Fetal Tachyarrhythmias

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Objectives

- Epidemiology of fetal tachyarrhythmia
- Normal rhythm assessment by fetal echocardiography
- Common fetal tachyarrhythmia mechanisms
- Diagnosing different fetal arrhythmias with case studies
- Fetal Atrial Flutter and Supraventricular Tachycardia (FAST) Therapy trial
- Fetal tachyarrhythmia management
- Prognosis of different type of fetal tachyarrhythmias

Normal fetal conduction system

- Heart begins to beat at 22 days of gestation
- AV synchrony demonstrated by 6 weeks post conception
- Fully maturated by 16 weeks of gestation
- Produces regular rhythm
  - Normal heart rate 110-160 bpm
  - Beat-to-beat variation of 5-15 bpm

Fetal tachyarrhythmia epidemiology

- Estimated incidence of 1:1000-4000 pregnancies
- Leading cause of fetal heart failure, prematurity and perinatal death
- Risk of hydrops
  - >50% in sustained arrhythmia
  - Risk increases with younger gestational age and faster rates
  - With hydrops, 17-35% risk of mortality, despite treatment

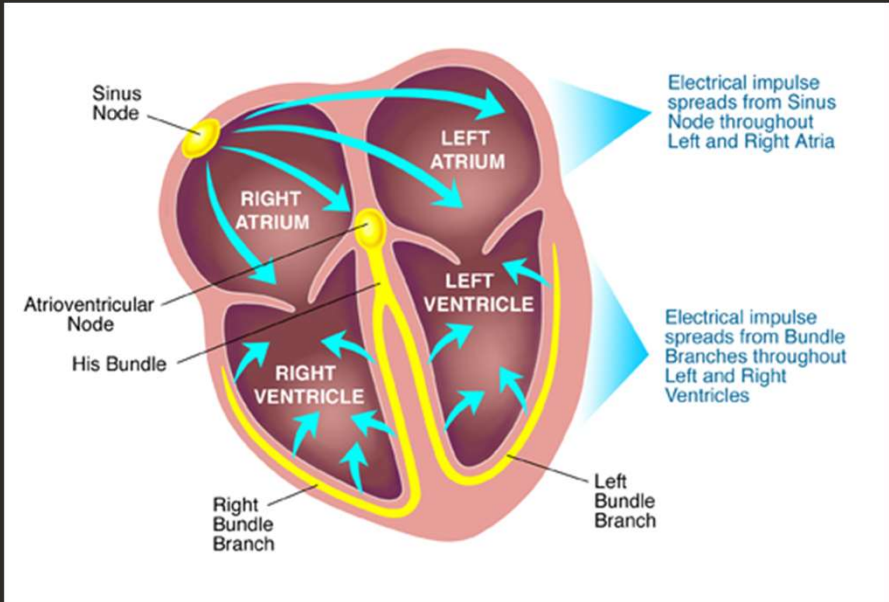
Fetal arrhythmia distribution

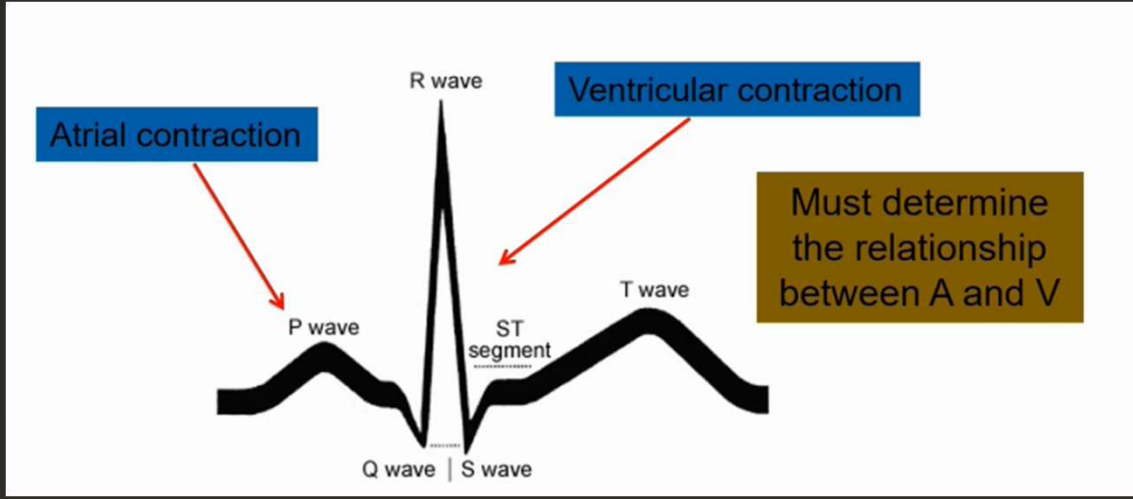
Type and distribution of arrythmias in 1384 fetuses

Type	Number
Premature atrial contractions	1213
Supraventricular tachycardia	69
Complete heart block	39
Atrial flutter	21
2nd degree AV block	10
Sinus tachycardia	8
Ventricular tachycardia	7
Atrial fibrillation	4
Junctional tachycardia	2
Sinus bradycardia	2

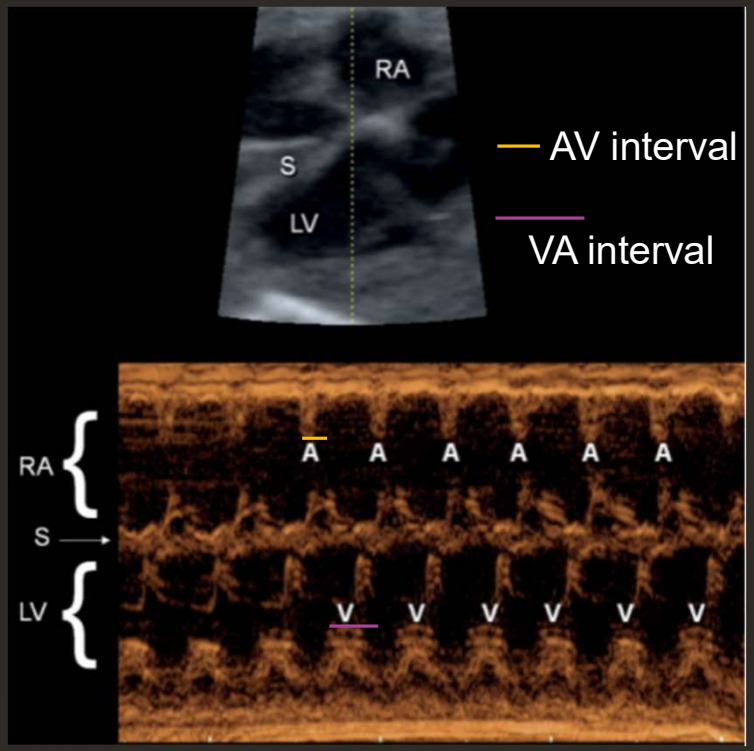
Adapted from: Kleinman, CS, Nehgme, R, Copel, JA. Maternal-Fetal Medicine, Principles and Practice, 5th edition, Saunders, 2004, p 466.

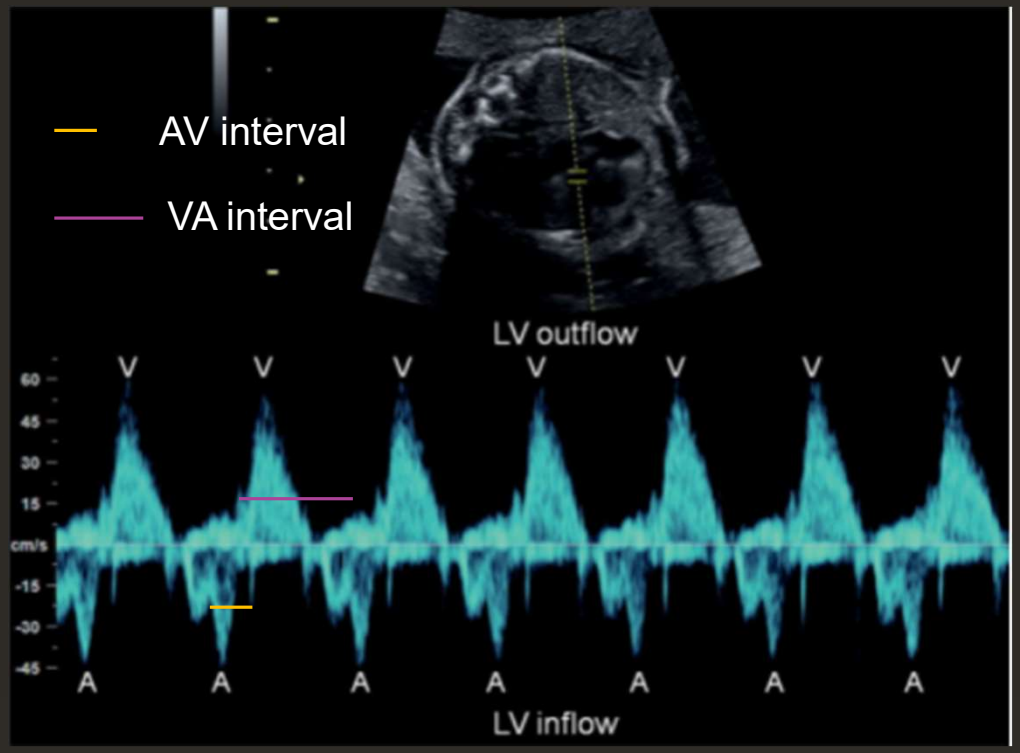
Normal sinus rhythm



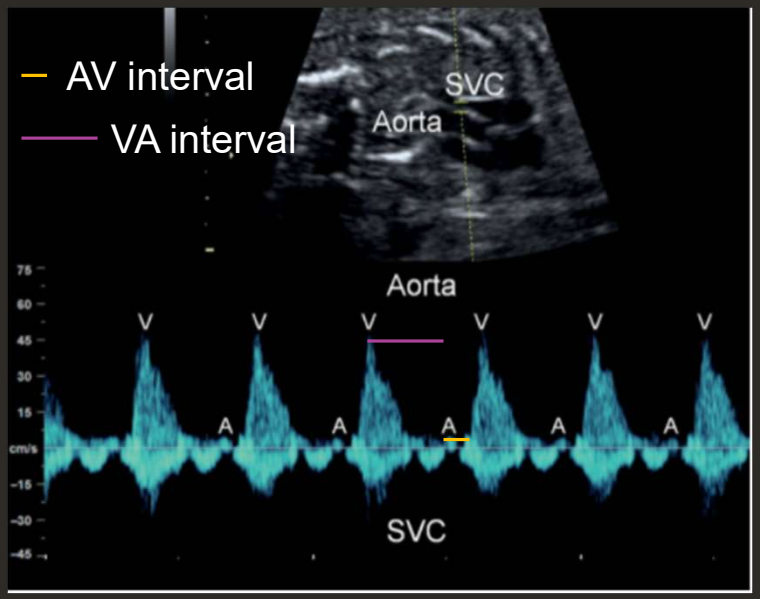


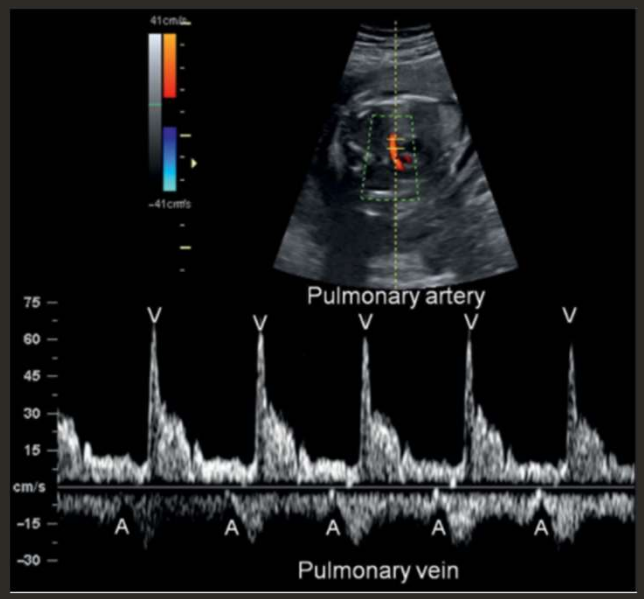
Normal rhythm fetal echo

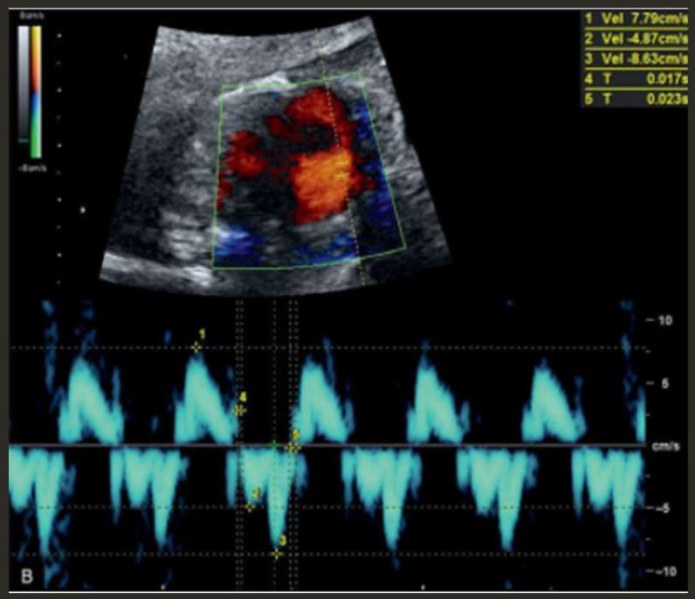




Normal rhythm fetal echo







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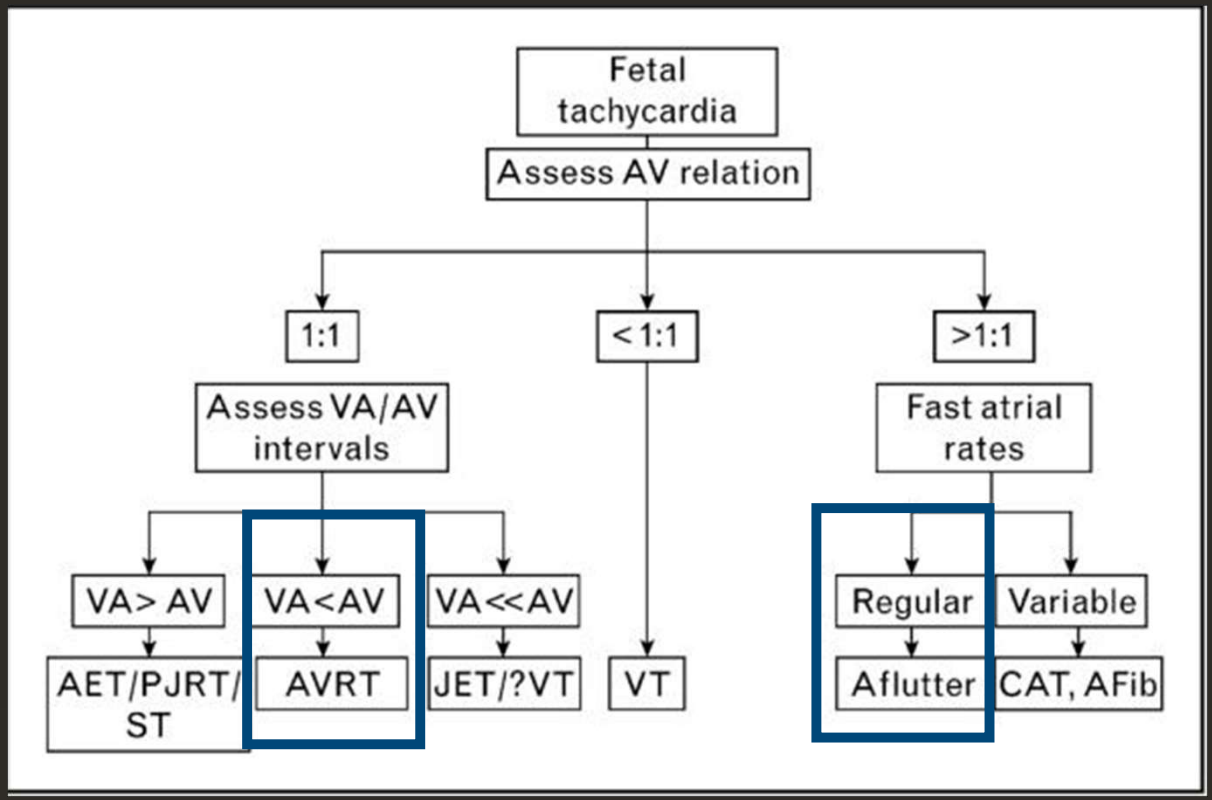
Fetal tachyarrhythmia types

- Atrioventricular reentrant tachycardia via an accessory pathway (AVRT)
- Atrioventricular nodal reentry tachycardia (AVNRT)
- Atrial flutter
- Atrial ectopic tachycardia (AET)
- Sinus tachycardia (ST)
- Permanent Junctional Reciprocating Tachycardia (PJRT)
- Junctional Ectopic Tachycardia (JET)
- Ventricular tachycardia (VT)

Fetal tachyarrhythmia differentiation



Fetal tachyarrhythmia differentiation

Tachycardia	Rhythm	AR	AV conduction	VR	AV interval
Re-entrant SVT	Regular	220-300	1:1	220-300	VA < AV VA >70<100 ms
Atrial ectopic tachycardia	Irregular (or chaotic)	>160-250	1:1	Variable	VA > AV VA >100 ms
Atrial flutter	Variable	350-500	2:1, 3:1, 4:1	Variable VR < AR	
JET	Regular	180-240	<1:1 or 1:1	180-240	VA ≥ AV >100 ms
VT	Variable	Variable VR > AR	<1:1 or 1:1	180-300	VA < AV
ST	Regular	180-200	1:1	180-200	AV=VA

SVT: Supraventricular tachycardia, JET: Junctional ectopic tachycardia, VT: Ventricular tachycardia, ST: Sinus tachycardia, AR: Atrial rate, VR: Ventricular rate, AV: Atrioventricular interval time, VA: Ventriculoatrial interval time

Total fetuses, n	159
Fetuses with AF, n (%)	45/159 (28)
Age at diagnosis, wk	33.2±3.5

Fetuses with SVT, n (%)	114/159 (72)
Age at diagnosis, wk	29.1±6

2011 *Circulation* Jaeggi et al

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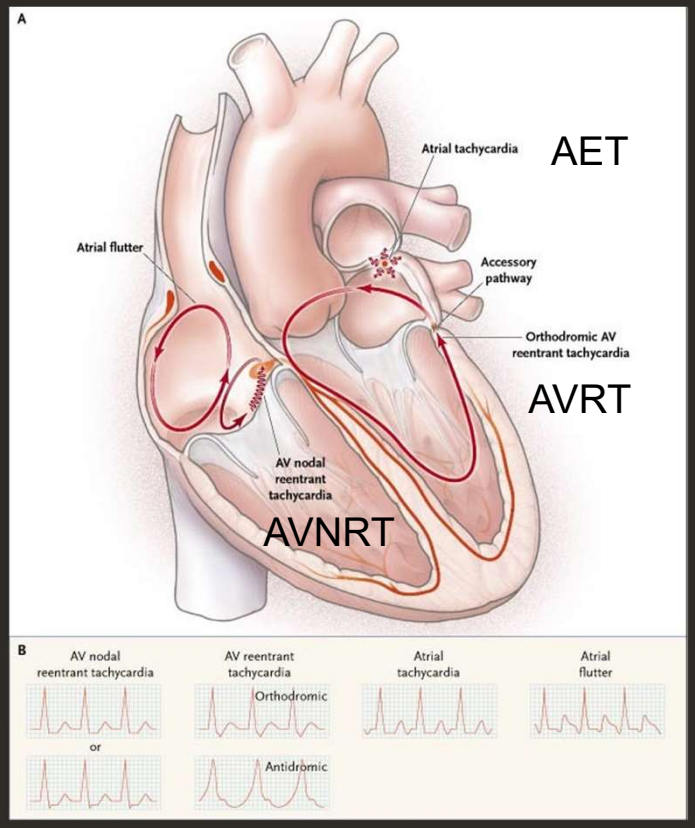
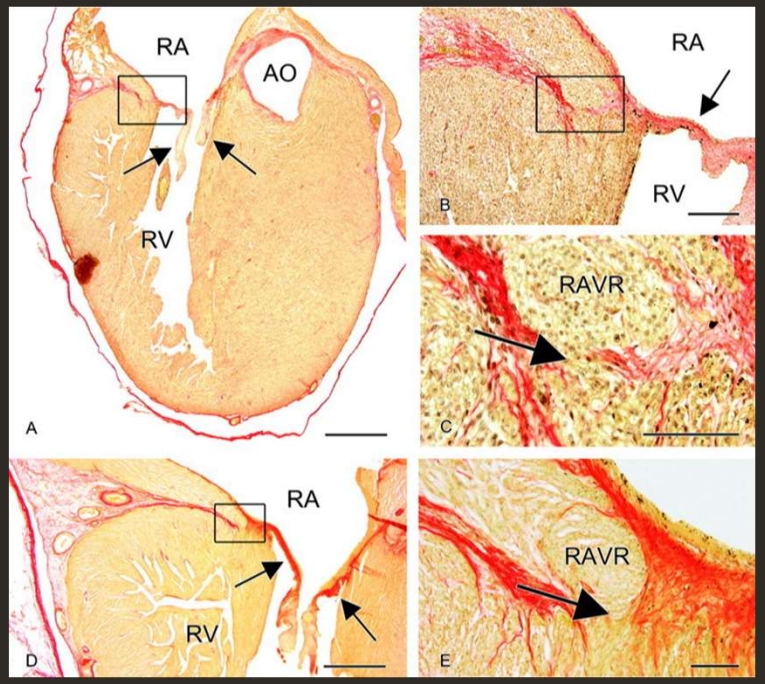
SVT mechanisms



Accessory pathways in the developing heart



Hahurij et al Circulation 2008

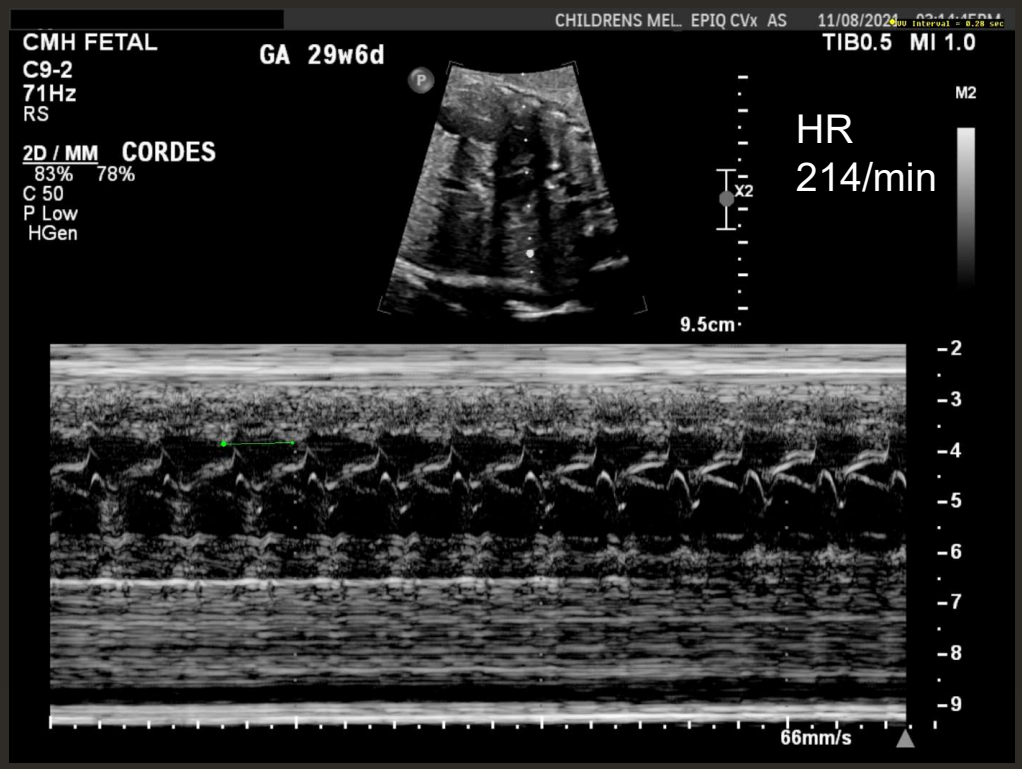
Case 1

- 35-year-old G6P3 female referred at 29 6/7 weeks of gestation for fetal tachycardia evaluation
- No other pregnancy complications
- No active maternal medications
- No family history arrhythmias, congenital heart disease or sudden cardiac deaths

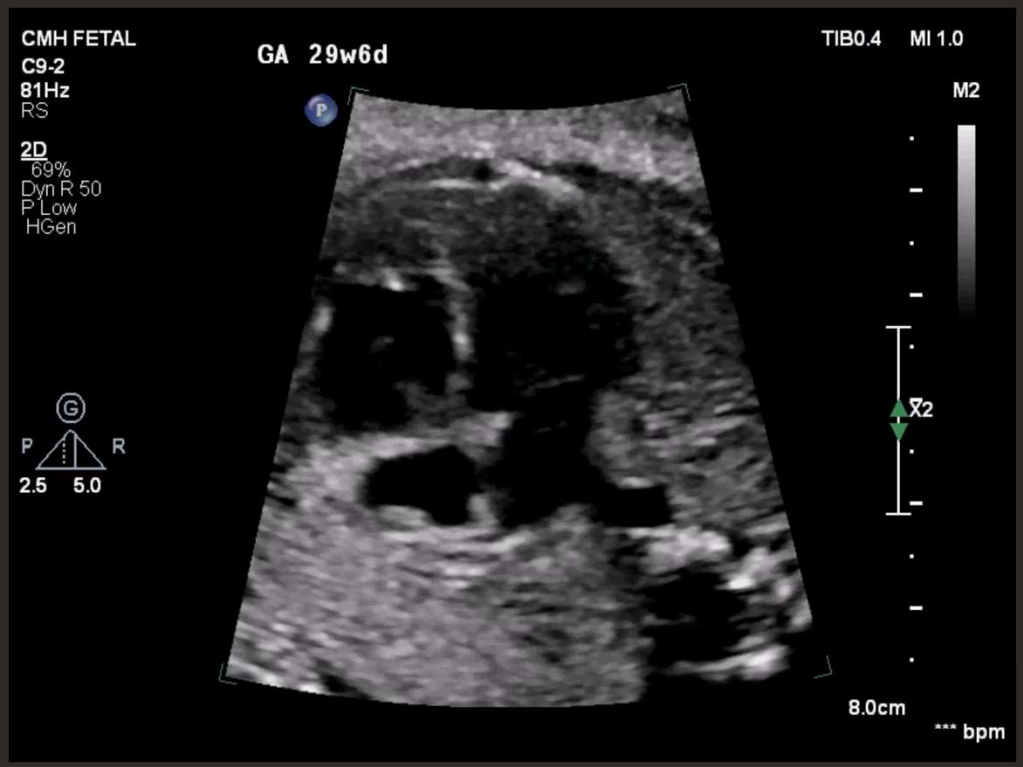
Initial situs sweep

2D/ M Mode


CMH FETAL
C9-2
79Hz
RS
2D
73%
Dyn R 50
P Low
HGen
CORDES
GA 29w6d
TIB0.3 MI 1.0
M2
X2
9.5cm
*** bpm
P
R
2.5 5.0


CHILDRENS MEL. EPIQ CVx AS
CMH FETAL
C9-2
71Hz
RS
2D / MM
83% 78%
C 50
P Low
HGen
CORDES
GA 29w6d
TIB0.5 MI 1.0
M2
X2
9.5cm
HR
214/min
66mm/s

4-Ch Cine tachycardia



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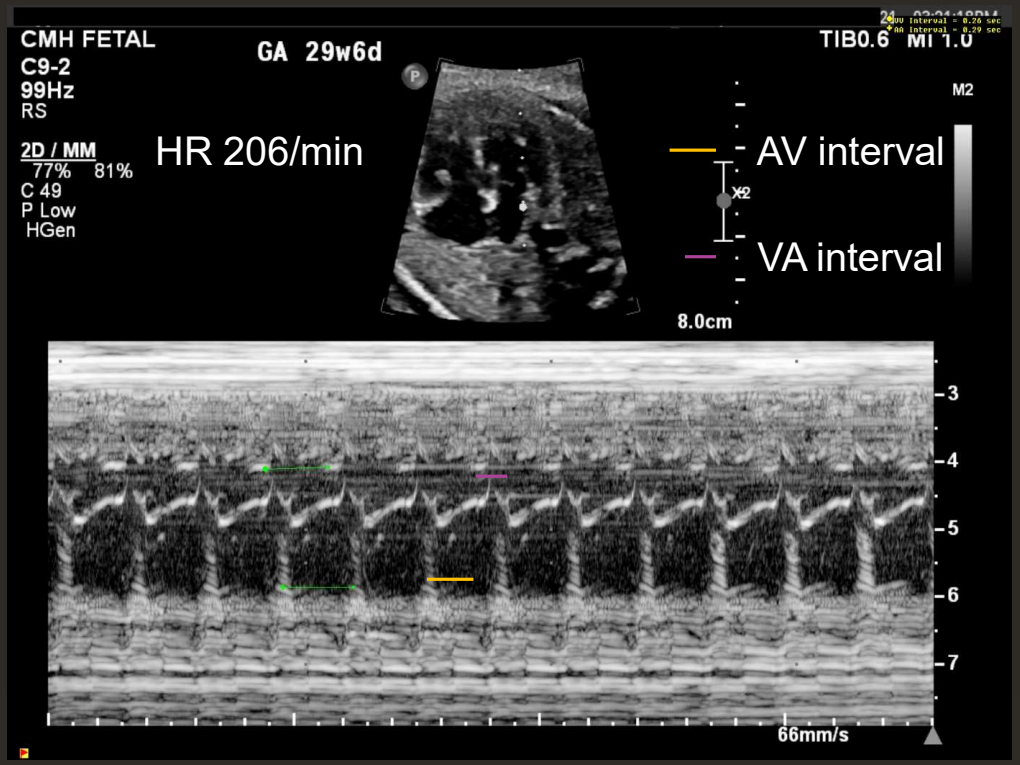
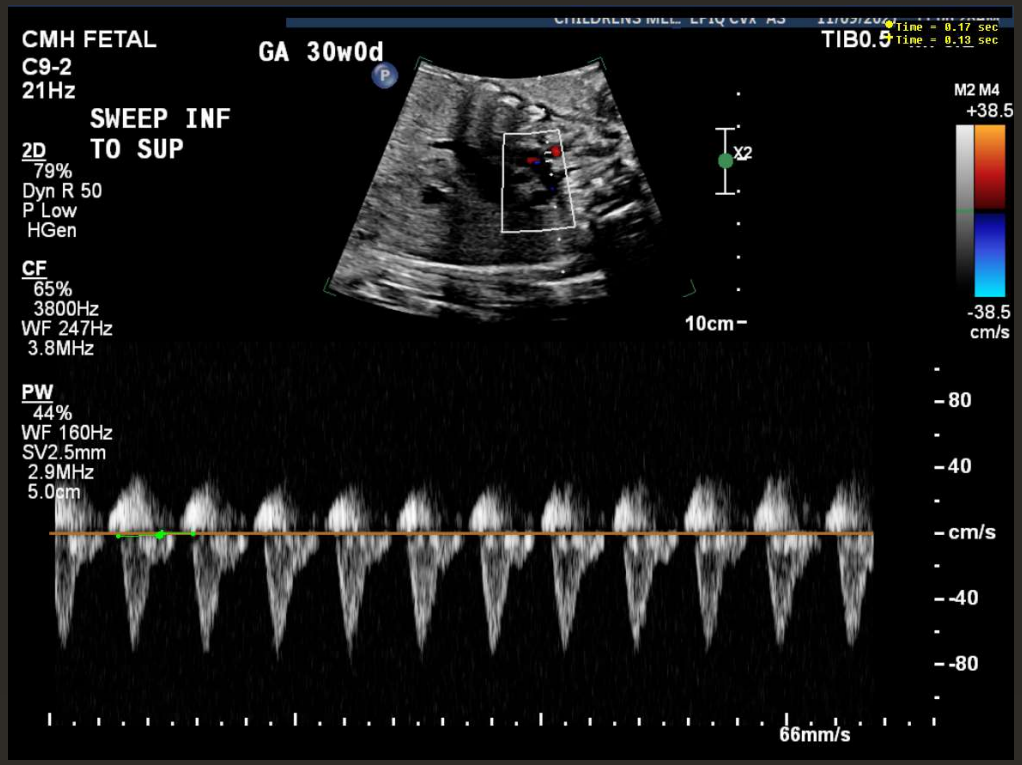
M mode, SVC/Ao doppler





Case 1 course

- Initial inpatient admission for observation showed 20% SVT
- Fetal echo following day slightly >50% SVT
- Another repeat follow up fetal echo the following day with only two episodes of SVT
- Repeat another echo 2 days later with mostly SVT
- Started on Flecainide 100mg PO TID
- Repeat echo 2 days later with less SVT
- Now last seen at 36 6/7 weeks in all sinus rhythm

Case 2

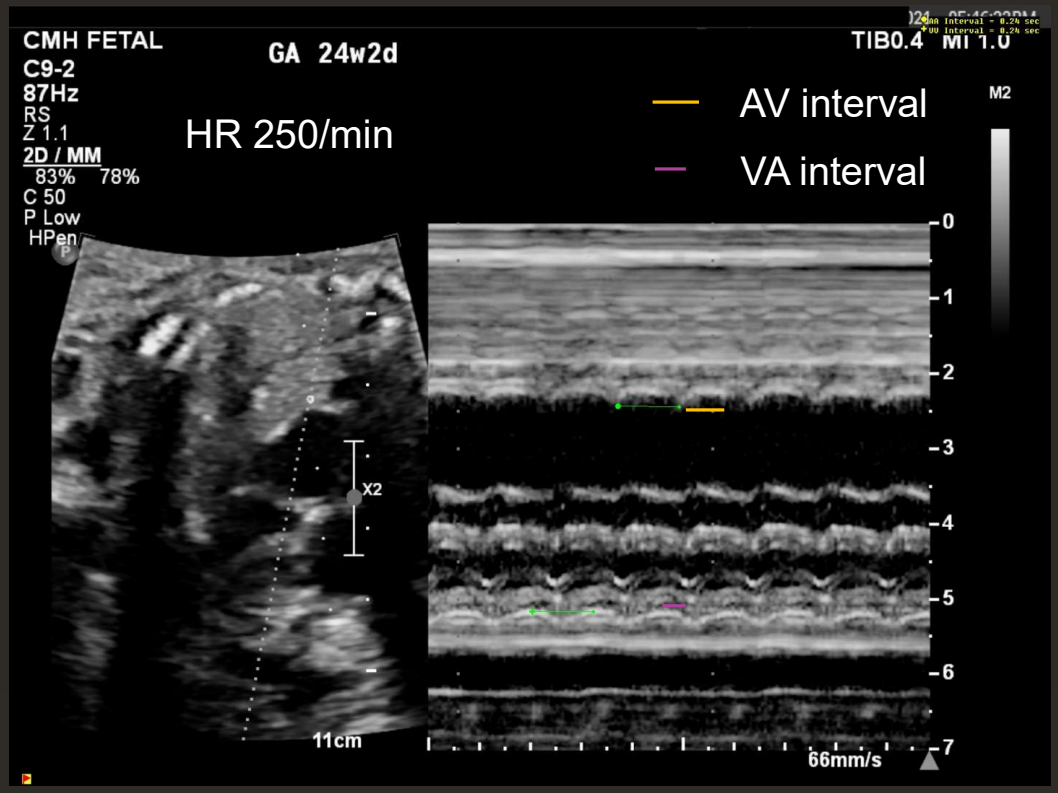
- 29-year-old G3P1 female referred at 24 2/7 weeks of gestation for fetal arrhythmia evaluation
- Pregnancy complicated with borderline elevated blood pressures
- No maternal medications except prenatal vitamins
- No significant family history

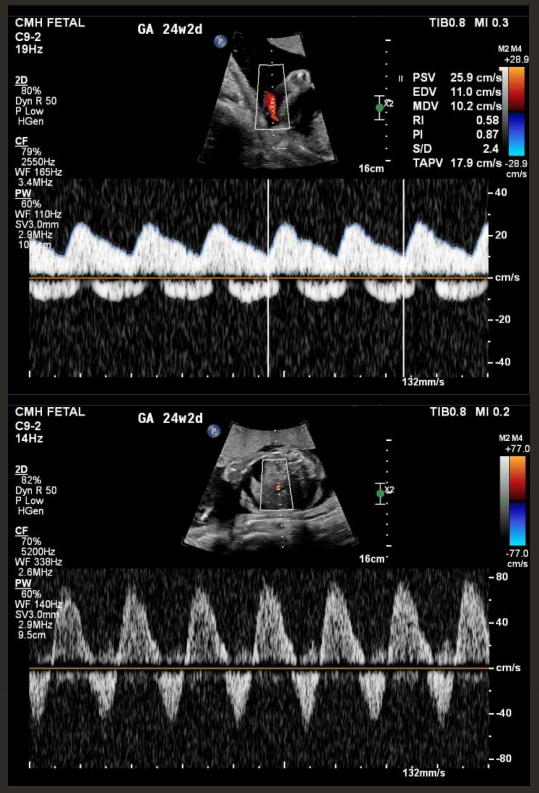
Initial situs sweep

4-Ch Cine


CMH FETAL
C9-2
66Hz
RS
2D
69%
Dyn R 47
P Low
HPen
GA 24w2d
TIB0.8 MI 0.9
M2
X2
12cm
*** bpm
G
R
2.4 4.8

M Mode, UA/UV, DV





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Case 2 course

- Initial inpatient admission
- Maternal baseline BMP, ECG, cardiology consult
- Digoxin load and Flecainide initiated
- Repeat fetal echo 2 days - still sustained SVT but slower rate 210-220s (from 240-250s). Digoxin to maintenance dosing
- Repeat fetal echo 2 days – intermittent SVT 25-50%
- Serial improvement thereafter

Case 2 Postnatal course

- Full term infant (39 weeks) born via SVD
- Birth weight 3.65 kg
- Baseline EKG without any preexcitation
- Normal echocardiogram except for PFO/PDA
- Observed postnatally for 5 days
- No SVT!!
- Last seen ~ 1 month of age and no SVT and no meds

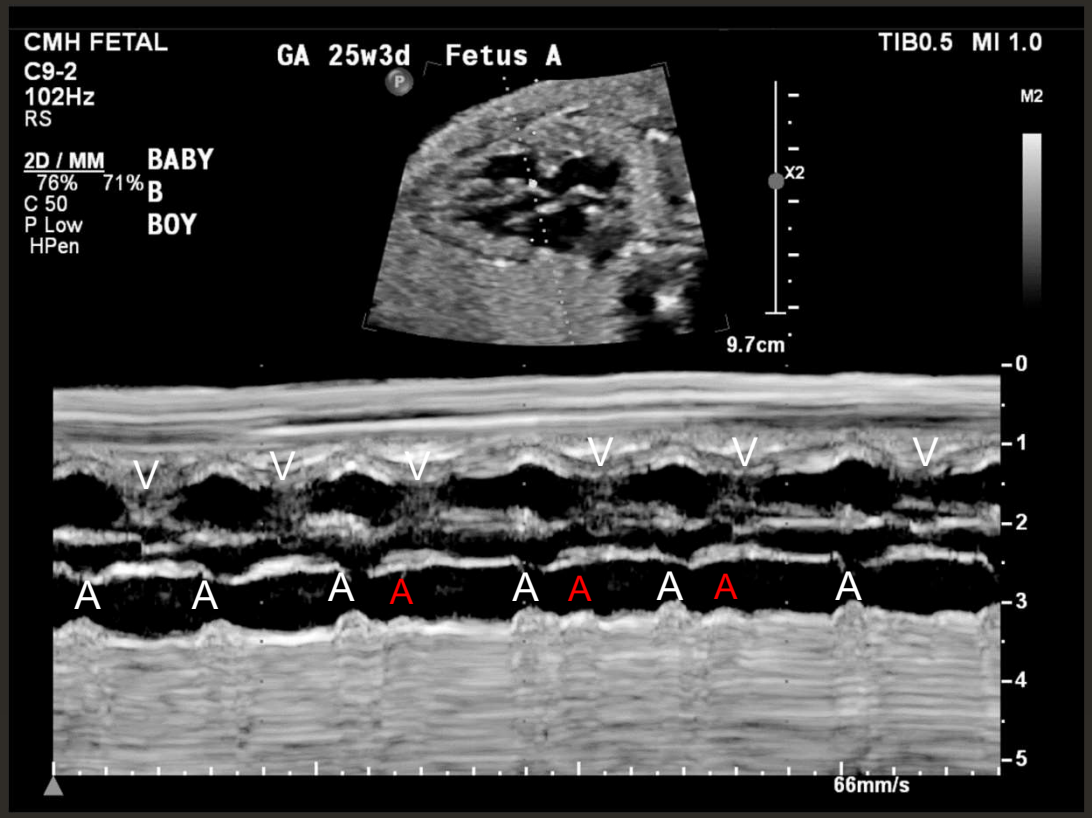
Case 3

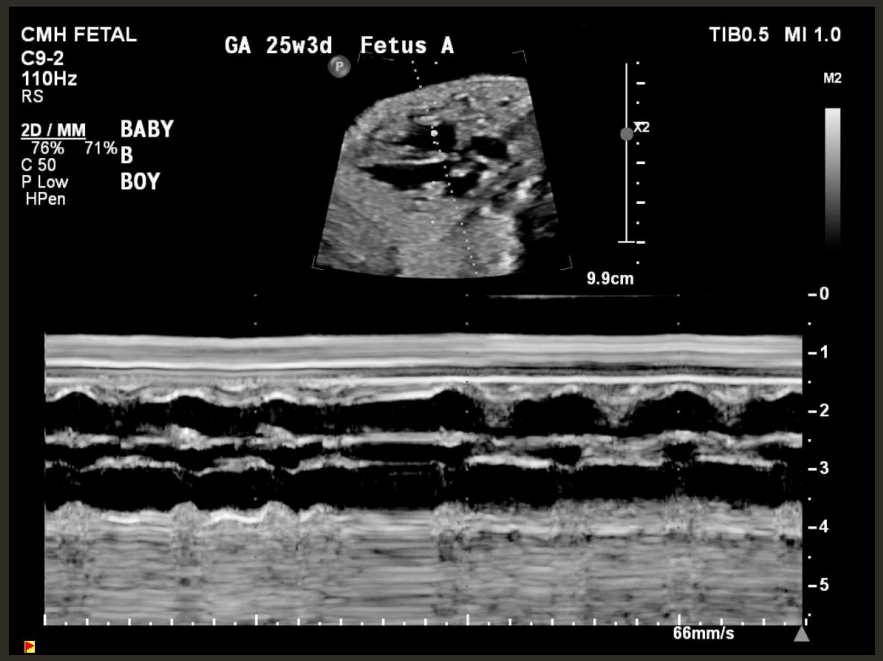
- 32-year-old referred at 25 3/7 weeks for fetal intermittent SVT evaluation in a twin gestation
- Maternal history of PACs, PVCs and atrial fibrillation. On verapamil stopped prior to pregnancy
- Negative family history

4 chamber sweep

- Most fetal arrhythmias are isolated
- Structural heart disease in 10% of fetuses with tachycardia:
  - Ebstein anomaly
  - Tumors
  - Atrial septal aneurysm
  - Ventricular aneurysm
  - HLHS
  - CAVC

M Mode





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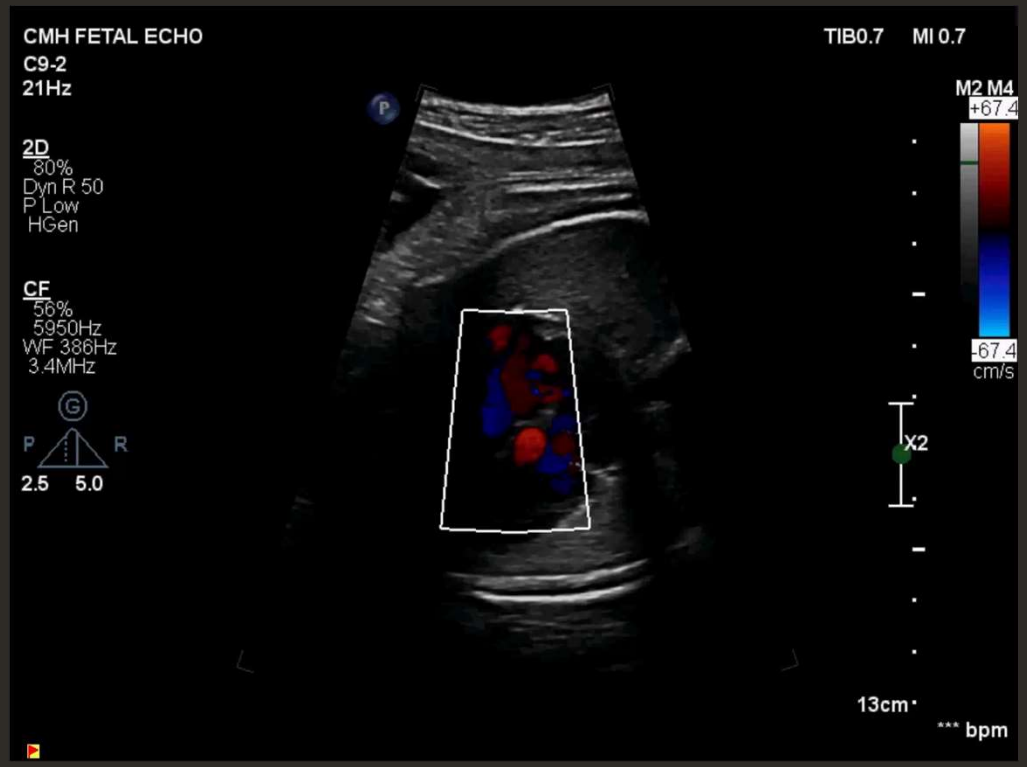
Case 3 Course

- No sustained arrhythmia prenatally
- Twin infant delivered at term via SVD
- EKG with preexcitation
- No SVT
- No medications
- Being followed for the mass
- Genetic testing for tuberous sclerosis negative

Case 4

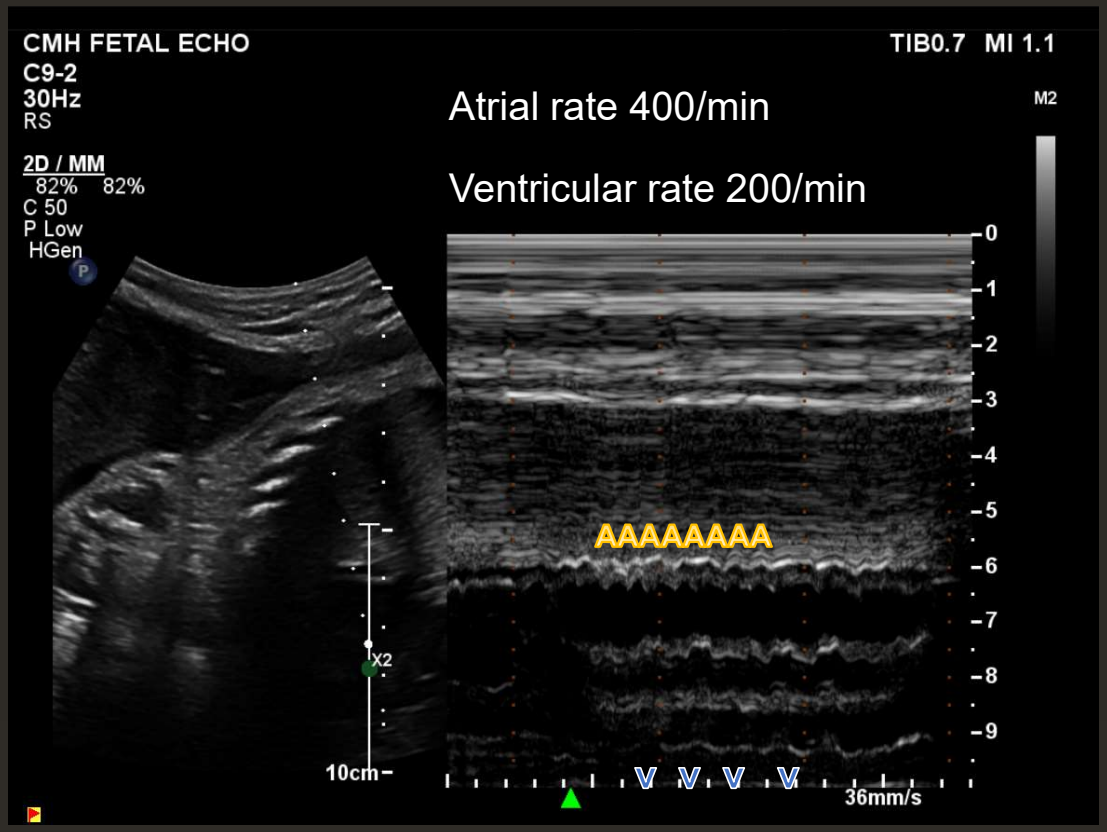
- 36-year-old female referred at 37 weeks gestation for fetal arrhythmia
- Negative family history
- No medications except iron and prenatal vitamins

2D and color 4 Chamber



Children's Mercy

M Mode


CMH FETAL ECHO
C9-2
30Hz
RS
2D / MM
82% 82%
C 50
P Low
HGen
TIB0.7 MI 1.1
M2
Atrial rate 400/min
Ventricular rate 200/min
AAAAAAAA
V V V V
10cm
36mm/s
0
1
2
3
4
5
6
7
8
9

Case 4 course

- Followed for 1 week
- Counselled for labor induction with difficulty to monitor vs. C. Section
- 38-week infant delivered via C. Section
- Birth weight 2.7 kg
- EKG: Normal sinus rhythm
- Echo: PFO/PDA
- Observed for 3 days
- No arrhythmia and has remained arrhythmia free in follow up

FAST trial

- Prospective multi-centered trial
- Study components:
  - Three prospective RCT sub-studies (FAST RCT) to determine the efficacy and safety of specific transplacental drug regimens
  - A prospective observational cohort study (FAST registry) seeks to establish an international database of fetal SVA management done to date. CMH is a FAST registry site
- Primary outcome: Proportion of term deliveries of live-born children with normal cardiac rhythm (Term ≥ 37 weeks gestation)
- Secondary outcome: Efficacy of different treatment options

FAST Registry Inclusion

Inclusion Criteria:

- Written informed maternal consent
- Fetal AF or SVT with or without hydrops
- Tachyarrhythmia that is significant enough to consider prenatal treatment:
- Gestational age <36 + 0 weeks at time of enrollment
- Singleton Pregnancy
- Healthy mother with ± normal pre-treatment cardiovascular findings:
  - ECG within normal range
  - Maternal resting heart rate ≥ 50 bpm
  - Maternal systolic BP ≥ 85 mmHg
- Patients who are being observed without treatment can be enrolled

FAST Registry Exclusion

- Primary delivery for postnatal cardioversion
- Antiarrhythmic fetal treatment for more than 2 days at time of enrollment
- Any maternal-fetal conditions associated with high odds of premature delivery and/or death
- History of significant maternal heart condition (open heart surgery; sick sinus syndrome; long QT, Brugada syndrome; ventricular tachycardia; WPW syndrome; high-degree heart block; cardiomyopathy)

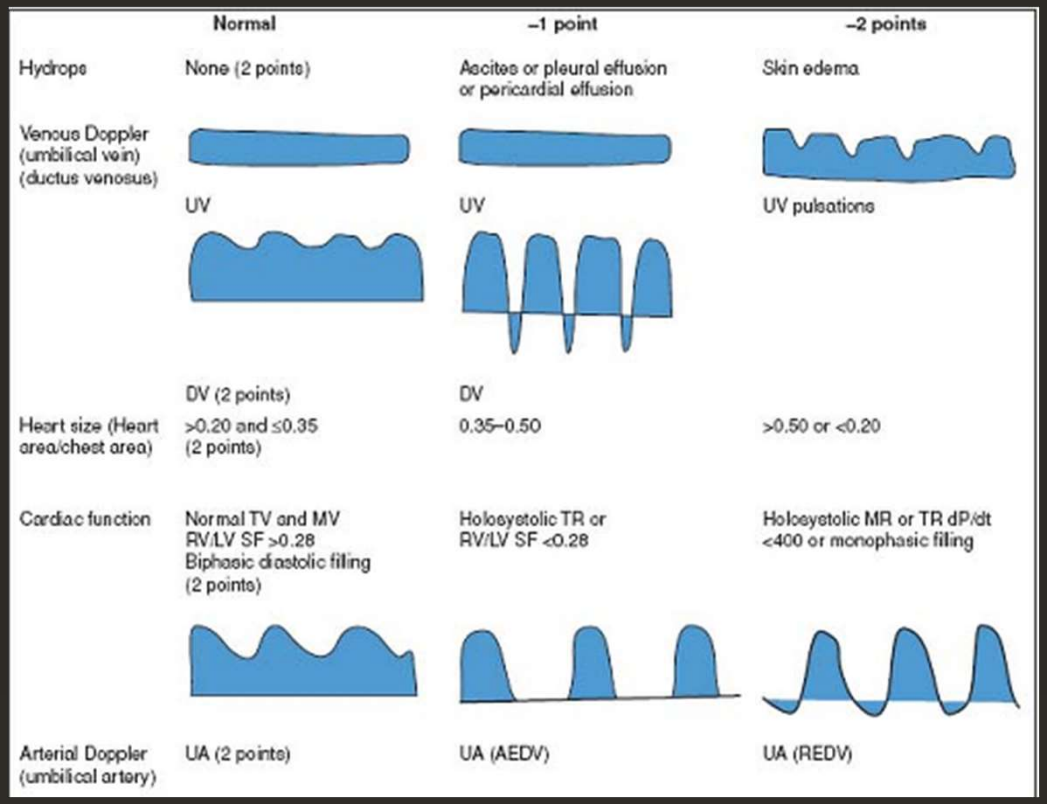
Recent FAST numbers

Global Site Recruitment	RCT	Registry	TOTAL
Recruited between 16-Jul-2021 and 23-Nov-2021	4	17	21
TOTAL as of 23 Nov 2021	63	214	**279**

Key reporting elements prior to tachyarrhythmia treatment

- Gestational age
- Diagnosis clearly as one of SVT with/without hydrops or AF with/without hydrops
- Arrhythmia pattern: Brief (10%), Intermittent (10-49% of time in tachycardia), Incessant (50-99%) or permanent
- Atrial rate during tachycardia
- Ventricular rate during tachycardia

Fetal cardiovascular function



	Normal	–1 point	–2 points
Hydrops	None (2 points)	Ascites or pleural effusion or pericardial effusion	Skin edema
Venous Doppler (umbilical vein) (ductus venosus)	UV DV (2 points)	UV DV	UV pulsations
Heart size (Heart area/chest area)	>0.20 and ≤0.35 (2 points)	0.35–0.50	>0.50 or <0.20
Cardiac function	Normal TV and MV RV/LV SF >0.28 Biphasic diastolic filling (2 points)	Holosystolic TR or RV/LV SF <0.28	Holosystolic MR or TR dP/dt <400 or monophasic filling
Arterial Doppler (umbilical artery)	UA (2 points)	UA (AEDV)	UA (REDV)

When to treat?

Term vs Preterm

Hydrops?

Intermittent vs Incessant

Mode of delivery desired

Approach to therapy

Approach to therapy of fetal tachyarrhythmias

Gestational age	Rate (beats/minute)	Persistence	Hydrops	Therapy sequence
≥37 weeks	200 to 220	Low or Moderate	No	▪ Observe ▪ Aim for term delivery
		Incessant	No	▪ Maternal transfer to pediatric cardiac center
	>220 to 240	Low	No	▪ Consider digoxin (outpatient regimen)
		Moderate or Incessant	No	▪ Maternal referral to pediatric cardiac center ▪ Consider trial of flecainide
	>200	Any	Yes	▪ Prompt referral to pediatric cardiac center ▪ Anticipate delivery
<37 weeks	200 to 220	Low or Moderate	No	▪ Observe ▪ Aim for term delivery ▪ Trial of digoxin (outpatient regimen) reasonable ▪ Delivery at a pediatric cardiac center may be preferred
		Incessant	No	▪ Referral to pediatric cardiac center ▪ Brief trial of digoxin reasonable ▪ May require flecainide/sotalol
	>220 to 240	Low	No	▪ Consider digoxin (outpatient regimen) ▪ Incomplete control acceptable
		Moderate or Incessant	No	▪ Referral to pediatric cardiac center ▪ Brief trial of digoxin reasonable ▪ May require flecainide/sotalol
	>200	Any	Yes	▪ Prompt referral to pediatric cardiac center ▪ Brief or no trial of digoxin ▪ Flecainide or sotalol
		Any	Yes and preeclampsia	▪ Delivery

Persistence refers to the amount of time that the fetus is in the arrhythmia: Low (<25%), moderate (25 to 50%), incessant (>50%).

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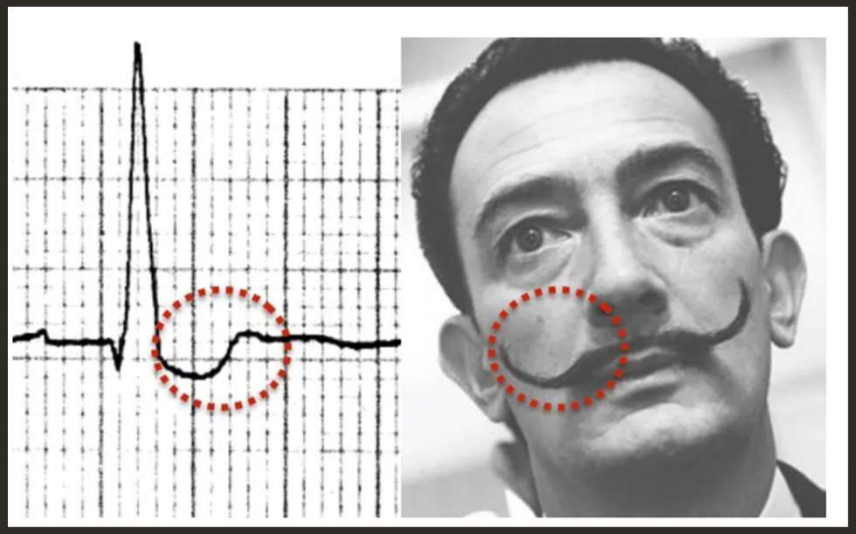
Common transplacental therapy drugs for tachyarrhythmias

Digoxin: long history as drug of first choice but more recent experience has challenged that recommendation

- Actions:
  - Direct suppression of AV node conduction
  - Enhanced vagal tone
  - Inotropic effect
  - Decreased ventricular rate to fast atrial arrhythmias
- Oral digoxin is well absorbed and transferred to fetus (F/M 0.8/1)
- Common patient complaints: nausea, vomiting, headaches, blurred vision, lethargy
- Digoxin toxicity: severe nausea/vomiting, sinus bradyarrhythmia/AV block, proarrhythmia

Digoxin EKG effects

- Downsloping ST depression “Salvador Dali sagging”
- Flattened, inverted or biphasic T waves
- PR prolongation



Digoxin dosing and monitoring

- Aim: Maternal trough *1.0-2.0 ng/ml*
- Oral or intravenous loading dose: 0.5mg q 12 (total 4 doses over 48 hours)
- Obtain maternal trough 11-12 hours after the 4th loading dose

Trough level (ng/ml)	Maintenance digoxin dose	Route
2 to <2.3	0.25 mg/day	*Oral*
1.5 to <2	0.375 mg/day	*Oral*
1.2 to <1.5	0.5 mg/day	*Oral*
0.8 to <1.2	0.75 mg/day	*Oral*
<0.8	1 mg/day	*Oral*
≥2.3	0 mg/day until digoxin level is <2 ng/ml	

- Daily maternal EKGs while loading and dosing adjustments
- Repeat maternal trough levels until stead state achieved

Flecainide

- Action: Inhibits Na channels, slowing conduction and increasing refractoriness of all cardiac tissues
- Well-absorbed and transferred to fetus within 3 days (F/M ratio 0.7-0.9)
- Therapeutic level: *0.2-1.0 µg/ml*
- Initial dosing 100mg PO TID
- Side effects: Headache, first-degree AV block, mild P and QRS widening, QTc ≤ 0.48s
- Toxicity: Visual/CNS symptoms, BBB, QTc ≥ 0.48s, maternal/fetal proarrhythmia

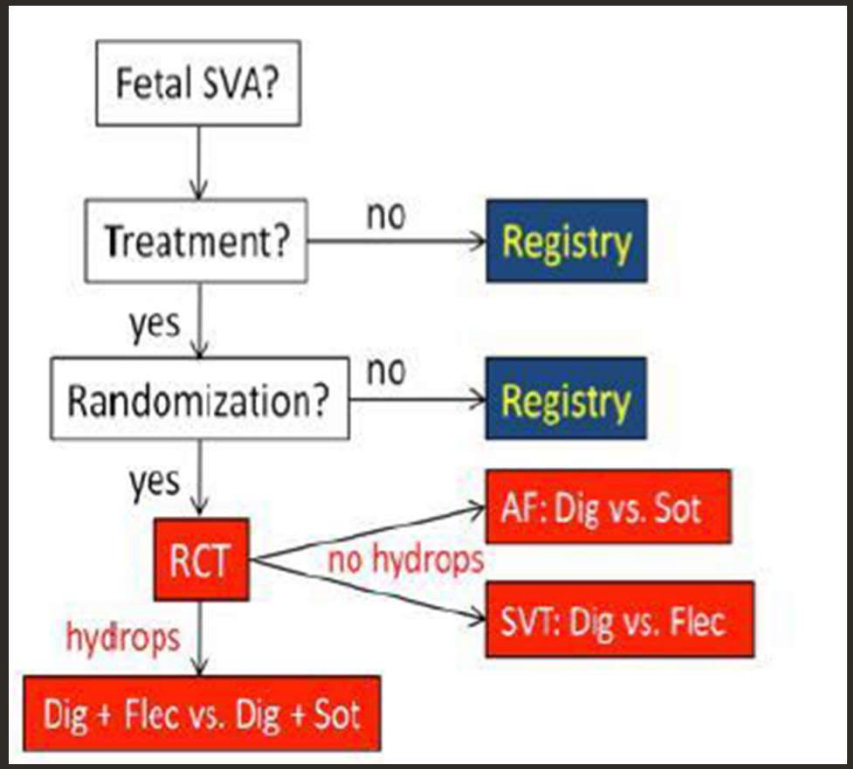
Sotalol

- Action: iKr channel and β-blocker, combined effects decrease heart rate and prolong actional potential and tissue refractoriness
- Well absorbed and transferred to fetus
- Usual starting dose 80mg PO TID or 120mg PO BID
- Side effects: Bradycardia, fist degree AV block, P and QRS widening, QTc ≤ 0.48 s
- Toxicity: Nausea/vomiting, dizziness, fatigue, QTc ≥ 0.48s, BBB, maternal/fetal proarrhythmia

Additional agents

Drug	Therapeutic Maternal Dose Range	Therapeutic Level and Effect	Toxicity
Amiodarone	LD: 1800–2400 mg/d divided every 6 h for 48 h PO; lower (800–1200 mg PO) if prior drug therapy MD: 200–600 mg/d PO Consider discontinuation of drug and transition to another agent once rhythm is converted or hydrops has resolved.	0.7–2.8 μg/mL Maternal/fetal sinus bradycardia, decreased appetite, first-degree AV block, P and QRS widening, QTc ≤0.48 s	Nausea/vomiting ++, thyroid dysfunction ++, photosensitivity rash, thrombocytopenia, BBB, QTc ≥0.48 s, maternal/fetal proarrhythmia, fetal torsades with LQTS, fetal goiter, neurodevelopmental concerns
Propranolol	60–320 mg/d divided every 6 h PO	25–140 ng/mL First-degree AV block, bradycardia, increased uterine tone	Fatigue, bradycardia +++, hypotension+++, AV block, fetal growth restriction, increased uterine tone
Lidocaine	LD: 1–1.5 mg/kg IV followed by infusion of 1–4 mg/min	1.5–5 μg/mL	Nausea/vomiting ++, CNS symptoms, proarrhythmia
Mexiletine	600–900 mg/day divided every 8 h PO	0.5–2 μg/mL	Nausea/vomiting ++, CNS symptoms, proarrhythmia
Magnesium sulfate	LD: 2–6 g IV over 20 min followed by 1–2 g/h Treatment for >48 h is not recommended but redosing may be considered if VT recurs	<6 mEq/L Monitor patellar reflex	Fatigue, CNS symptoms, STOP for loss of patellar reflex and/or levels of >6 mEq/L Levels >5 mEq/L associated with maternal changes on ECG and proarrhythmia


pharmacy
Rx
?
pharmacy
Rx


Fetal SVA?
Treatment?
no
Registry
yes
Randomization?
no
Registry
yes
RCT
AF: Dig vs. Sot
no hydrops
SVT: Dig vs. Flec
hydrops
Dig + Flec vs. Dig + Sot

Monitoring

- Close surveillance with cardiology and perinatology services
- Important to recognize that 1st line treatment effects are incremental
- It takes several days to build fetal therapeutic drug levels
- Resist temptation to prematurely change to 2nd line therapy prior to at least 3 days of therapy unless:
  - Worsening fetal state (new hydrops)
  - SVA pattern (>20% increase in SVA rates/duration)
- Once sustained cardioversion achieved, do not change treatment until birth if treatment is well tolerated and arrhythmia does not recur

Prognosis

In utero

- Mortality rates
  - No hydrops - 0%
  - Hydrops – 17- 35%

Hydrops unlikely for HRs <220/min

Hydrops unlikely with brief and intermittent arrhythmia

Postnatal

- Control of rhythm facilitated after birth
- SVT 1/3 1/3 1/3 rule

Atrial flutter prognosis

- Without CHD
  - Excellent
  - “One and done”
  - Therapy beyond first event not indicated
- With CHD
  - Depends

References

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- 1988 *JACC,* Fetal atrial septal aneurysm: A cause of fetal arrhythmias
- Fetal Atrial Flutter & Supraventricular Tachycardia (FAST) Therapy Trial, USA Study Protocols

Thank you!

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- Fetal cardiology team
- Jennifer Nelson
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