Evaluation and Treatment of Fetal Bradycardia

Children's Mercy Fetal Cardiology Education Series: February 8, 2022

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Disclosures

- No relevant disclosures

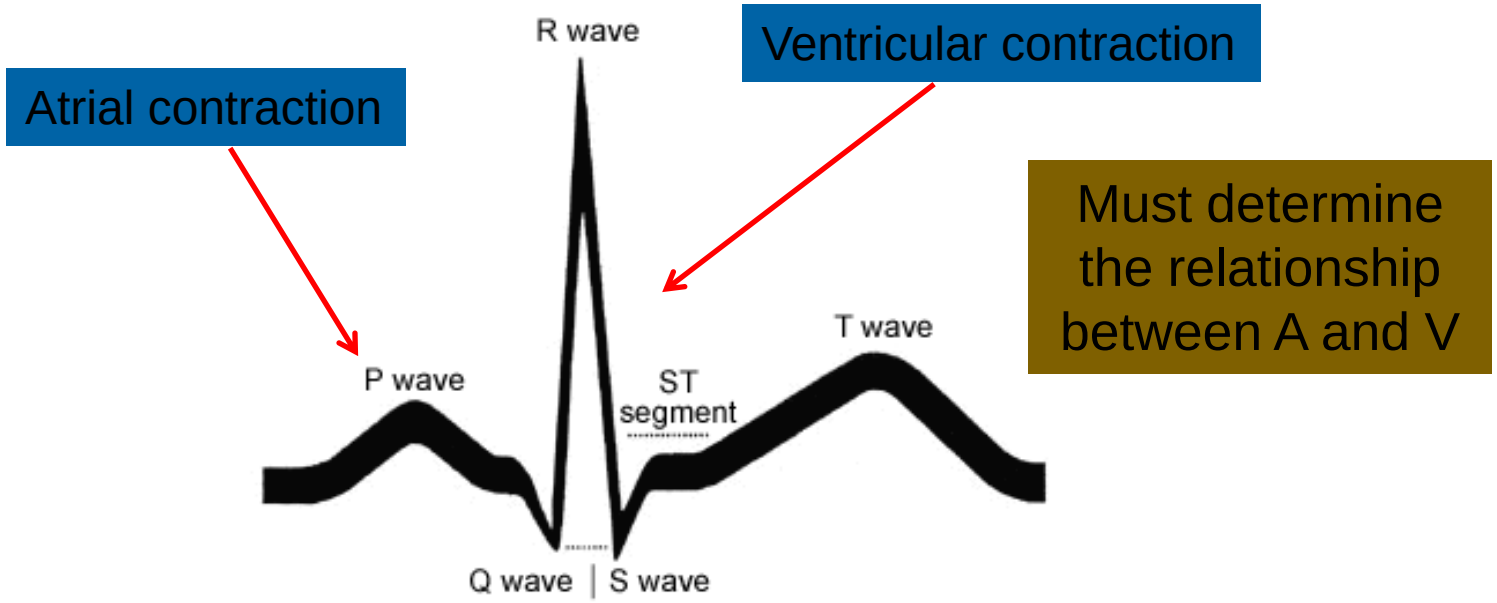
Overview

- Fetal rhythm background and diagnosis review
- Fetal bradycardia differential diagnosis
  - Sinus bradycardia
  - Blocked atrial bigeminy
  - Long QT Syndrome
  - Atrioventricular (AV) Block
- Prognosis
- Surveillance
- Treatment and Delivery

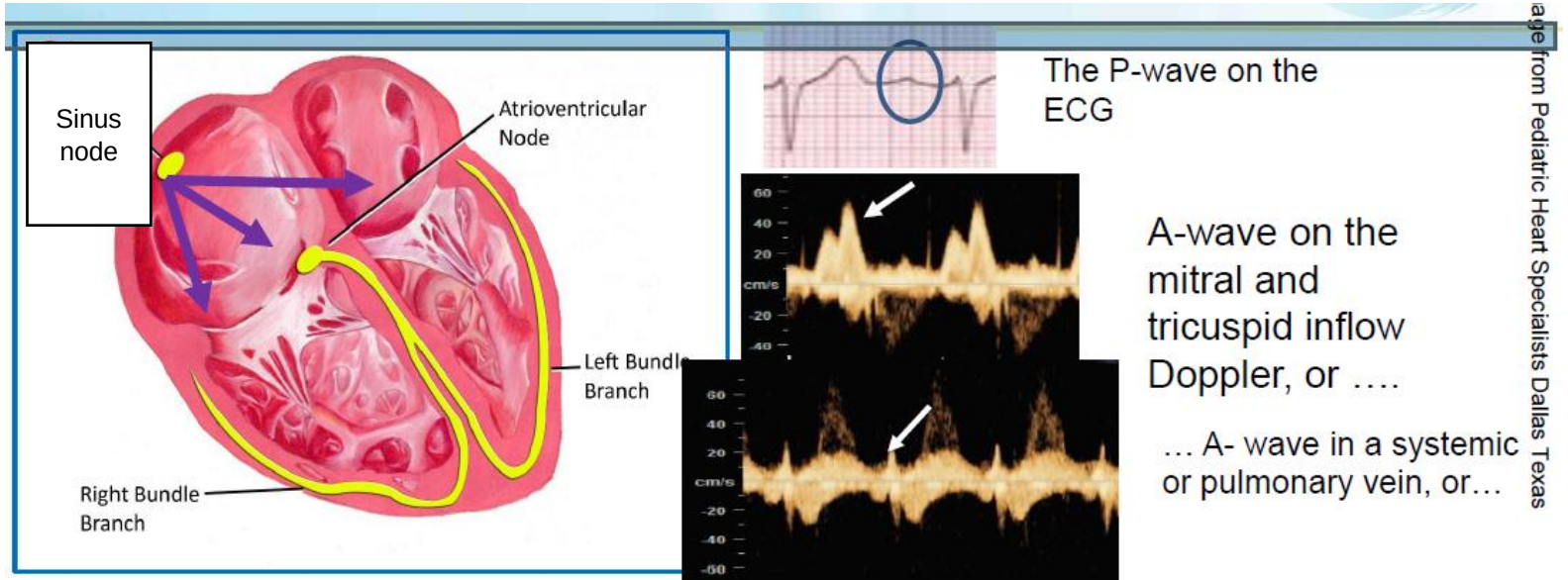
Fetal Rhythm Review

- Heart begins to beat at 22 days of gestation
- By 6 weeks post-conception, AV synchrony can be demonstrated
- Normal fetal heart rate is age-dependent
  - 6 weeks – 100 bpm
  - 9 weeks – 170 bpm
  - 14 weeks – 150 bpm
  - 20 weeks to term – 140 bpm
- Beat-to-beat variation 5-15 bpm
- Generally, 120-160bpm considered "normal"
- Intrapartum definition of bradycardia is <110bpm

Fetal Echo Arrhythmia Diagnosis Review



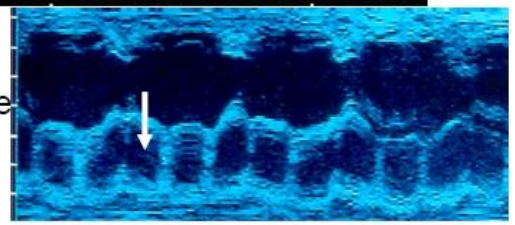
The normal cardiac conduction system



The P-wave on the ECG

A-wave on the mitral and tricuspid inflow Doppler, or ….

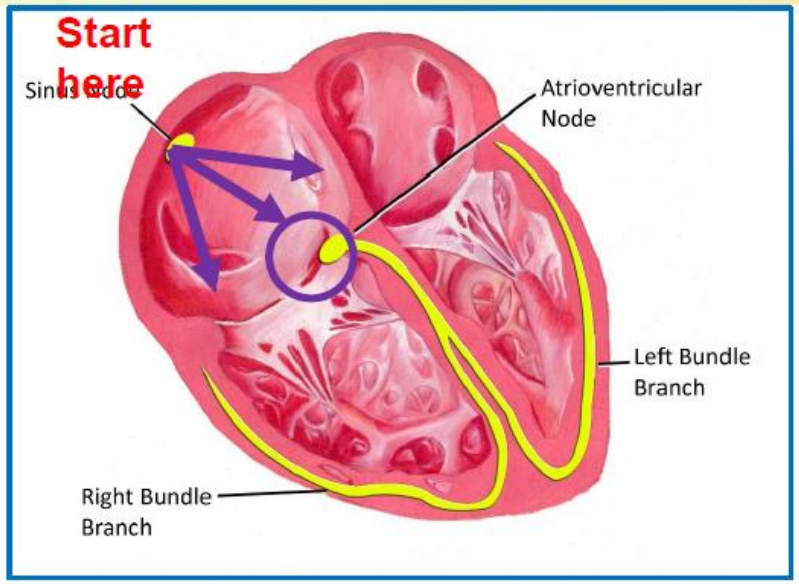
… A- wave in a systemic or pulmonary vein, or…



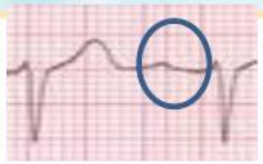
Atrial contractions on simultaneous atria/ventricular m-mode

- The pacemaker region of the heart is the sinus node located in the right atrium
- It fires off and the impulse spread across the right and left atria and they contract
- Atrial contractions correspond to:

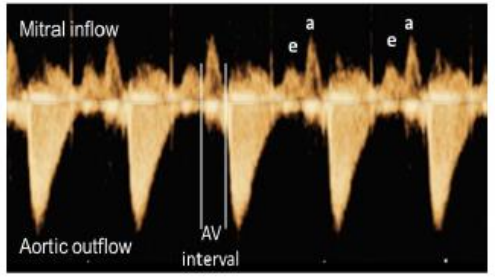
The normal cardiac conduction system



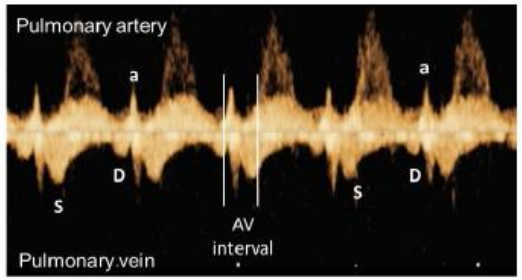
- The impulses are slowed at the AV node.
- This slowing corresponds to the PR or AV or mechanical PR interval
- If the AV node is abnormal, impulses are delayed (1° AV block), intermittently or not at all conducted (2° and 3° AV block



The PR interval on ECG



The AV interval… on mitral inflow and aortic outflow….

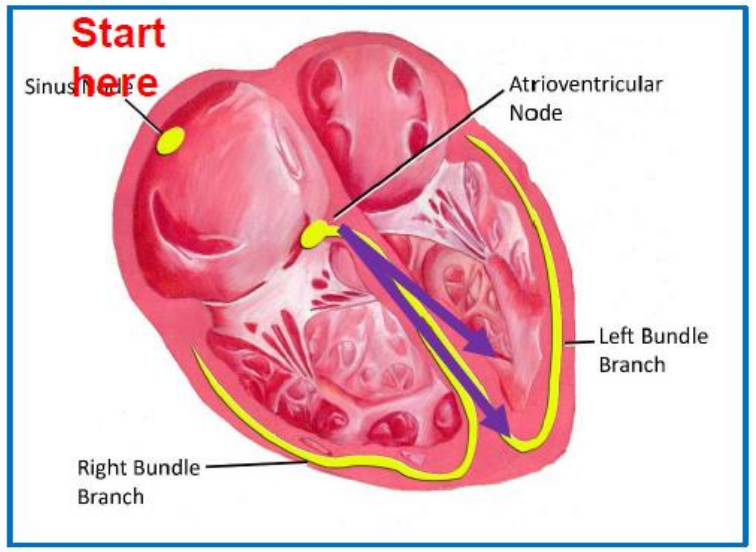


…or any systemic vein and artery

Image from Pediatric Heart Spe
Dallas Texas

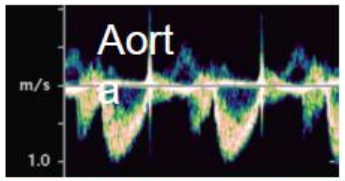
The normal cardiac conduction system

The normal cardiac conduction system

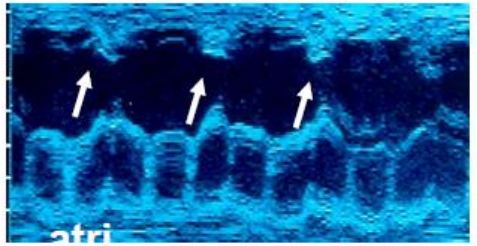


- The impulses are conducted down the HIS purkinjie system and the bundle branches.

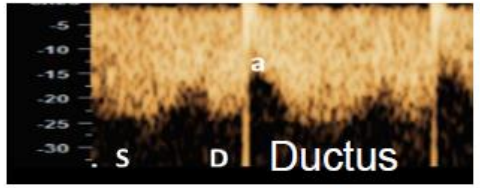
The QRS on ECG



Great vessel pulsed Doppler



Ventricular contractions on simultaneous atrial and ventricular m-mode



S-wave of systemic or pulmonary vein

Image from Pediatric Heart Specialists Dallas Texas

Fetal Bradycardia: Background

- FHR decreases during gestation from 175bpm at 19 weeks to 138 bpm at 40 weeks
- Definition: HR >3rd percentile for gestational age
- Incidence of fetal arrhythmias in general is 1-2% of all pregnancies and account for 10-20% of referrals to fetal cardiologists
- Fetal Bradycardia is rare, only ~5% of all arrhythmia referrals
- Congenital complete heart block (CCHB) can be fatal in utero

Fetal Bradycardias by Type

- Sinus Bradycardia
- Blocked atrial bigeminy
- Long QT Syndrome
- AV block
  - 1st degree Heart block
  - 2nd degree heart block
    - Mobitz Type I
    - Mobitz Type II
  - **Complete Heart block**

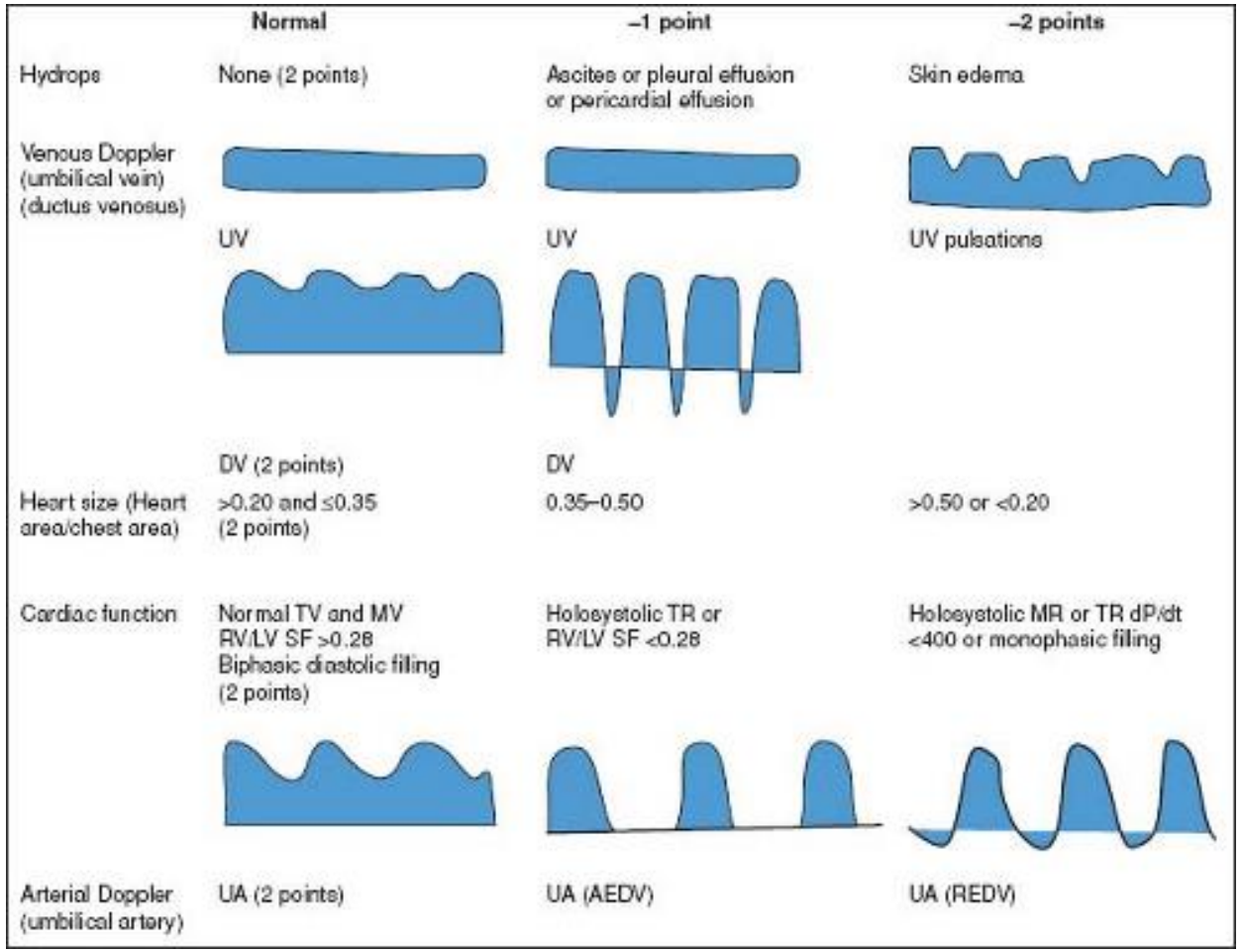
Fetal Echo Bradycardia Evaluation

- Assess fetal well-being
- Assess anatomy
- Diagnose rhythm

Fetal Arrhythmia Evaluation: Fetal Well Being

- Assess Anatomy and Degree of Heart Failure

Cardiovascular Profile Score



Fetal Bradycardia and Associated Lesions

	Structural defect	Normal Structure
'Sinus"	• Heterotaxy • (ectopic multiple or absent sinus node)	• Chromosome/CNS abnormality • IUGR/Maternal medication/Distress • LQTS • Familial SB/"Sinus node "dysfunctior • Anti-SSA antibodies
Junctional		• Anti-SSA antibodies
AV Block	• L-transposition • Left atrial isomerism • Situs solitus and AV canal defect	• LQTS • Anti-SSA antibodies
Blocked atrial bigeminy	• Any defect	• No association

Fetal Bradycardia Rhythm Diagnosis

- Step 1: Determine Rate and Regularity
- Step 2: Determine Number of As and Vs and AV relationship
- Step 3: Measure Mechanical PR interval

Fetal Bradycardias: Regular or Irregular?

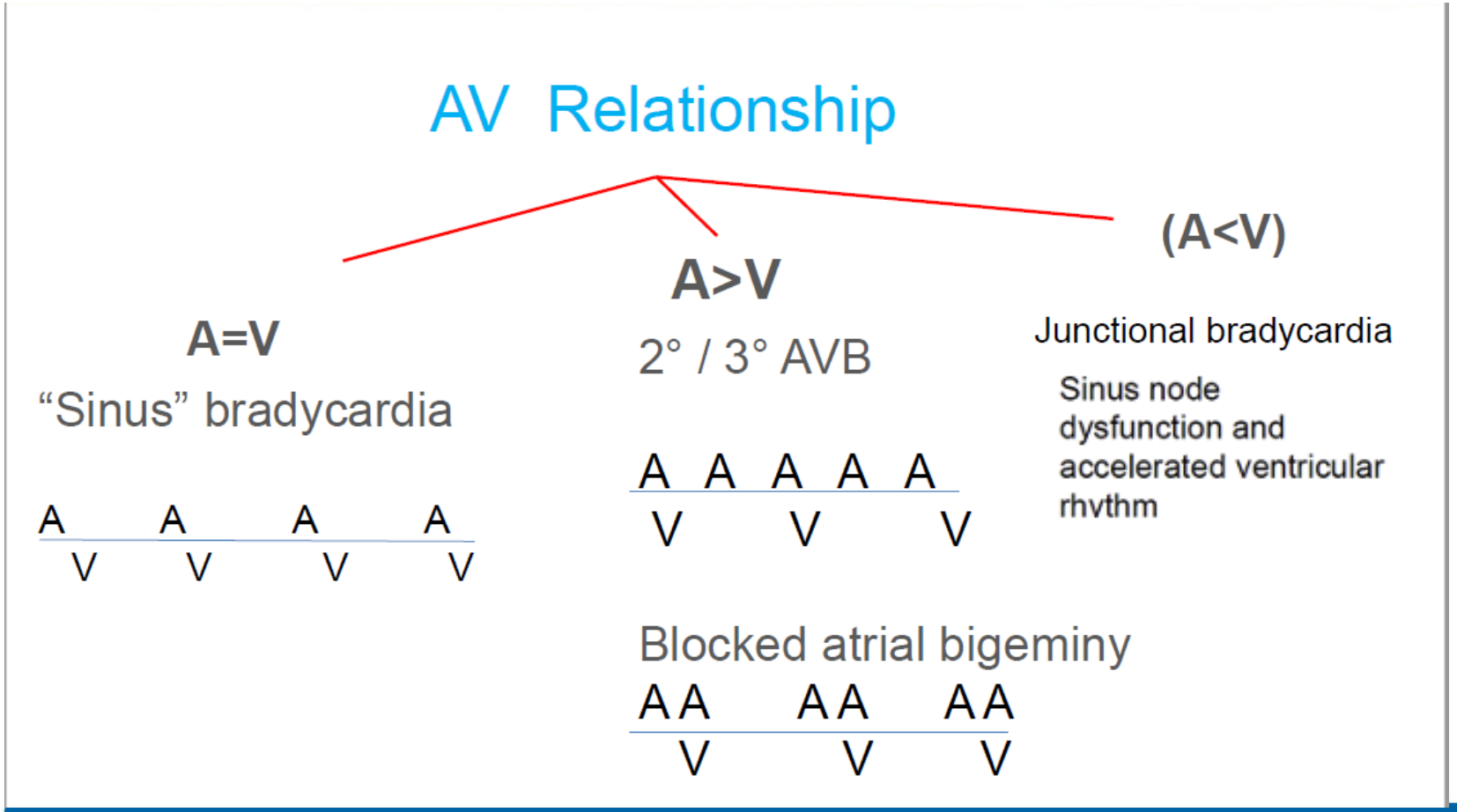
Regular:

- Sinus Bradycardia
- Complete Heart block
- Long QT Syndrome
- Blocked atrial bigeminy
- 2:1 Mobitz Type II heart block

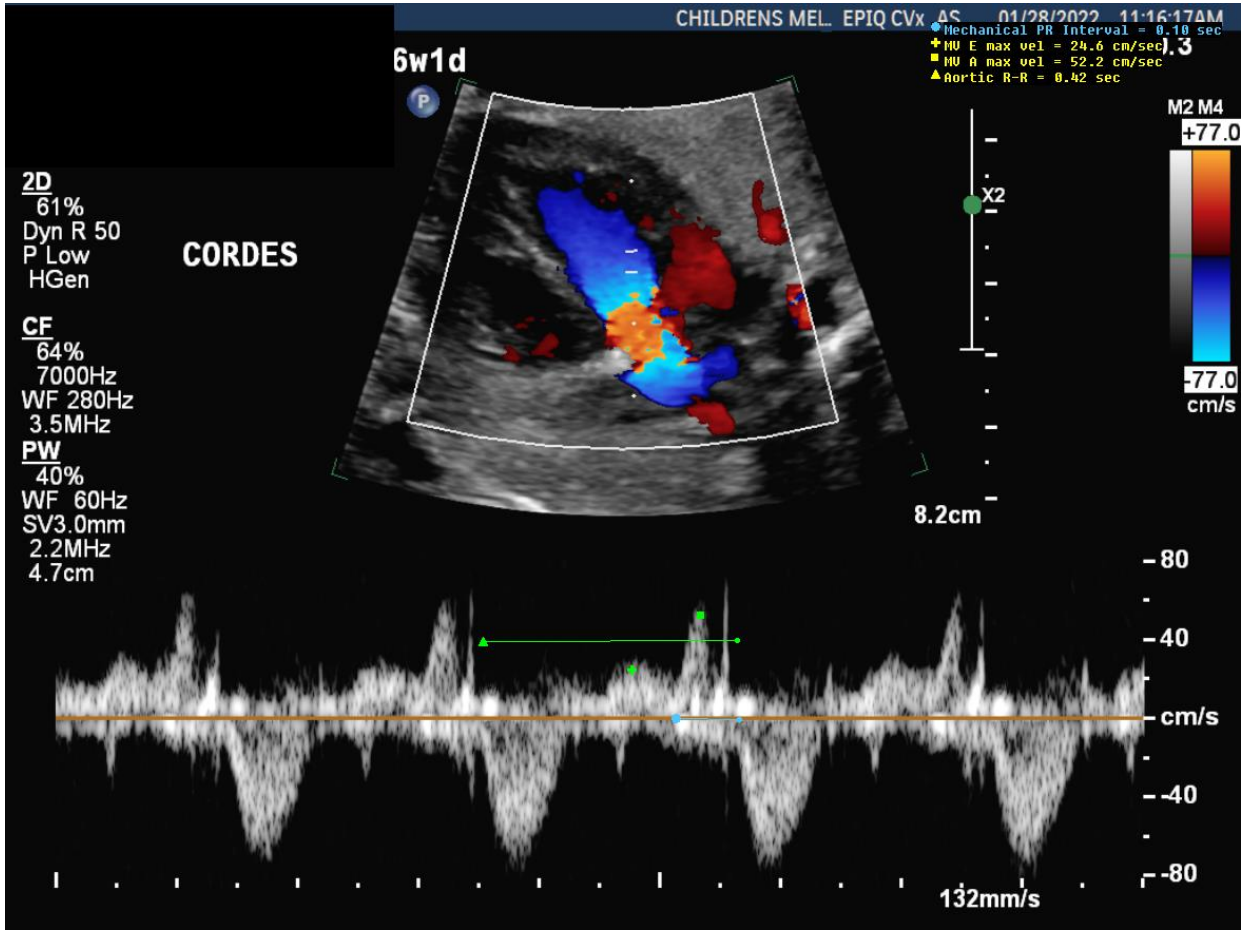
Irregular:

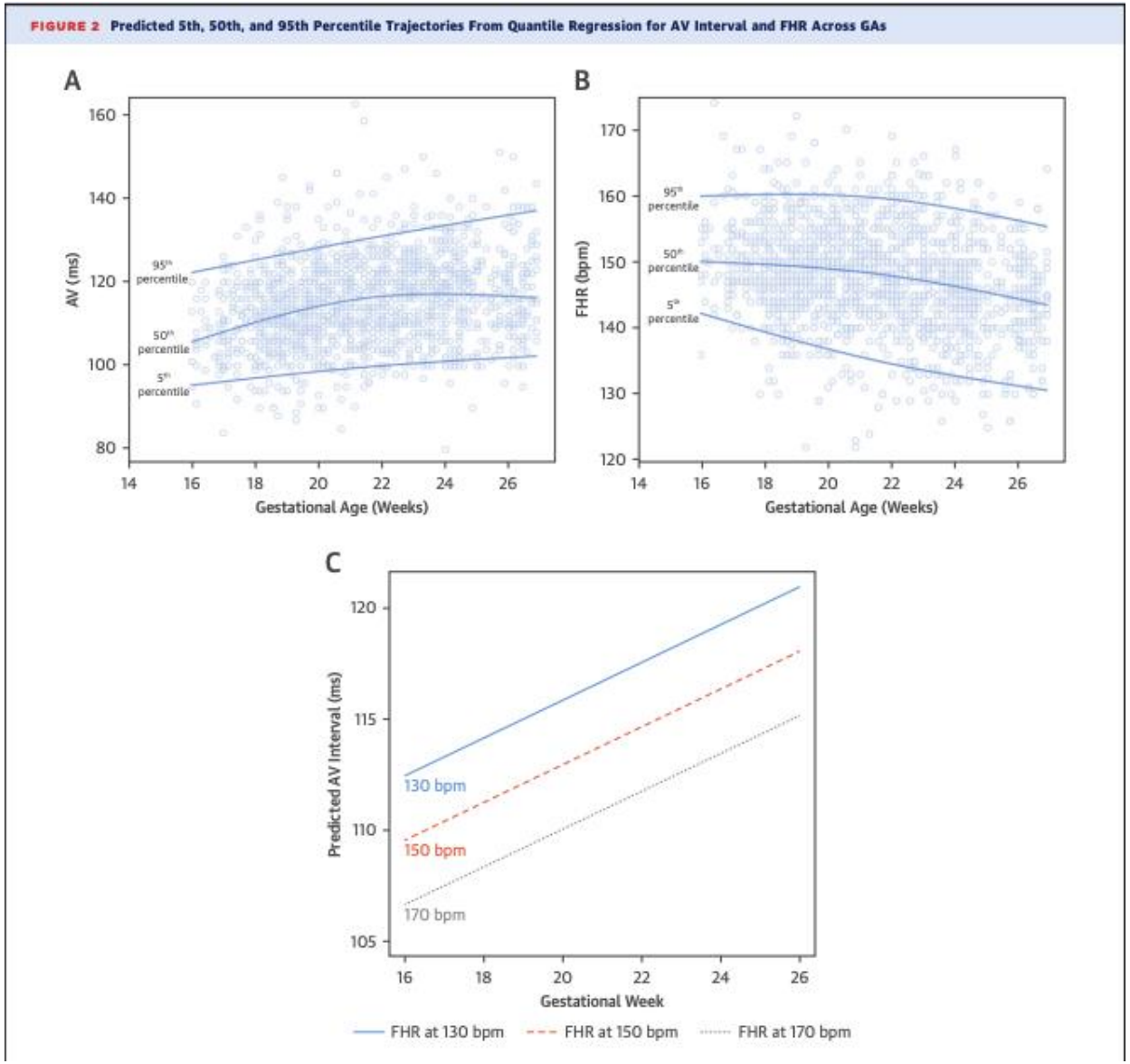
- Blocked atrial ectopic beats
- Intermittent Mobitz Type II Heart block
- Mobitz Type I Heart block
- Sinus node dysfunction with ventricular ectopic beats

Assessment of Fetal Bradycardia by AV relationship



Mechanical PR Interval





AV interval >150ms is abnormal,

Mechanical PR interval overestimates the actual fetal AV interval

Sinus Bradycardia

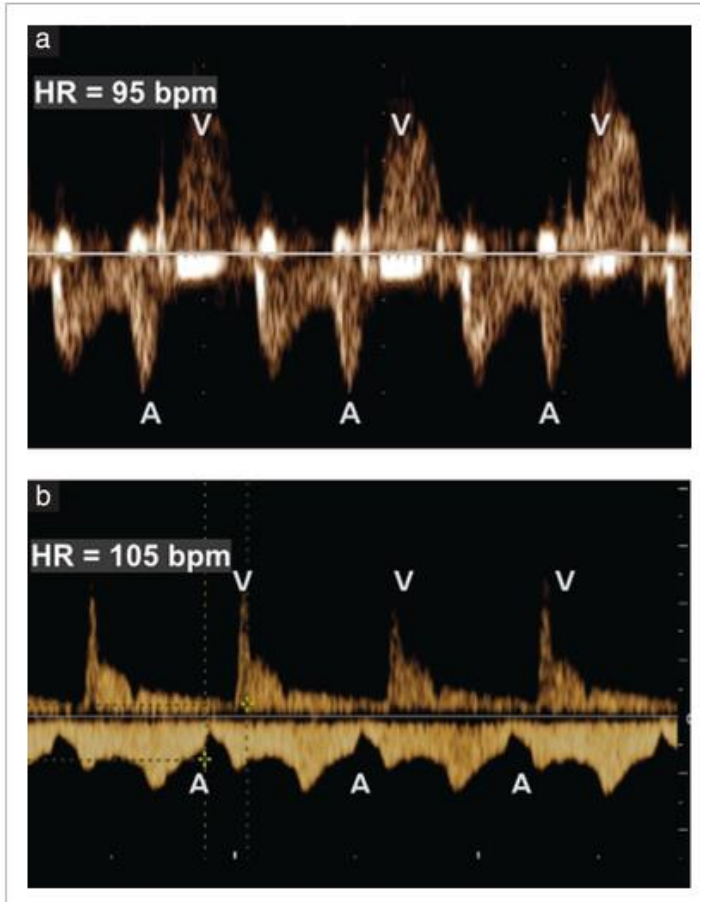
- Regular 1:1 AV conduction with rate <110 bpm
- Uncommon, generally well-tolerated in absence of structural or functional defect
- Rare Genetic abnormalities
  - Loss of function mutations in cardiac sodium channel SCN51
  - Mutation in pacemaker HCN4 ion channel
- Damage to normal sinus node
  - Viral or bacterial infection
  - Maternal SSA antibodies

Sinus Bradycardia work-up

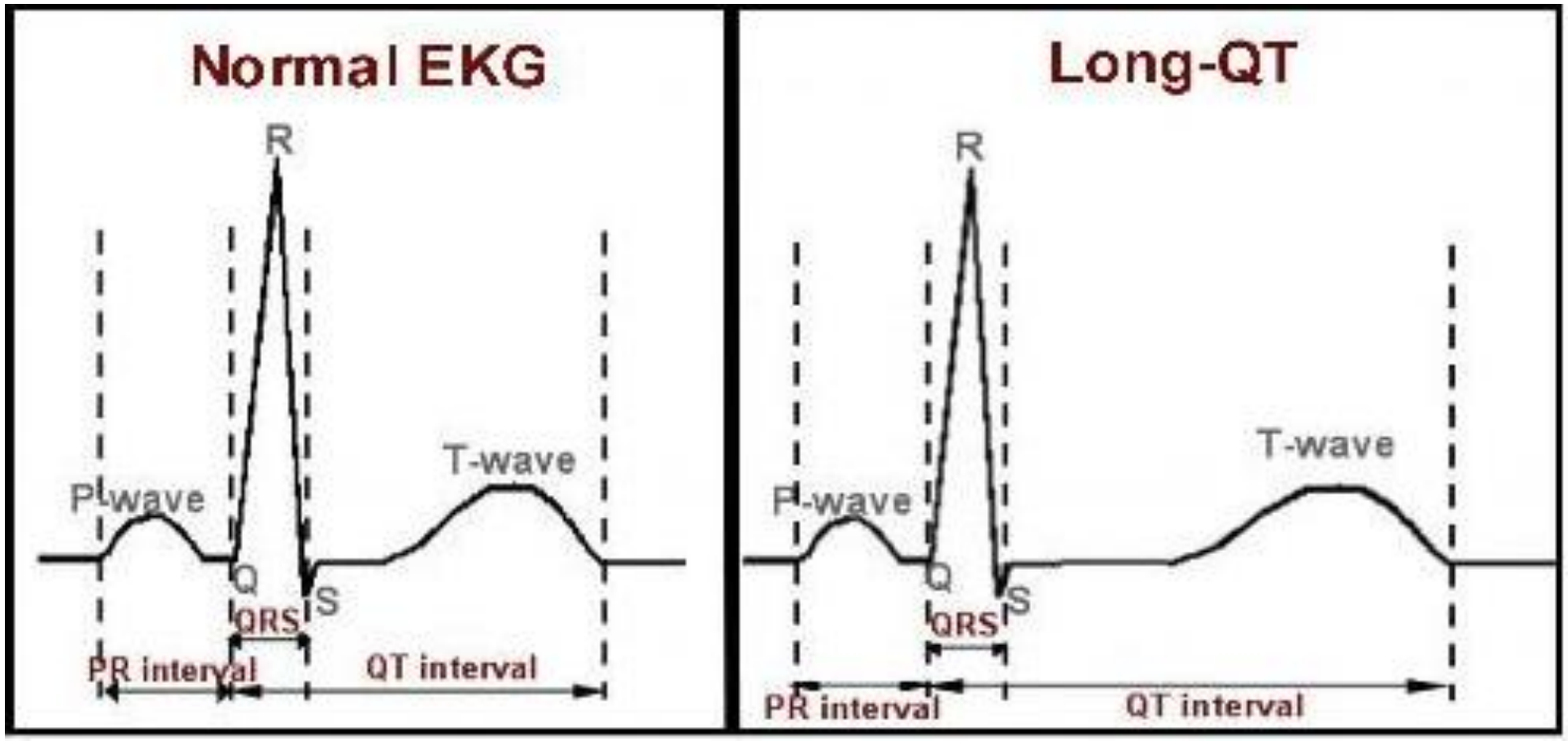
- Ensure no extracardiac reasons for bradycardia
- Check maternal anti-SSA antibodies
- Parental ECG and detailed family history to rule out LQTS
  - Focus on syncope, sudden death, SIDS, drownings
- Consider fetal MCG

Sinus Bradycardia

- Regular
- 1:1 AV conduction
- Normal AV interval



Fetal Bradycardia: Long QT Syndrome



Long QT Syndrome

- Genetic abnormality of the sodium and potassium channels regulating cardiac repolarization occurring in 1/2000 subjects
- •> 600 mutations in 12 susceptibility genes have been found
- •1/3 are novel mutations
- •25% are genetically elusive
- Typically presents in adolescence or young adulthood with syncope, sudden death or cardiac arrest BUT
- 10% of ostensibly normal IUFD and SIDS are secondary to LQTS mutations
- Only 1/7000 identified before birth

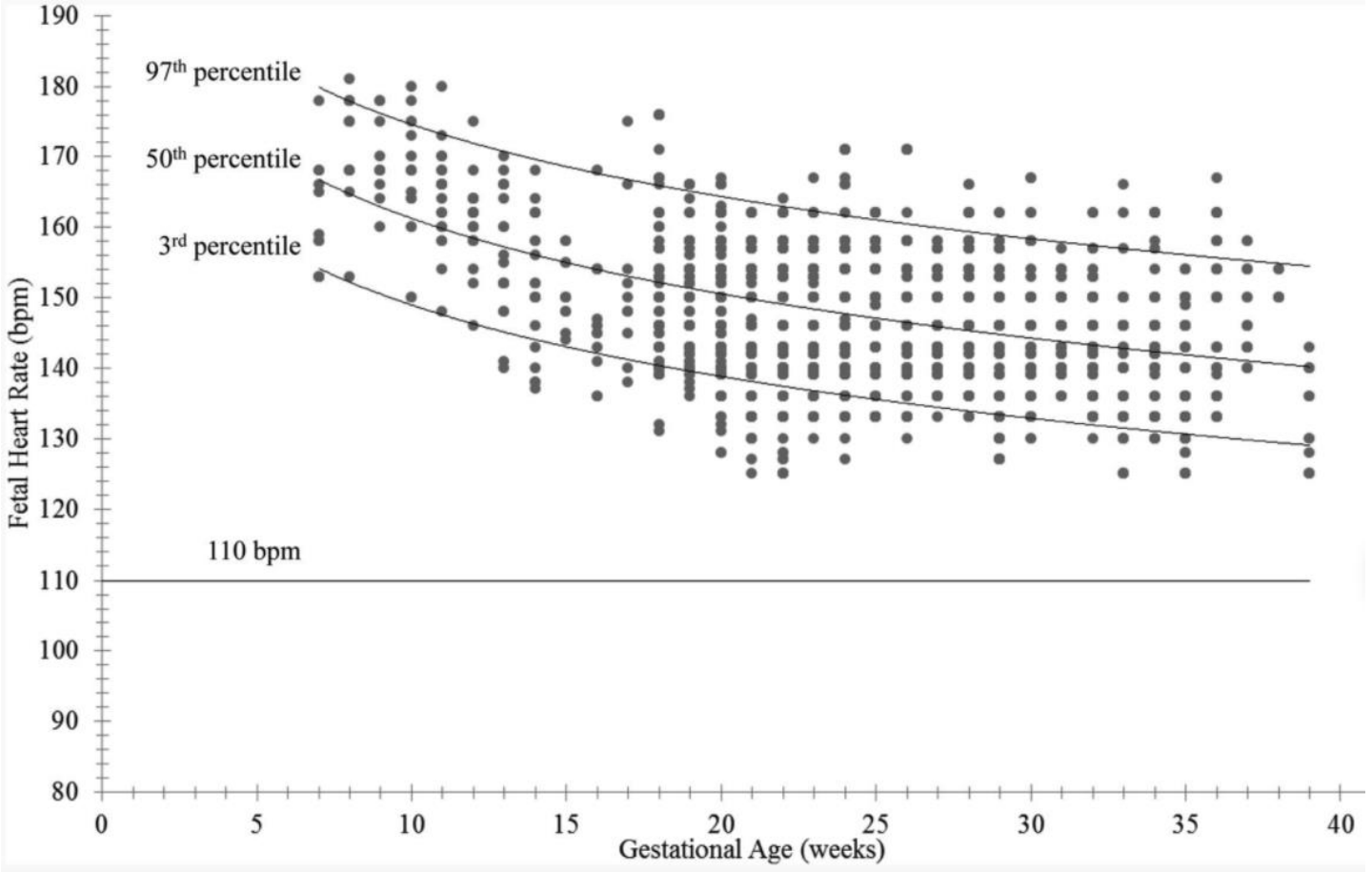
Fetal Long QT Syndrome

- "Mild" regular 1:1 AV conduction bradycardia with Fetal HR <3rd percentile for GA but >110bpm may be only clue
- Signature fetal rhythm abnormalities:
  - 2nd degree AV block
  - Torsades de Pointe
  - However, only occur in ~25% of fetuses
  - Cannot be accurately diagnosed via fetal echo
- Parental ECGs are imperative

Fetal Long QT Syndrome Diagnosis

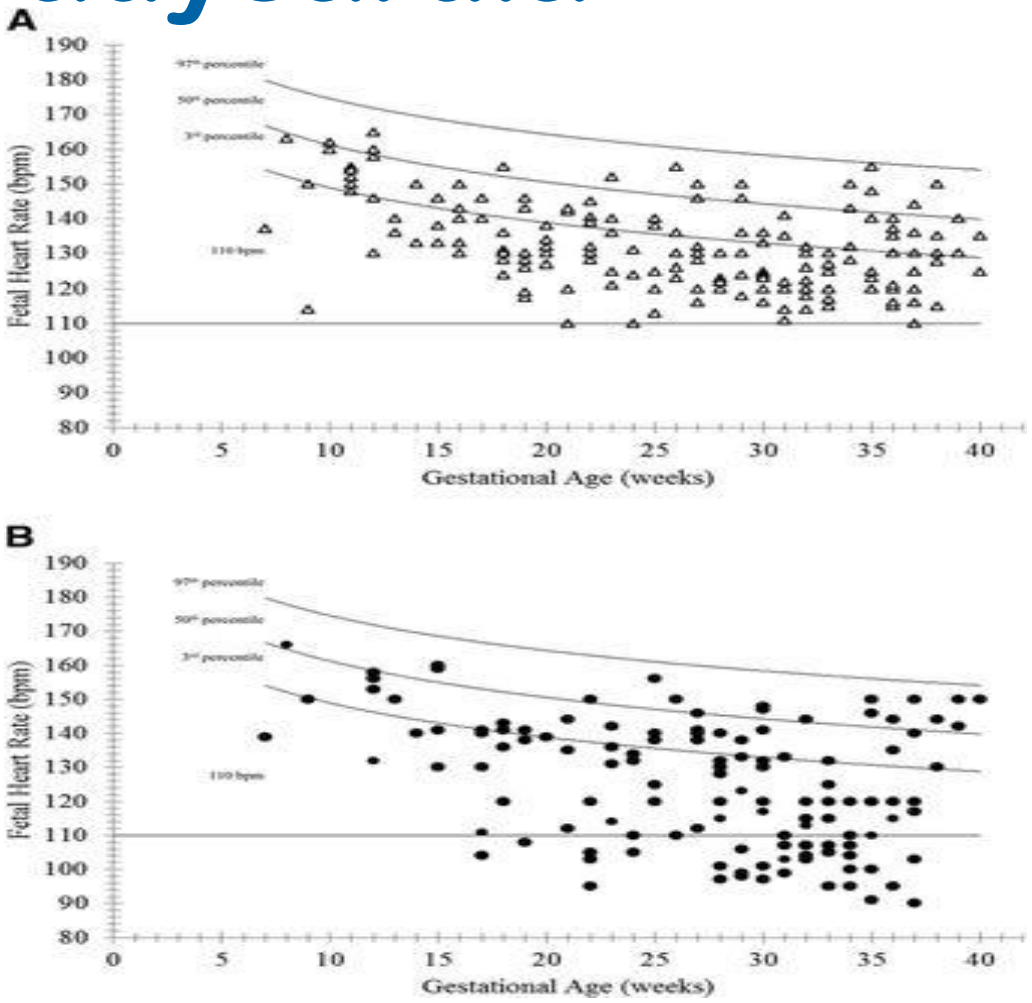
- Must have high index of suspicion:
  - Structurally normal heart with any of the below:
    - Low baseline FHR 110-130bpm
    - Sinus Bradycardia <110bpm
    - Ventricular arrhythmias
    - 2nd degree heart block
    - Signs of unexplained heart failure
- Fetal MCG can make diagnosis

Normal fetal heart rate curves by GA



Jason L. Mitchell. Circulation. Fetal Heart Rate Predictors of Long QT Syndrome, Volume: 126, Issue: 23, Pages: 2688-2695, DOI: (10.1161/CIRCULATIONAHA.112.114132)

Long QT Syndrome and Sinus "Bradycardia"

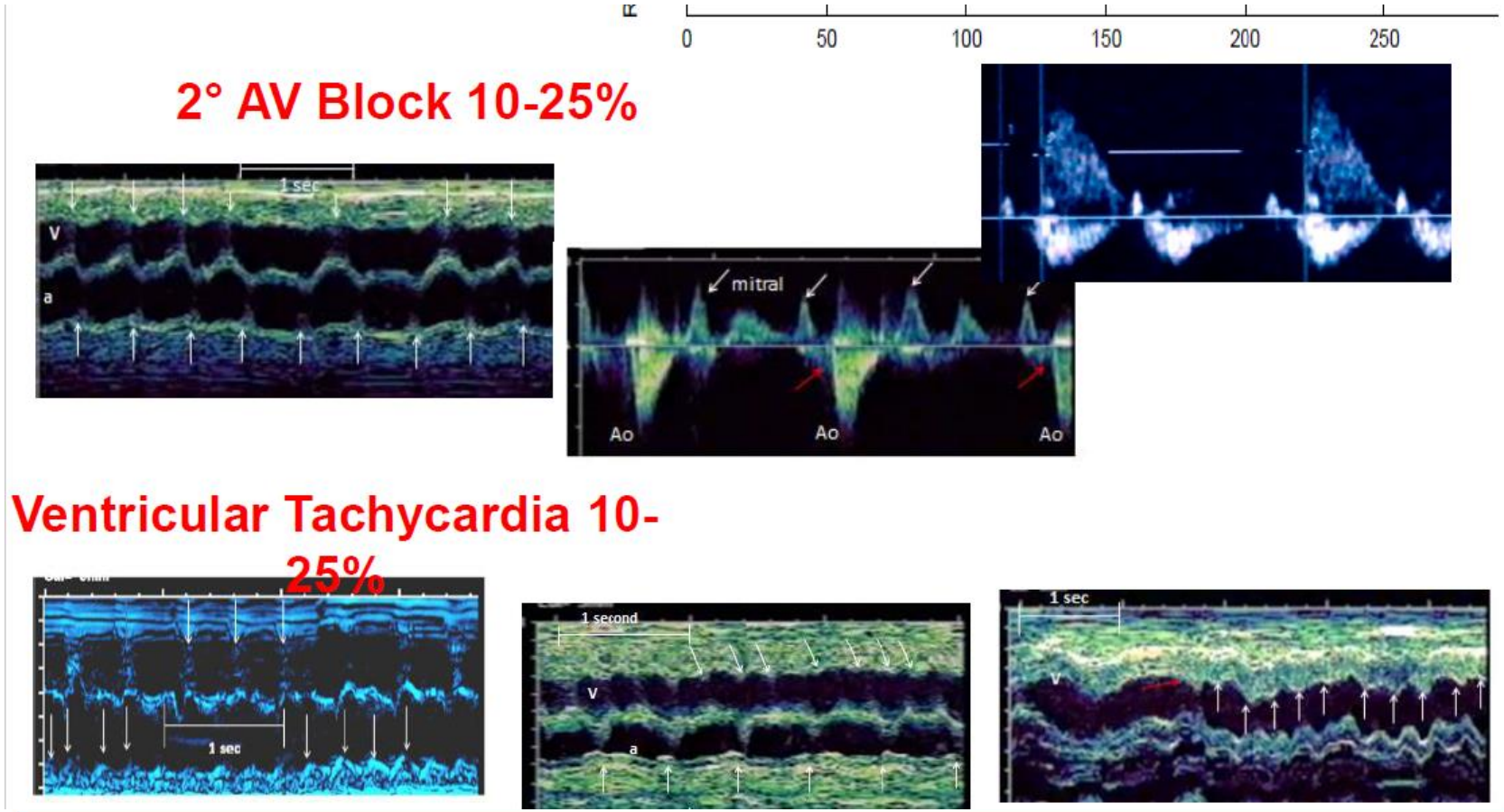


Jason L. Mitchell. Circulation. Fetal Heart Rate Predictors of Long QT Syndrome, Volume: 126, Issue: 23, Pages: 2688-2695, DOI: (10.1161/CIRCULATIONAHA.112.114132)

Long QT Syndrome and heart “block”

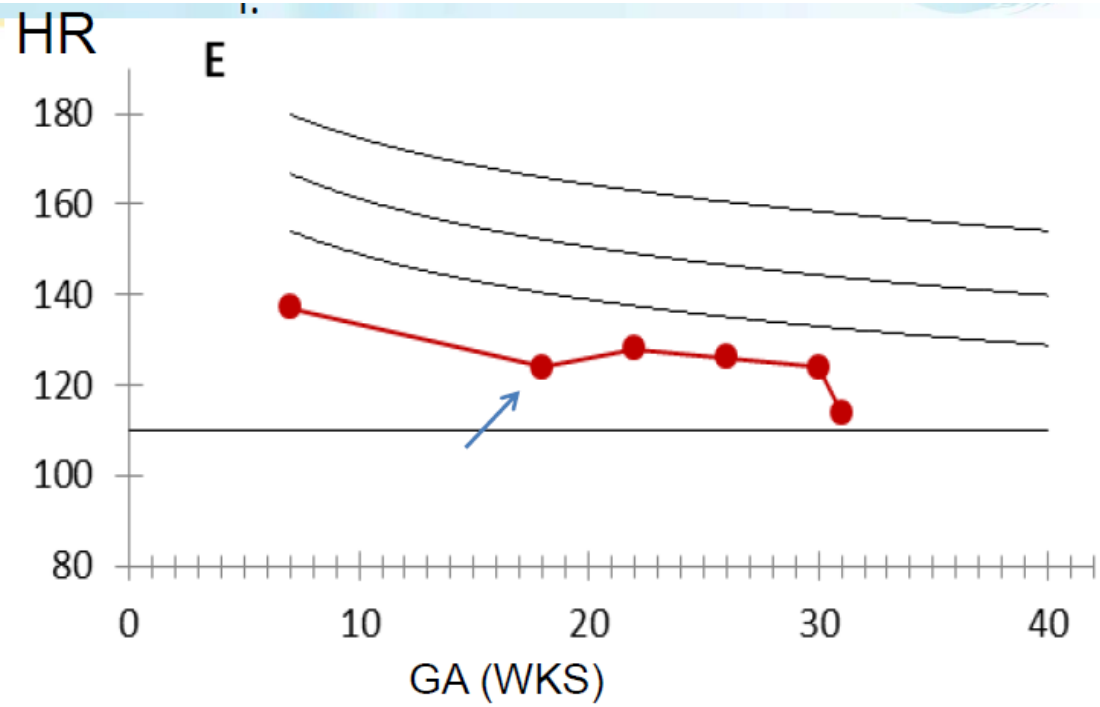
- QT interval is so long that atrial electrical impulse occurs during refractory period of ventricle
- The ventricle is not “ready” to receive another impulse, thus the atrial impulse does not result in ventricular contractions

Long QT Syndrome Signature Arrhythmias



"FHR a little lower than what I see at this GA"

- No family history of LQTS
- Parents QTcs normal
- No syncope, cardiac arrest
- OB history positive for 1 miscarriages at 23 weeks



Infant found to have KCNQ1 mutation G314D

Long QT Syndrome: Prognosis and Treatment

- Frequent fetal echo evaluation surveilling for fetal well-being and arrhythmias
- Complete post-natal work-up required
- LQTS accounts for >10% of SIDS
  - Prenatal suspicion can guide postnatal evaluation and prevention of SIDS
- No specific in utero treatment unless ventricular arrhythmias seen

Blocked atrial bigeminy

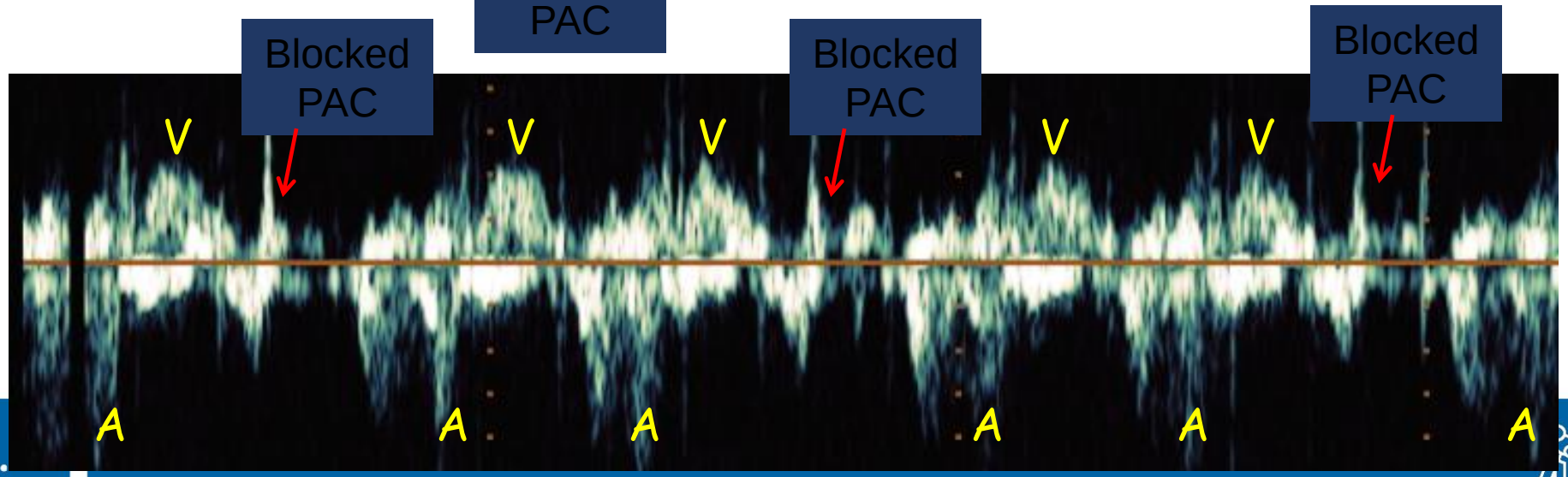
- Regular ventricular rate, A>V, irregular A-A interval
- FHR often <100bpm
- Most common cause of irregular heart rhythm
- Can be associated with slow or normal FHR
- Early atrial beat comes in before ventricle is ready to receive another beat, meaning, ectopic beat is blocked
- No hemodynamic significance, but MUST be distinguished from pathologic 2:1 AV block
  - The Great Pretender
- Accurate measure of A-A interval is key

Fetal Irregular Rhythm:

Premature Atrial Contractions

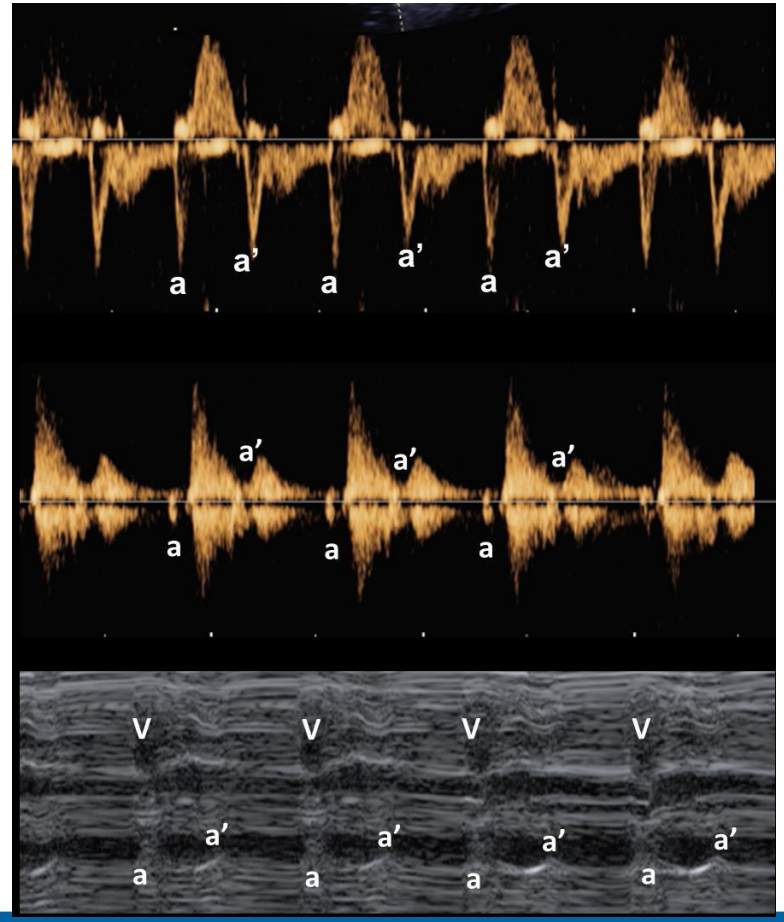
Blocked PAC

Non-conducted PACs

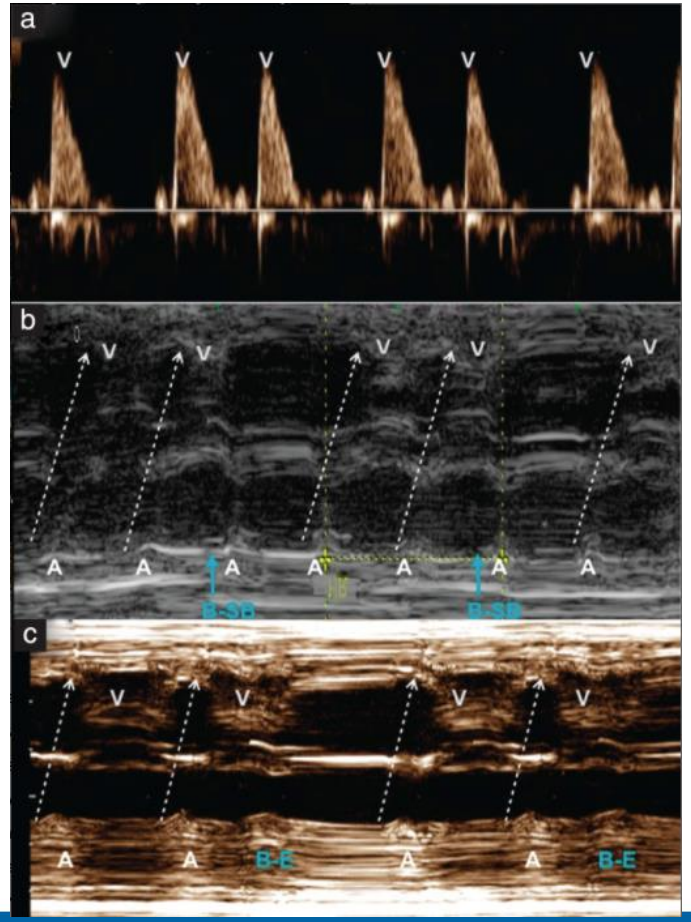


Blocked atrial bigeminy

Distance Between a-a’ is less than the distance from a’ - a

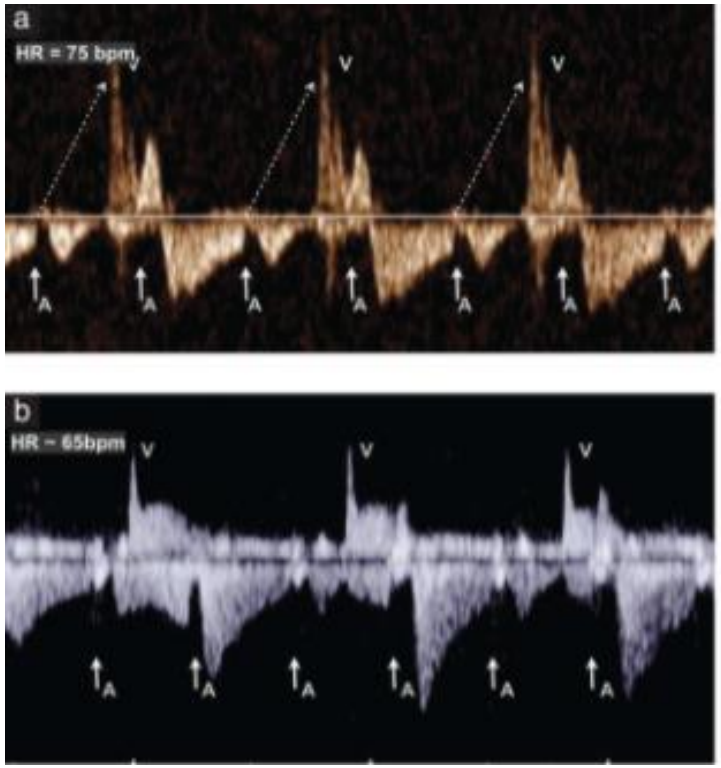


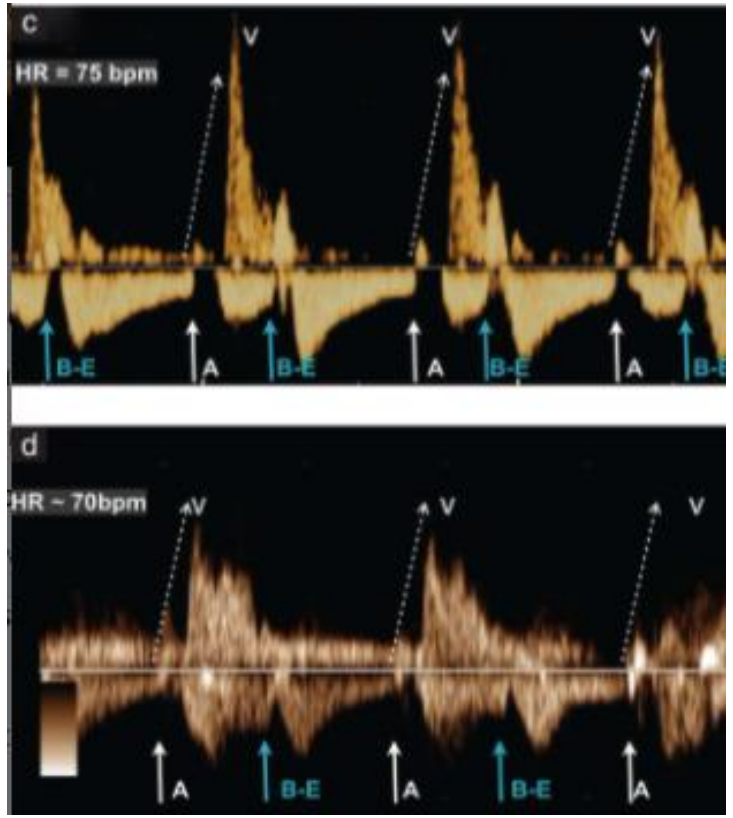
Irregular Rhythm: Blocked atrial ectopy versus pathologic AV block



Primary bradycardia: keys and pitfalls in diagnosis
J.S. Carvalho, USOG 2014

Regular Rhythm: Blocked atrial ectopy v. pathologic AV block





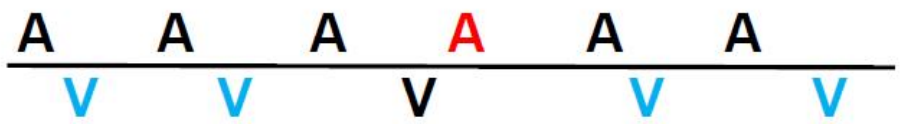
Management of Atrial and Ventricular Ectopy

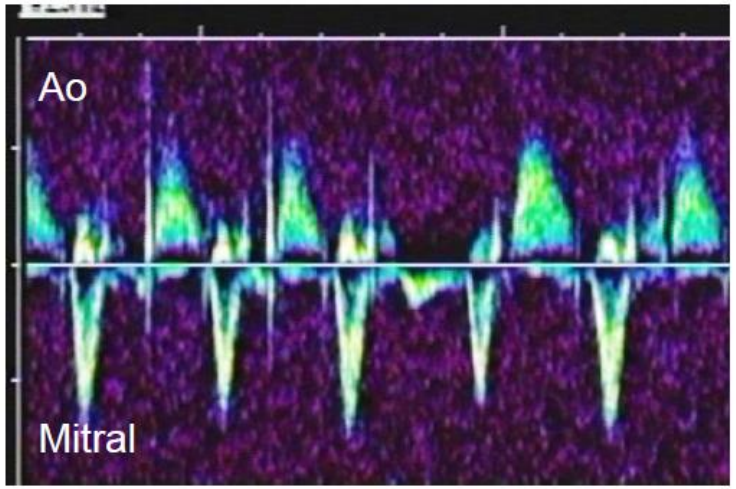
Atrial Ectopy	Ventricular Ectopy
1. Confirm normal structure	1. Confirm normal structure
2. Weekly FHR auscultation	2. Consider infectious etiology
3. Monthly fetal echo if ectopy persists	3. R/o Tumors and diverticulum, consider LQTS
4. Postnatal ECG if ectopy persists	4. Weekly FHR auscultation; consider home Doppler
	5. Monthly fetal echo if ectopy persists
	6. Postnatal ECG

Fetal Bradycardia: AV block

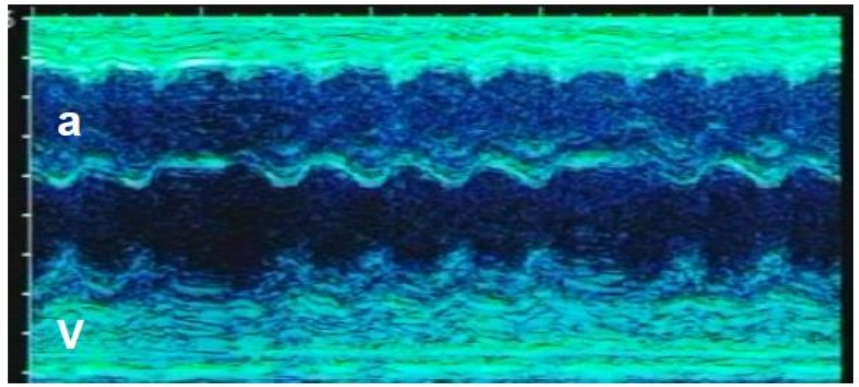
- 1st degree AV block
  - Prolonged mechanical PR interval >170ms
  - A=V
  - regular
- 2nd degree AV block
  - Mobitz Type I
  - Mobitz Type II
  - A>V, but A-V relationship exists
  - Irregular or regular
- 3rd degree (complete) AV block
  - A>V
  - No A/V relationship
  - Regular
  - FHR ~50-90 bpm

Fetal Bradyarrhythmia: Mobitz
Mobitz Type I 2nd degree block



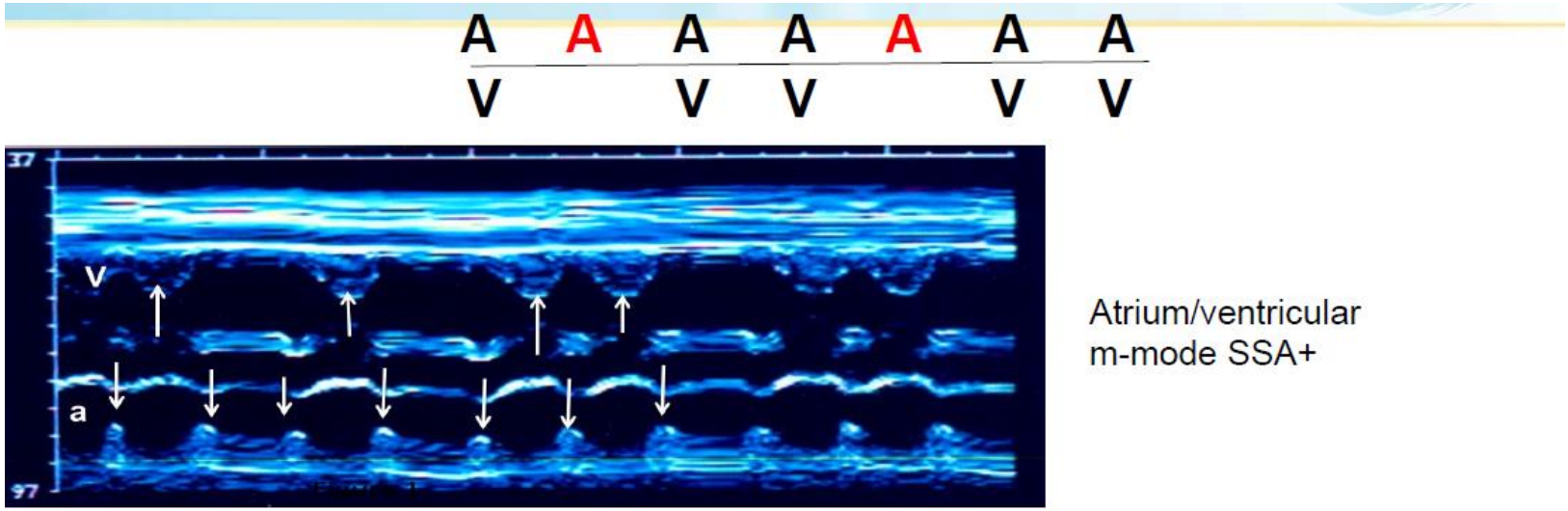


Mitral Inflow/aortic outflow Doppler SSA+



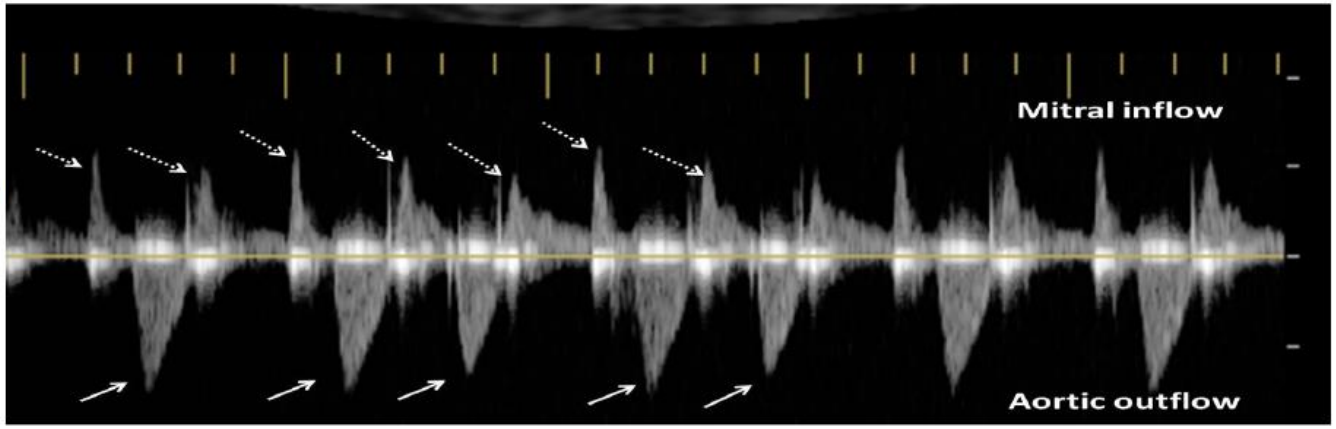
Atrium/ventricle M-mode SSA+

Fetal Irregular Rhythm: Intermittent Mobitz II AV block

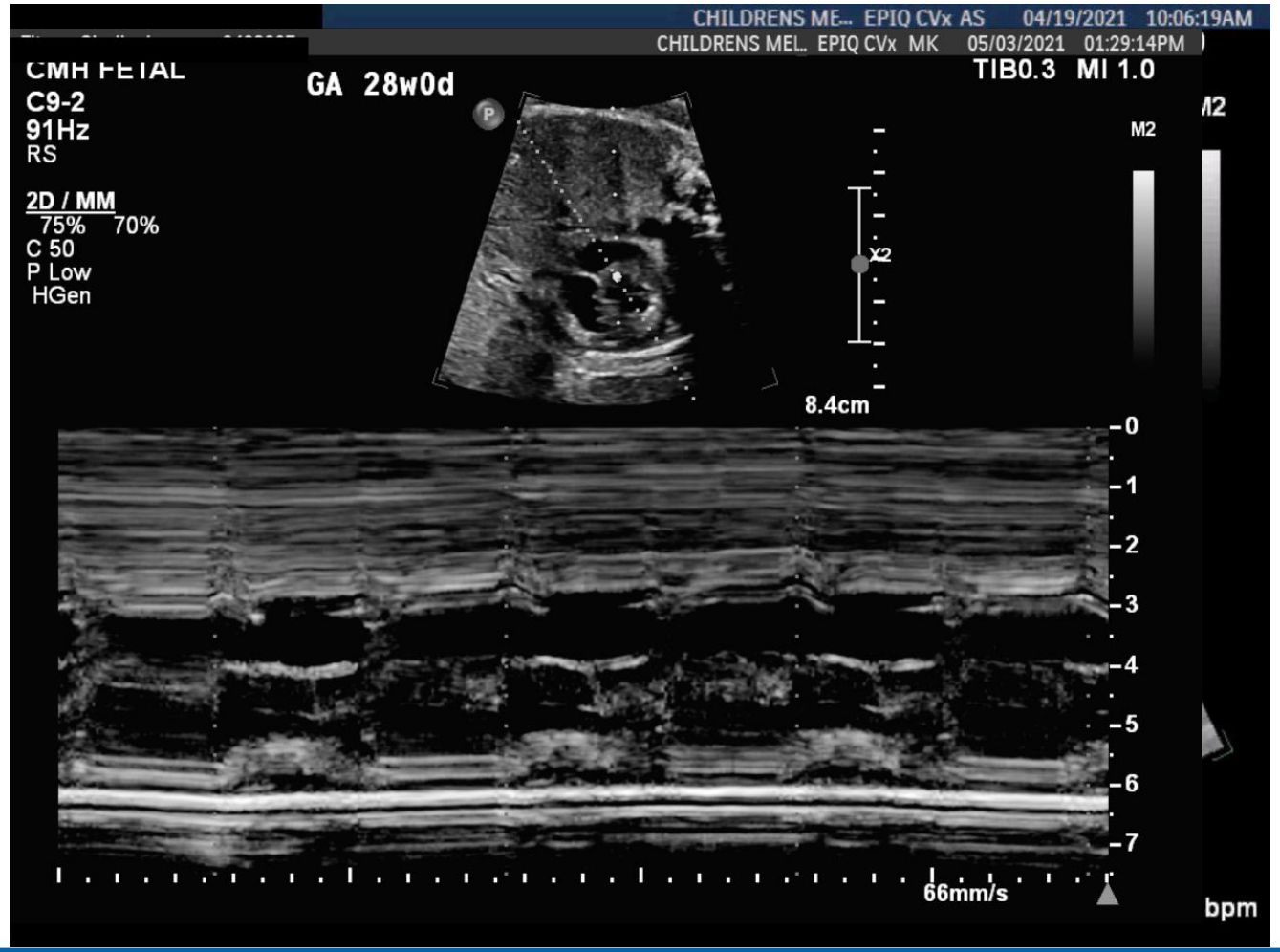


Atrium/ventricular m-mode SSA+

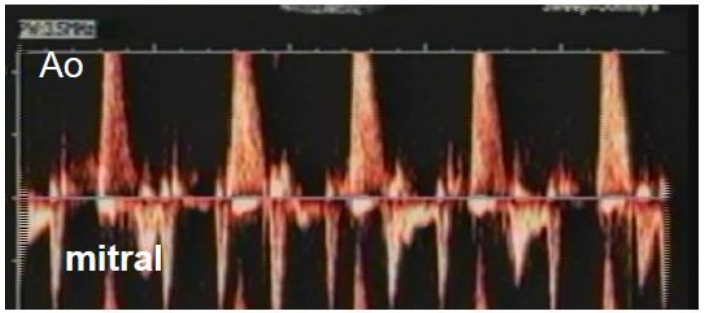
Mitral Inflow/aortic outflow Doppler SSA+

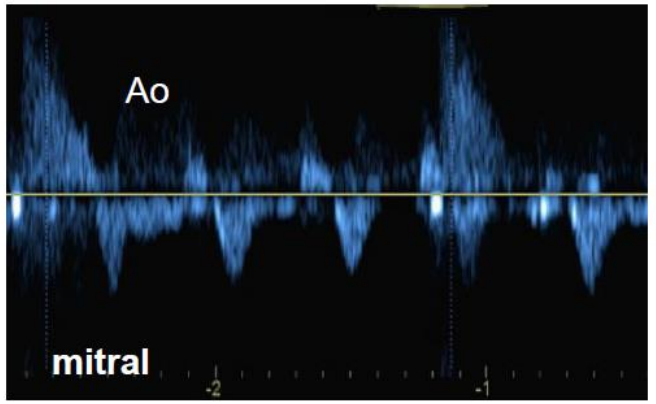


Complete 3rd degree Heart Block

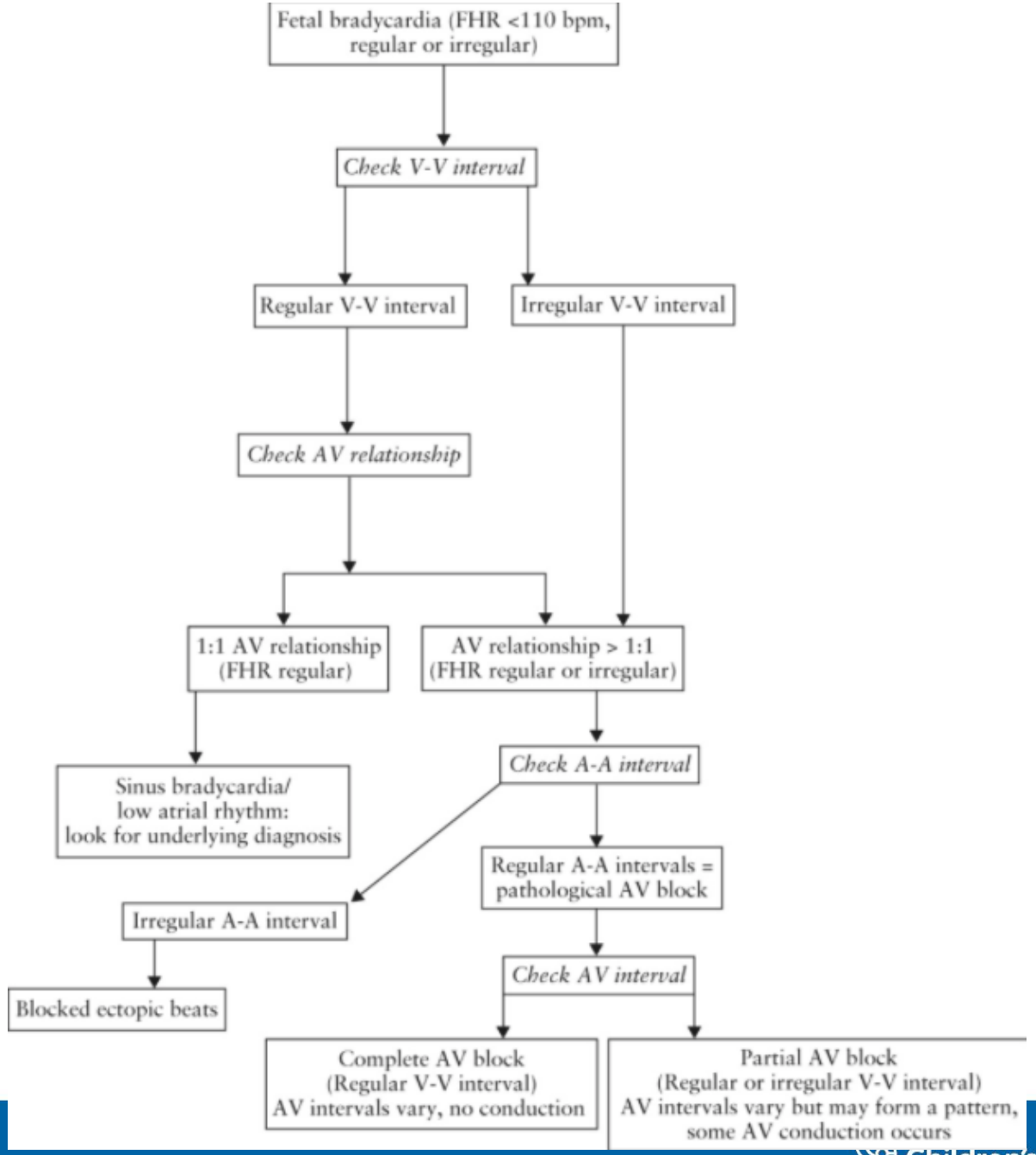


Complete Heart Block and Cardiomyopathy





Fetal Bradycardia Diagnosis Flowchart Review



Fetal Bradycardia: AV Block

- Inflammation and/or scarring (fibrosis) of the AV node secondary to maternal autoantibodies or a structurally abnormal AV node prevents electric signals from the atria from reaching the ventricles
- Almost all inflammatory or scarring AVB develops in the second trimester of pregnancy (18-26 weeks of gestation), but placental transfer of offending maternal autoantibodies can occur as early as 11 weeks gestation
- Heart block secondary to complex structural disease can occur as early as 13 weeks

AV block can be associated with:

- Structurally and genetically normal heart
  - **SSA antibody mediated disease**
  - Maternal metabolic disease or medications
  - Viral infections
- Structurally and genetically abnormal heart
  - Long QT Syndrome
  - Other channelopathies
- Congenital heart disease
  - Heterotaxy (Left atrial isomerism)
  - Congenitally corrected transposition of the great arteries

Fetal AV block secondary to SSA antibodies

- Fetal AVB secondary to anti-Ro/SSA antibodies “neonatal lupus” spectrum
- Fetal AVB occurs in 2% of pregnant women who carry anti-Ro/SSA antibodies
- 20% in utero mortality rate for immune mediated congenital heart block
- 2/3 of fetuses who survive require pacemaker implantation after birth, most within first 10 days
    - Prognosis is excellent if ventricular function is preserved after pacemaker implantation
  - 10% will develop cardiomyopathy in first year of life
    - Antibodies can also affect myocardium

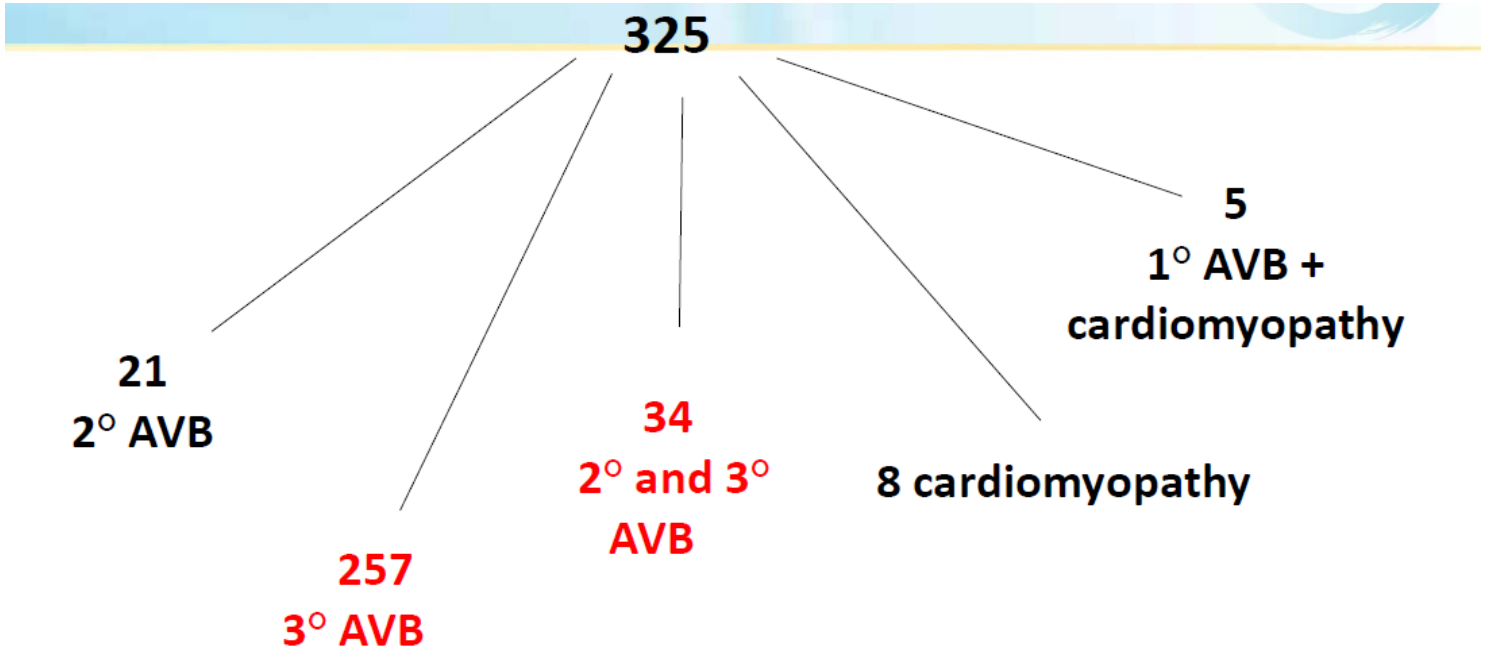
What are SSA Antibodies and who has them?

- Autoantibodies which react with a protein in all cells and can damage fetal AV node and myocardium
- Some individuals with anti-Ro/SSA antibodies have known autoimmune diseases such as lupus or Sjogren's syndrome, but most (~2/3) do not have identified autoimmune disease at time of CCHB diagnosis
  - Currently no universal screening for SSA antibodies in pregnant women
- Risk to develop CHB in SSA positive pregnancies is slightly higher in those with active disease
- **Risk of heart block in subsequent pregnancies after previously affected child is 9x higher, i.e. ~18% risk**

Presentation and Progression of SSA-antibody mediated Heart block

- Goal is early identification and treatment
  - Currently face challenges in both identifying and knowing which fetuses would benefit from treat
- Complete (3rd degree heart block) is likely irreversible and is often initial presenting rhythm
- Early (first or 2nd degree heart block) is potentially treatable BUT
- Progression from 1st/2nd degree heart block to Complete heart block can be rapid (<24-48 hours)
  - Weekly or biweekly monitoring may be insufficient to detect this period and treat to prevent CAVB
- In addition, some cases of fetal first degree AVB do not progress to higher grade block during pregnancy or after delivery

Fetal Bradyarrhythmia:
Presentation of SSA-mediated cardiac disease



96% Signature rhythm of AV Block

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Surveillance of SSA+ Positive Mother

Congenital Heart Disease

Utility of Cardiac Monito
Risk for Congenital
The PR Interval and Dexame
(PRIDE) Prospecti

Deborah M. Friedman, MD; Mimi Y. Kim, ScD; Josh
Colin K.L. Phoon, MPhil, MD; Julie S. Glick
for the PRIDE Invest

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 16, 2018

Home Monitoring for Fetal Heart Rhythm During Anti-Ro Pregnancies

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Surveillance and Treatment to Prevent Fetal Atrioventricular Block Likely to Occur Quickly (STOP BLOQ)

Surveillance of SSA+ Positive Mother

- PRIDE (PR interval and Dexamethasone Evaluation) study-2010
- 95 pregnancies evaluated
- Weekly fetal echoes performed from 16-26 weeks, bi-weekly 26-34 weeks
- PR >150ms considered prolonged, i.e. 1st degree block
- 3 fetuses developed 3rd degree AV block at 19-23 weeks GA, none had preceding abnormal PR interval on screening fetal echoes within 1-2 weeks prior
- 2 fetuses with PR >150ms detected prior to 22 weeks, reversed with treatment with dexamethasone

Surveillance of SSA+ Positive Mother: Home Monitoring

- 315 SSA+ mothers from 16 centers observed prospectively
- Ambulatory fetal heart monitoring
  - Handheld home Doppler operated by mothers, concerning rhythm sent to fetal cardiologist
  - 273 (87%) completed monitoring protocol, maternal stress/anxiety evaluated and in general found to be empowering to mother
- Monitoring Protocol:
  - Baseline echocardiogram at 16-19 weeks
  - Surveillance:
    - Fetal echoes every week or every other week up to 26 weeks
    - Twice a day FHRM
    - Diagnostic fetal echo if concerns about FHRM
    - Routine OB care after 26 weeks

Cuneo et. al Surveillance for Fetal AV Block by Home Monitoring *JACC 2018*

Surveillance of SSA+ Positive Mother: Home Monitoring

- 3 fetuses developed AVB between 18-22 weeks gestation
  - All detected by FHRM and confirmed by fetal echo
  - All treated with dexamethasone and IVIG after detection
  - All with normal fetal echoes for both rhythm and function 2-4 days preceding FHRM
    - All fetal echoes performed after abnormal FHRM demonstrated EFE or AVVI in addition to rhythm abnormality that was not present on preceding echo

Cuneo et. al Surveillance for Fetal AV Block by Home Monitoring *JACC 2018*

Surveillance of SSA+ Positive Mother: Home Monitoring

- Fetus #1, irregular rhythm on FHRM
  - Fetal echo performed same day with intermittent 2nd degree AV block and 1st degree AV block
  - **restored to sinus rhythm**
- 2 other fetuses with 3rd degree AV block at time of diagnostic fetal echo did not reverse with treatment
  - Fetus #2 with detected bradycardia on FHRM, fetal echo 8 hours later
  - Fetus #3, irregular rhythm on FHRM, waited 12 hours before calling cardiologist after repeat HRM demonstrated FHR <100bpm, fetal echo 8 hours later

Cuneo et. al Surveillance for Fetal AV Block by Home Monitoring *JACC 2018*

Surveillance of SSA+ Positive Mother: Home Monitoring

- No instances of first degree AVB progressing to 2nd-degree AVB
- No missed cases of AVB
- 50% false positive rate (11/21)
  - Other non AVB abnormalities found were PACs and frequent sinus pauses
  - Functional fetal echo abnormalities only found on AVB patients

Treatment of Heart block

- No standardized medical therapy exists
  - Still do not know who benefits from treatment the most and at what dosages
- Goals of treatment are 2-fold:
  - Prevent progression to higher-degree AV block
  - Decrease risk for development of fetal distress and progression to hydrops secondary to myocardial involvement

Treatment of Heart block

- Oral Corticosteroids
  - reduced immune-mediated AV-node and myocardial damage
  - Highest benefit during emergent CCHB (first-or second-degree AV block) or those with fetal hydrops
  - Maternal and fetal deleterious side effects occur, so dose is often decreased as pregnancy progresses
- Beta-adrenergic therapy
  - Generally used in patients with FHR <55bpm and signs of fetal cardiac impairment (hydrops, AVVR)-can increase FHR by 10-15%
  - Data mixed whether this improves outcomes
- IVIG
  - Reduced circulating maternal antibodies to reduce placental transmission
  - Mixed results in the literature, not used for first degree AV block, reserved for 2nd degree AV block or those with concerns for ongoing myocardial inflammation
  - Requires inpatient admission
- Fetal Pacing
  - Experimental, potentially coming in future, not realist option now
  - Very high risk, issues with placement and lead dislodgement

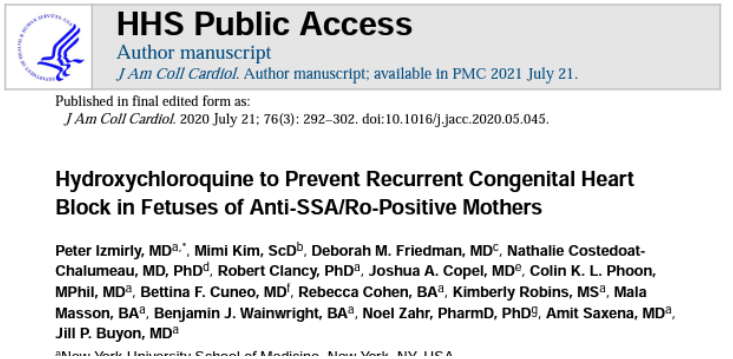
Post-Natal Management Complete Heart Block

- For non-CHD immune mediated CHB, generally recommend delivery at 37 weeks
  - C-section often recommended given inability to monitor for fetal distress during labor
- For high-risk infants with hydrops and/or ventricular dysfunction, must balance risk of demise with risks related to prematurity:
  - Technical aspects of pacing in small infants
  - Possible need for cardiac transplantation for cardiomyopathic infants
  - If non-immune and associated with CHD, must consider needed intervention and ductal dependency and lung prematurity

STOP BIOQ Trial

- **S**urveillance and **T**reatment t**O** **P**revent Fetal AV **B**lock **L**ikely to **O**ccur **Q**uickly
- Over thirty participating sites across the US and Canada
- A prospective observational trial with 3 steps:
  - Screening for high titer antibodies
  - Surveillance by FHRM 3X daily and weekly or biweekly echo
  - Treatment of 2° AVB identified by FHRM and confirmed by echo
    - 1st degree AVB (PR>170ms): Dexamethasone 8mg daily x 10 days, then 4mg/daily through 28 weeks, then 3mg through 29 weeks, then 2mg daily through delivery
    - 2nd degree AVB: IVIG 1g/kg within 12 hours of detection by home monitoring and 6 hours of confirmation by fetal echo
- Primary outcome: percentage of 2nd degree AVB patients with normal rhythm at delivery
- Secondary outcomes: percentage of 1st degree AVB patients with normal rhythm at delivery, extra-nodal cardiac disease, rhythm at one year of age

Prevention of SSA Heart Blo



Published in final edited form as:
J Am Coll Cardiol. 2020 July 21; 76(3): 292–302. doi:10.1016/j.jacc.2020.05.045.

Hydroxychloroquine to Prevent Recurrent Congenital Heart Block in Fetuses of Anti-SSA/Ro-Positive Mothers

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- Prospective study of pregnant mothers with previous pregnancy complicated by immune-mediated heart block
- Hydroxychloroquine 400mg daily given prior to completion of 10 weeks GA throughout pregnancy
- Recurrence rate decreased to 7.4% from historical rate of ~18-20%

Recommendations for SSA-Positive Pregnancy Monitoring

- Fetal Cardiology Evaluation starting at 16 weeks
- Weekly evaluation until 28 weeks
  - At minimum, fetal echoes every 2 weeks
  - Evaluation should include BPPS and/or CVS (if heart rate concerns)
  - Consider 2-3x daily ambulatory FHRM for selected patients
- In the absence of AVB, fetal echoes should continue every 2-4 weeks after 28 weeks until delivery due to risk of late myocardial complications

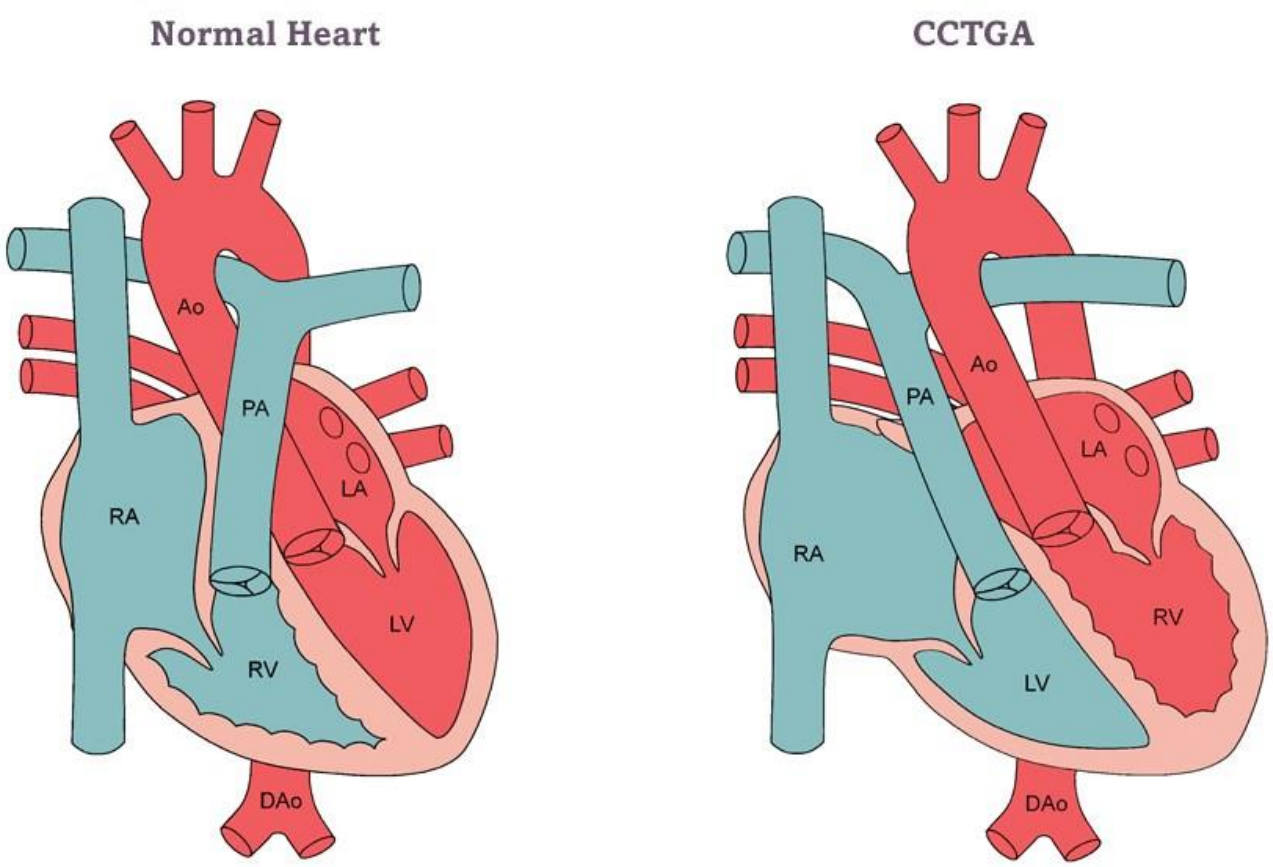
Recommendations for SSA-Positive Pregnancy Treatment

- Consider hydroxychloroquine initiation prior to 10 weeks gestation
- Consider dexamethasone for 1st or 2nd degree AVB +/- IVIG
- Consider sympathomimetics for Ventricular rate <55bpm or signs of hydrops
- Consider digoxin for cardiomyopathy
- No treatment recommended for sinus bradycardia, blocked atrial bigeminy
- Specialized delivery planning required for FHR <70bpm, cardiac dysfunction, or hydrops
- Hopefully more evidence coming with the STOP-Bloq trial

CCHB with structural heart disease

- L-Transposition of the great arteries
- Heterotaxy-polysplenia syndrome (left atrial isomerism)
- Less commonly in AVSD, other forms of CHD
- Can be associated with significant in-utero mortality, ranging from 5% (L-TGA) to 75-90% (left atrial isomerism)
    - Risk factors for mortality:
        - Hydrops
        - Ventricular rate <55bpm
        - Decreased LVEF or dilation
        - Presence of endocardial elastofibrosis
        - Significant AVV regurgitation

Congenitally Corrected Transposition of the Great Arteries



CHB with Heterotaxy Syndrome

CCHB with structural heart disease

- Still largely untreatable in-utero
- Goals are surveillance for fetal distress
- Consideration of beta-agonists +/- digoxin for signs of heart failure and/or hydrops
- Specialized delivery planning for FHR <55bpm and significant cardiomyopathy
    - Consideration of C-Section
    - Possible prostaglandin
    - Preparation for emergent temporary post-natal pacing
    - Often requires cardiology, CVOR and EP team on standby

Thank You

- Questions?

Acknowledgements

- Bettina Cuneo, MD, pioneer of fetal heart block and my mentor during training
- Children's Mercy Fetal Health Center sonographers, nurses, and my fetal cardiology and maternal fetal medicine physician colleagues
- The families who allow us to care for them