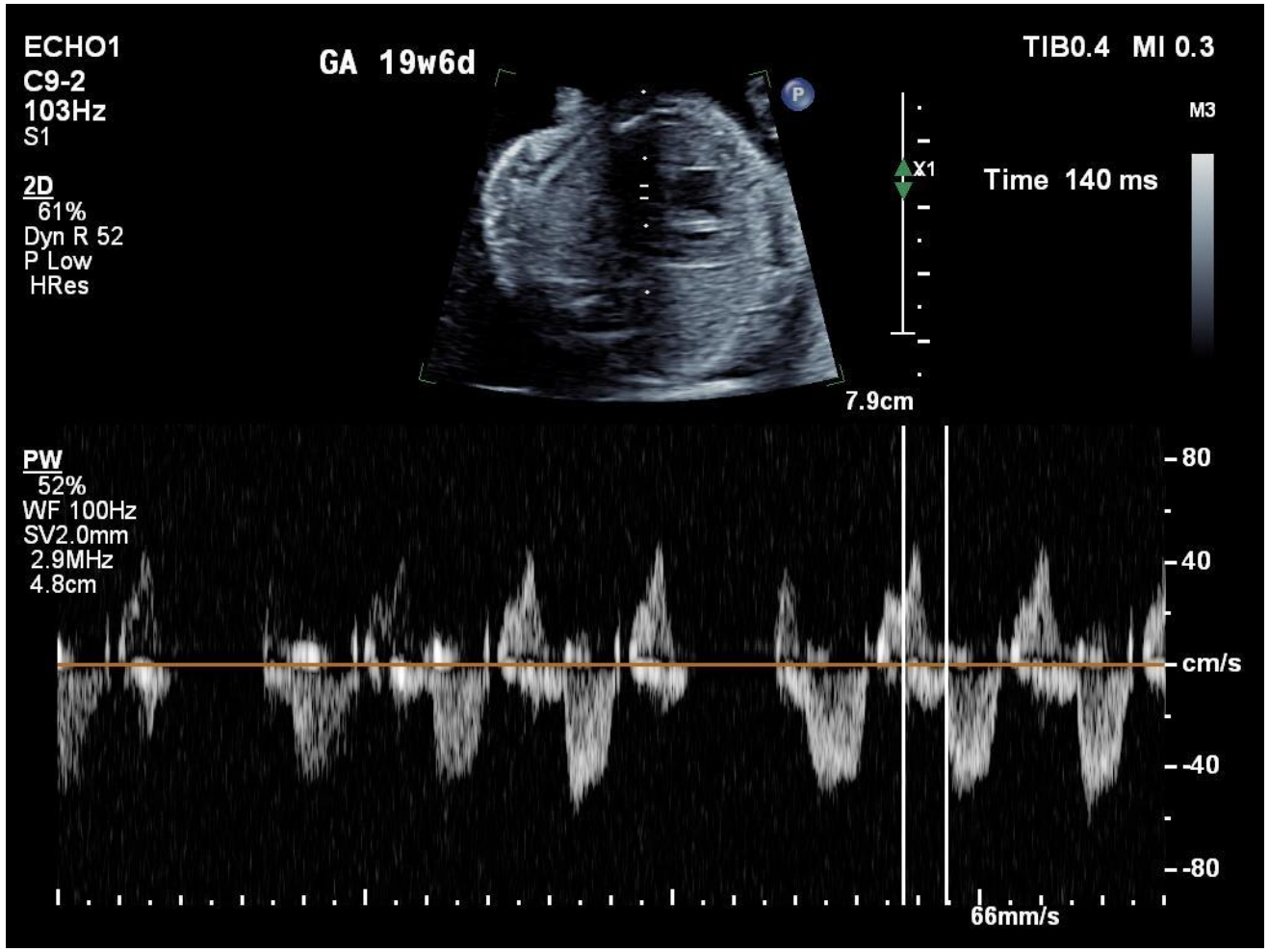


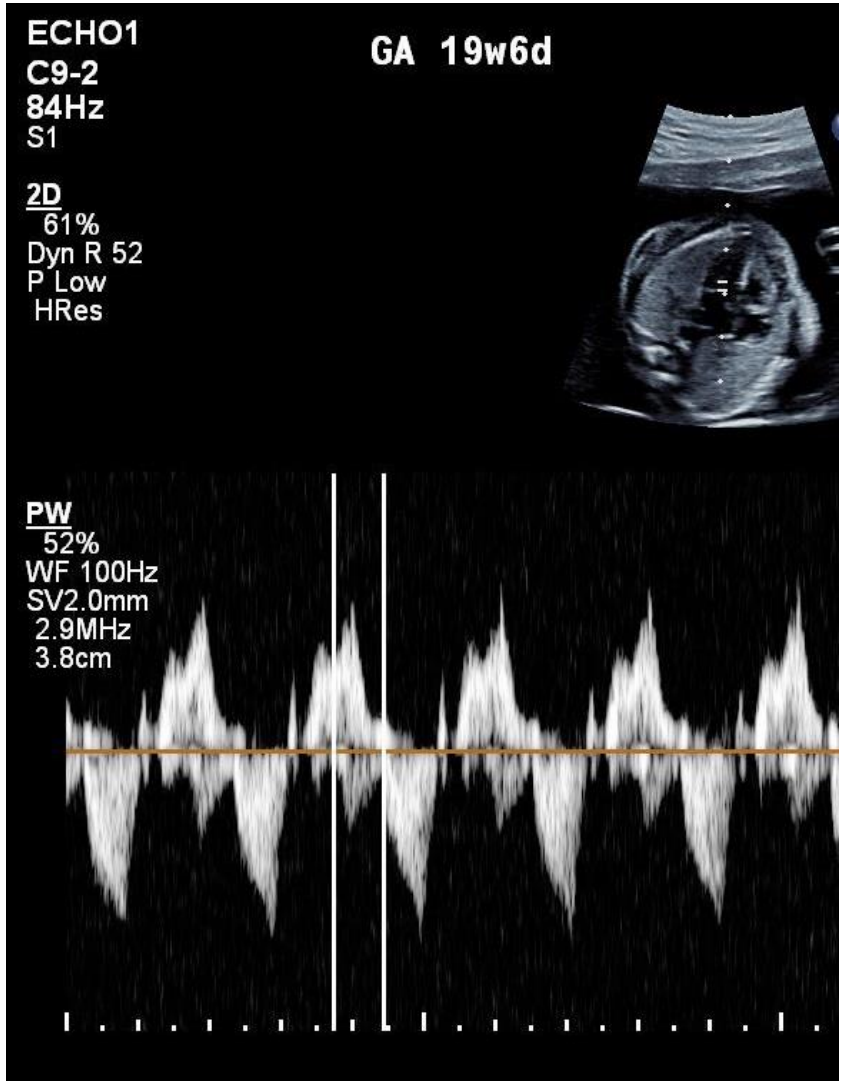
PVCs: 74% w. AVB

Non-sustained V tach: 27% w. AVB

Zhao H. et. al. Circulation 2008

6 Days After Treatment

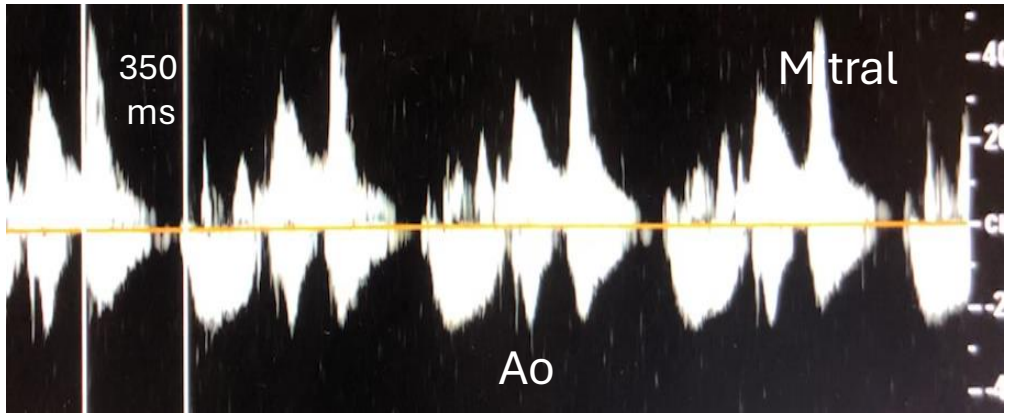




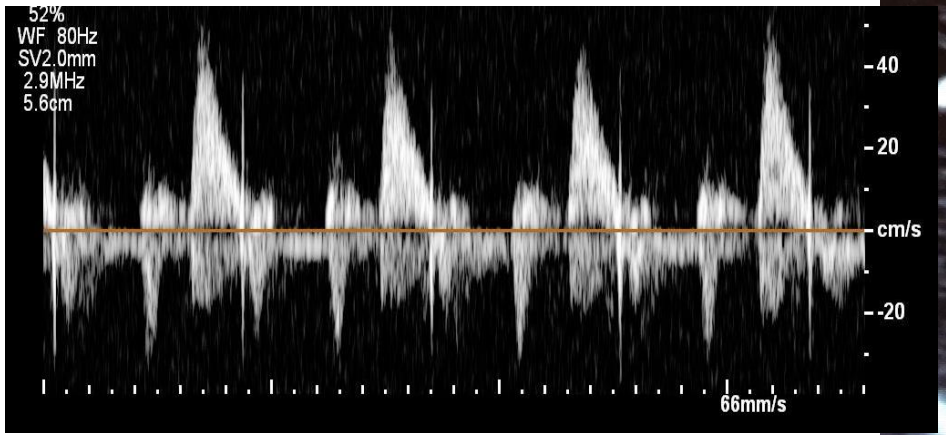
- G2P1 Anti-Ro Antibody positive mother
- Previously affected child with CAVB alive, paced
- 300 mg Plaquenil/day since before 2nd pregnancy

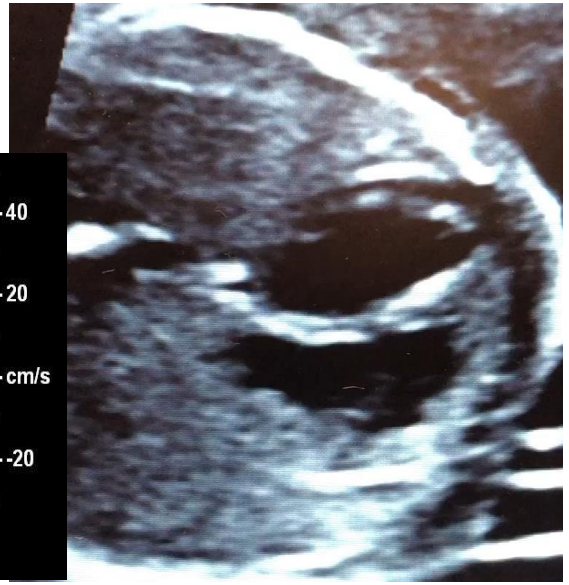
FHRM at 19W 0D 7:00 am 10:30 am

Echo, 2 hrs later



Echo, 4 hrs later





SID	HCQ	Titers	Prior NLE	GA ab FHRM	Nl FHRM-ab FHRM	Ab FHRM to echo	Rhythm
1	400	52 17,501 60 44,352	AVB	18 2/7	7 hrs (but not recognized)	72 hrs	3^0 AVB
2	400	52 97,414 60 35,556	No	20 2/7	12 hrs	4 hrs 30 min	2^0 AVB
3	200	52 13,522 60 19,491	No	21 4/7	12 hrs (but not recognized)	17 hrs	3^0 AVB
4	300	52 11,527 60 30,404	AVB	19 0/7	6 hrs	2 hrs	2 AVB
5	200	52 5,785 60 3,627	No	21 4/7	8 hrs	1 hr 20 min	2^0 AVB
6	0	52 3,262 60 20,181	Rash	19 6/7	12 hrs	45 min	2^0 AVB
7	0	52 103,348 60 67,365	No	18 4/7	11.2 hr	1 hr 35 min	2^0 AVB
8	200+ B	52 7,695 60 15,435	No	22 2/7	11 hrs	2 hrs	2^0 AVB
9	200	52 13,814 60 6,701	No	22 6/7	12 hrs	2 hrs	2^0 AVB
10	400+A	52 11720 60 61042	DCM JET	18 4/7	*	*	3^0 AVB

Buyon JP et. al. *A and R,* in press 2023

DCM = dilated cardiomyopathy; HCQ = hydroxychloroquine; JET – junctional ectopic tachycardia; B = belimumab; A = azothiaprin; AVB = AV block