FETAL MAGNETOCARDIOGRAPHY AND THE QUEST TO IDENTIFY THE FETUS AT RISK FOR STILLBIRTH

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DISCLOSURES

- Grant Support from NIH (RO1HL143485, RO1HL063174) and the Dr. Scholl Foundation
  - Support travel costs for the fMCG testing
- Optically-pumped Magnetometry is investigational for the fetus, SQUID fMCG is FDA approved
- Writing Committee: 2021 Heart Rhythm Society Consensus Statement on *Arrhythmias in Pregnancy*

We wish to thank the many families who have participated in this research, and the Fetal Care Centers and their Faculty and Staff from around the country for referring cases for evaluation

FETAL ELECTROPHYSIOLOGIC CHARACTERISTICS IN HIGH RISK PREGNANCIES ASSOCIATED WITH FETAL DEMISE – RO1HL143485

- Prospective, longitudinal observational study - 2019-2023
- Eligibility
  - 200 Pregnant females 18 and older
  - Clinically stable for travel and to recline
- Diagnoses
  - Mono twins
  - Hydrops fetalis
  - Gastroschisis
  - Congenital Heart Defects
  - Prior pregnancy ≥20 weeks GA, ending in unexplained stillbirth

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OVERVIEW OF PRESENTATION

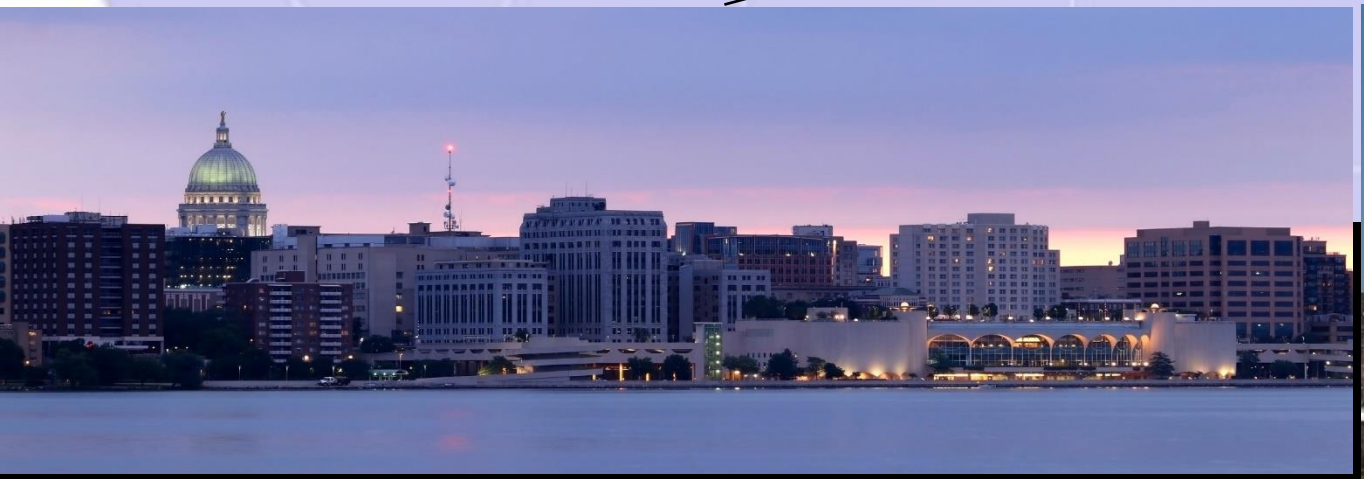
- What is stillbirth, why is it so prevalent, can it be prevented?
- Why is research during pregnancy important?
- What is fetal MCG, how can it contribute to understanding the risk factors for stillbirth?
- What other new methods besides fetal MCG are useful?
- Three cases to show how fMCG has benefitted some subjects at risk of stillbirth

- SMT, Inc
  Rice Lake

* Qu-Spin, Inc,
  Aurora, CO

- ETS Lindgren, Inc
  Woodddale, IL

- Applied Physics Systems, inc Silicon Valley
- Tristan Technologies, Inc, San Diego



Dr. Ronald T Wakai – Professor of Medical Physics

- Biomagnetism Laboratory
  - Device Development (FDA approvals, CPT codes, etc.)
  - Arrhythmia and LQTS research

Dr. Strasburger/Gretchen Eckstein/Patrick Noffke - Herma Heart Institute, Fetal Care Center specialists, and MCW/Marquette Biomedical Engineering

- Stillbirth Research
- Modeling of Arrhythmias

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Shared Medical Technology

Website | Directions | Save

5.0 ★★★★★ 1 Google review

Medical examiner in Rice Lake, Wisconsin

Since 1977

- MRI
- CT
- Ultrasound
- PET
- Nuc Med
- Mammography

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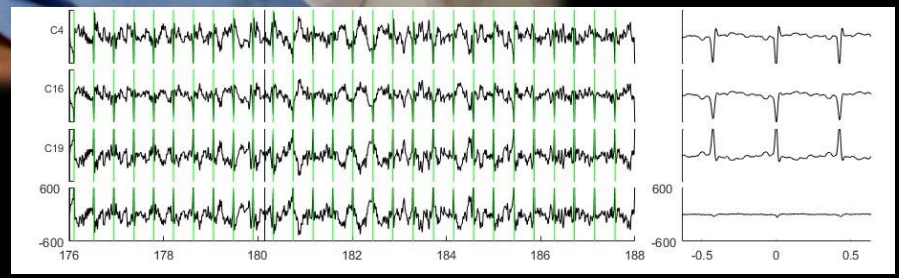
FETAL MAGNETOCARDIOGRAPHY

930 pregnant subjects have been evaluated since 1998

- Similar to ECG
- Real-time interp
- 15-40 weeks GA
- FDA approved
- AHA statement 2014, benefits>>risks



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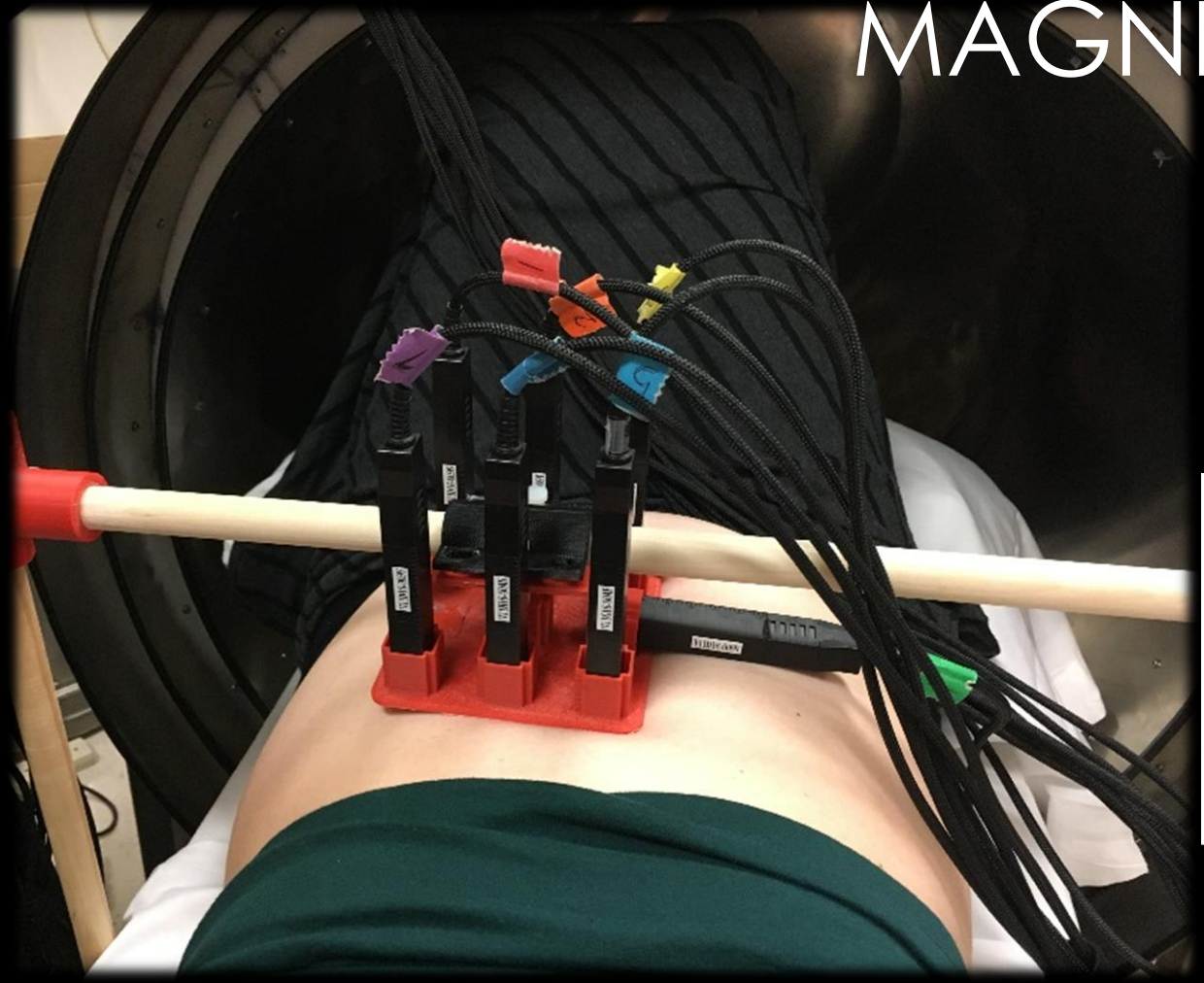
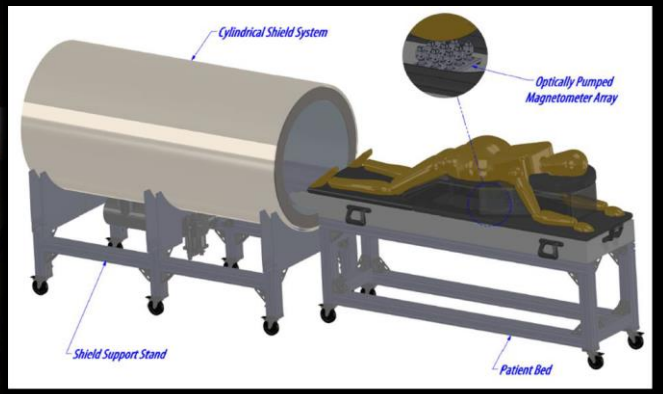
OPTICALLY-PUMPED MAGNETOMETRY

84 pregnant subjects since 2015

- Not yet FDA approved
- 1/10th $$
- New shielding material





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NEW TECHNOLOGIES AND THEIR ROLE IN IDENTIFYING THE FETUS AT RISK FOR STILLBIRTH

- FMCG
- FECG
- Advanced echo technologies
  - Myocardial strain
  - 3D/4D imaging
- MRI
- Genetic testing
  - Whole Exome Testing
- Improved autopsies

These technologies are synergistic and not used at the exclusion of the other

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INVESTMENT IN OBSTETRICAL INNOVATIONS: WHY IS IT SO IMPORTANT

KOGUTT ET AL JOBGYN 2020

TABLE

Total patents and aggregate venture capital data since 2000

	Patent data	Venture capital data					
	Total patents (% of total)	Capital invested (billion)	Companies (n)	Deals (n)	Investors (n)	Exits (n)	Largest deal (million)
Obstetrics	33,913 (0.4)	$1.1	136	337	407	0	$162
Orthopedics	378,349 (4.9)	$4.4	329	827	694	1	$154
Gastroenterology	44,832 (0.6)	$4.8	158	494	567	0	$162
Dermatology	58,897 (0.8)	$4.9	214	557	610	1	$104
Cardiology	1,082,010 (14.0)	$23.4	883	2670	2226	6	$500
Medicine (all specialties)	7,717,604	$334.0	20,226	52,760	18,854	62	$2200

Kogutt. Obstetric innovation. Am J Obstet Gynecol 2020.

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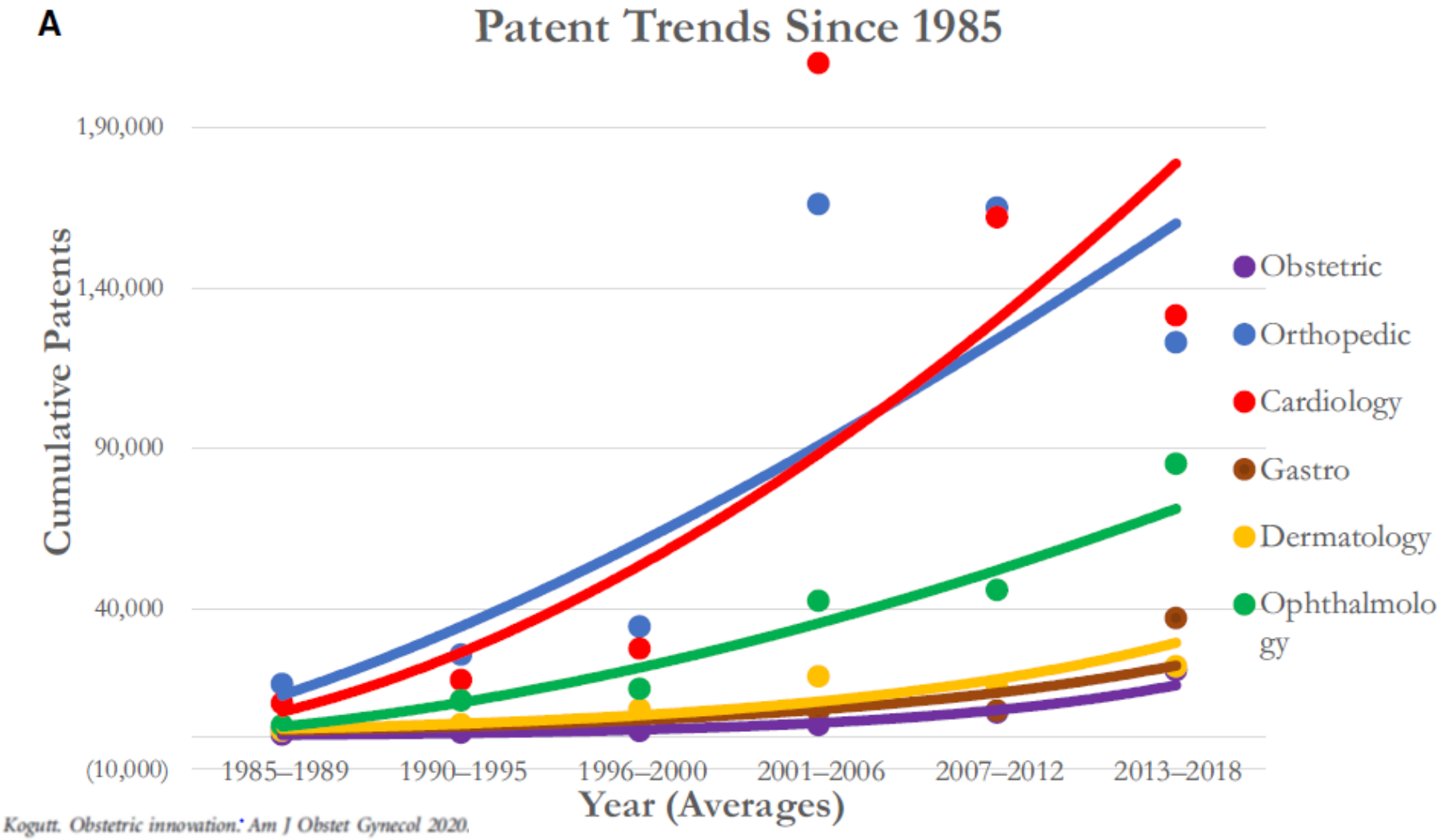
FIGURE 1
Patent trends



Kogutt. Obstetric innovation.' Am J Obstet Gynecol 2020.

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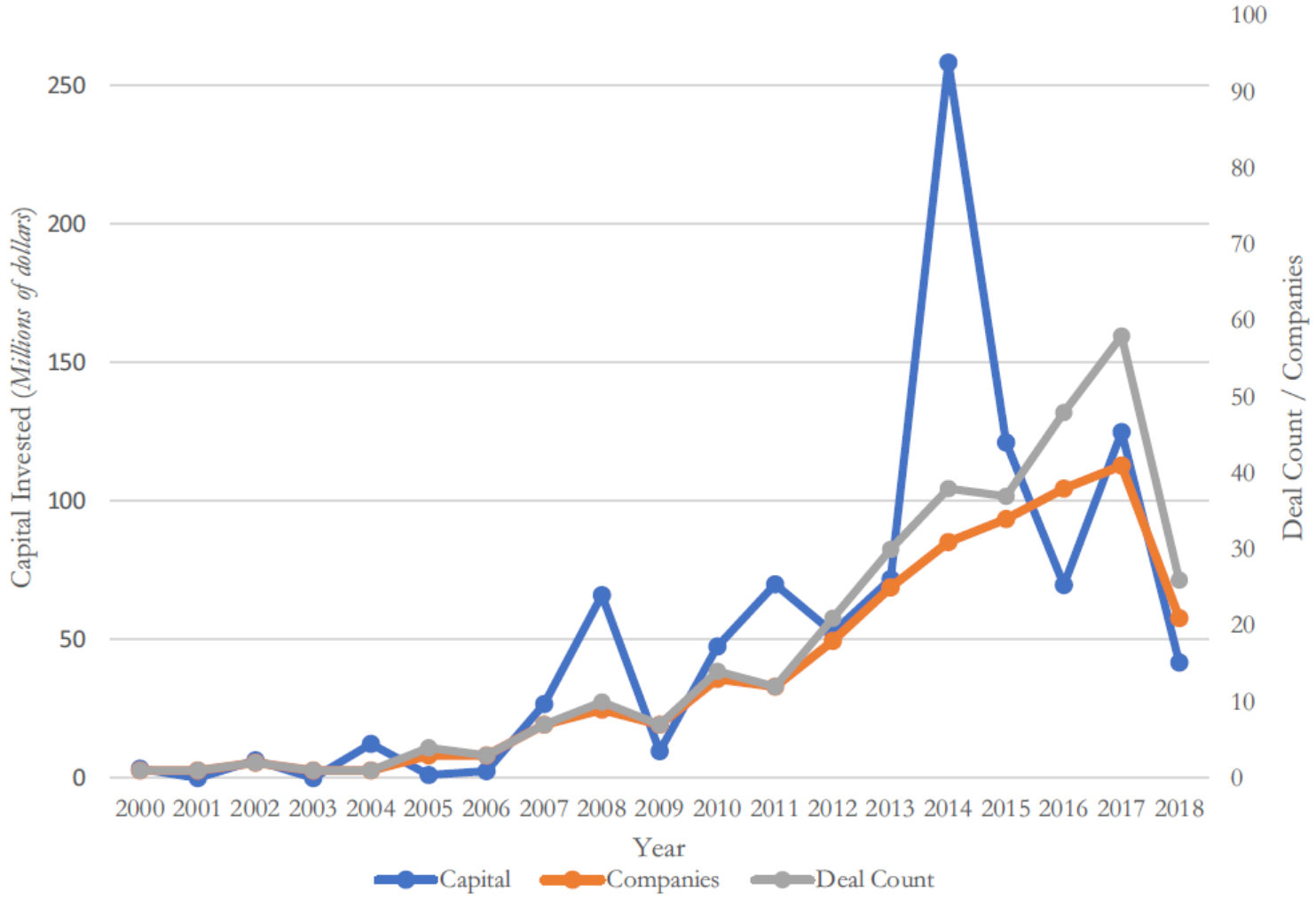
FIGURE 2

Venture capital trends within obstetrics since 2000



Kogutt. Obstetric innovation. Am J Obstet Gynecol 2020.

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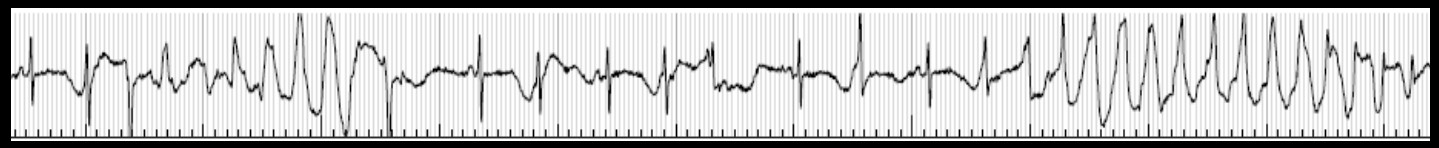
PRECIPITATION OF FETAL DEMISE (STILLBIRTH)

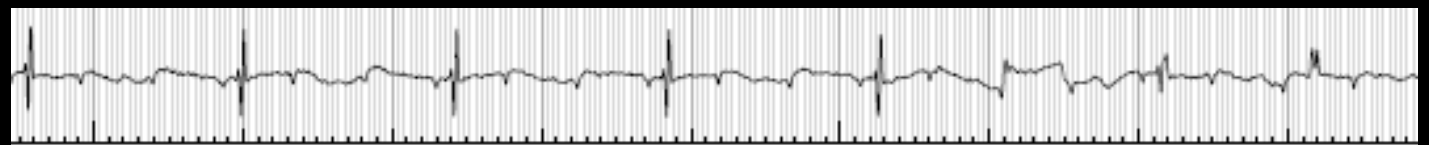
Placenta or cord defect
Pre-eclampsia or HTN
Birth or Genetic defect
Maternal/Fetal disease
Idiopathic 25-40%

Cord accident
Placental insufficiency, abruption
Metabolic
Nutritional
QT↑ Medication

Risk Factor + Acute event = Stillbirth

Rhythm, Conduction, or Repolarization Abnormality





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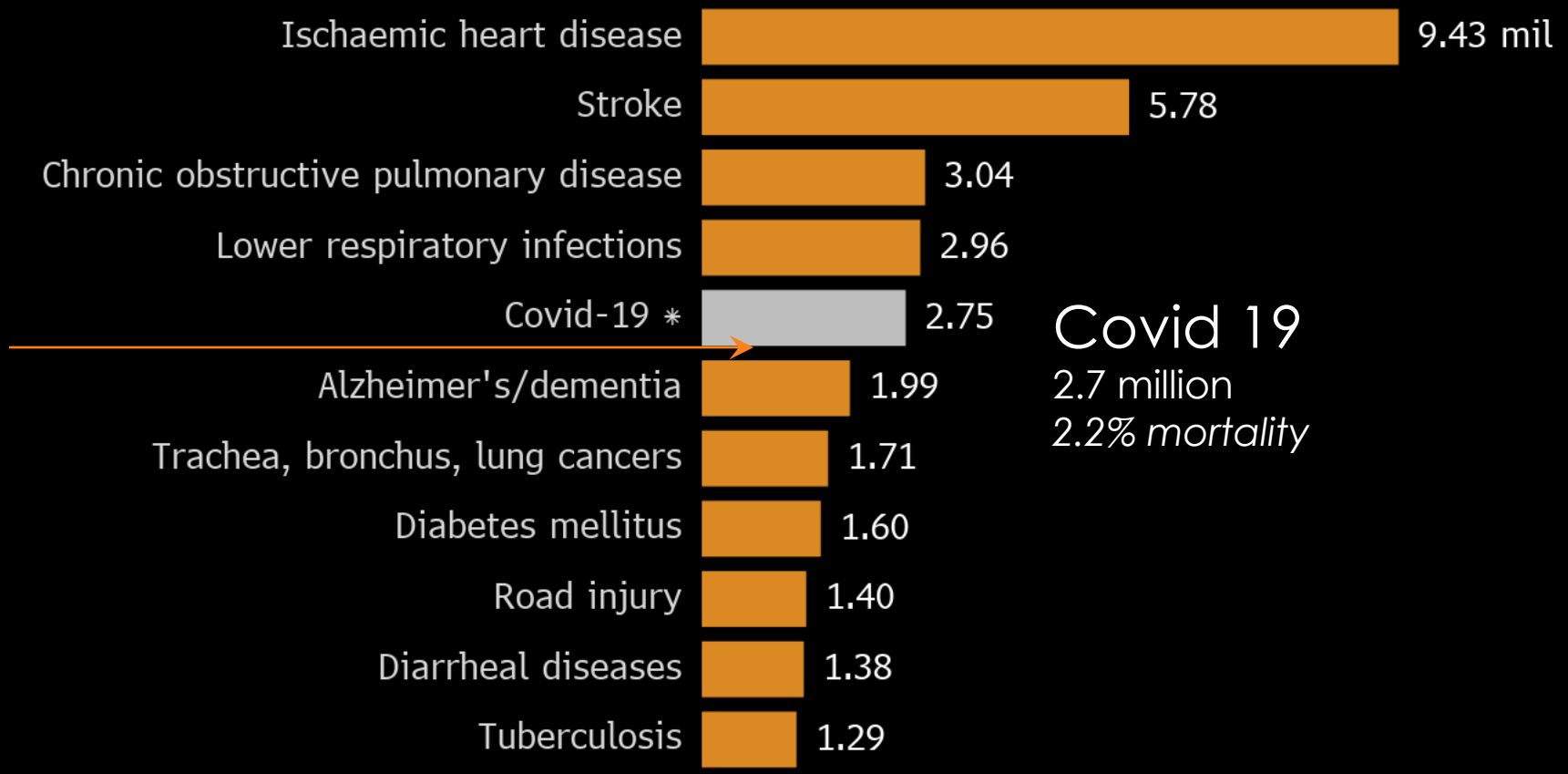
STILLBIRTH

- 5% of population is pregnant each year
- US - stillbirth is ≥20 wks GA, most of world ≥28 wks GA
- 1 in 72 births worldwide
- THIS IS AN UNDERESTIMATE, STILLBIRTHS ARE OFTEN UNDER-REPORTED IN DEVELOPING COUNTRIES
- Stillbirth is not decreasing even in developed countries!
- Even with present enhanced surveillance techniques, monitoring takes place only 0.03 – 0.1% of the pregnancy
  - Vast expanses of unmonitored time
- Fetus provides few clues that fetal demise will occur

Global Killer

By estimates, Covid-19 would rank among top 10 causes of death globally



Stillbirth

2.0 million

1% mortality

Covid 19

2.7 million

2.2% mortality

Source: WHO, Alan Lopez of the University of Melbourne
Note: Cause of death stats for 2016; Covid-19 fatalities estimate is a range between 2.5 million to 3 million

Bloomberg

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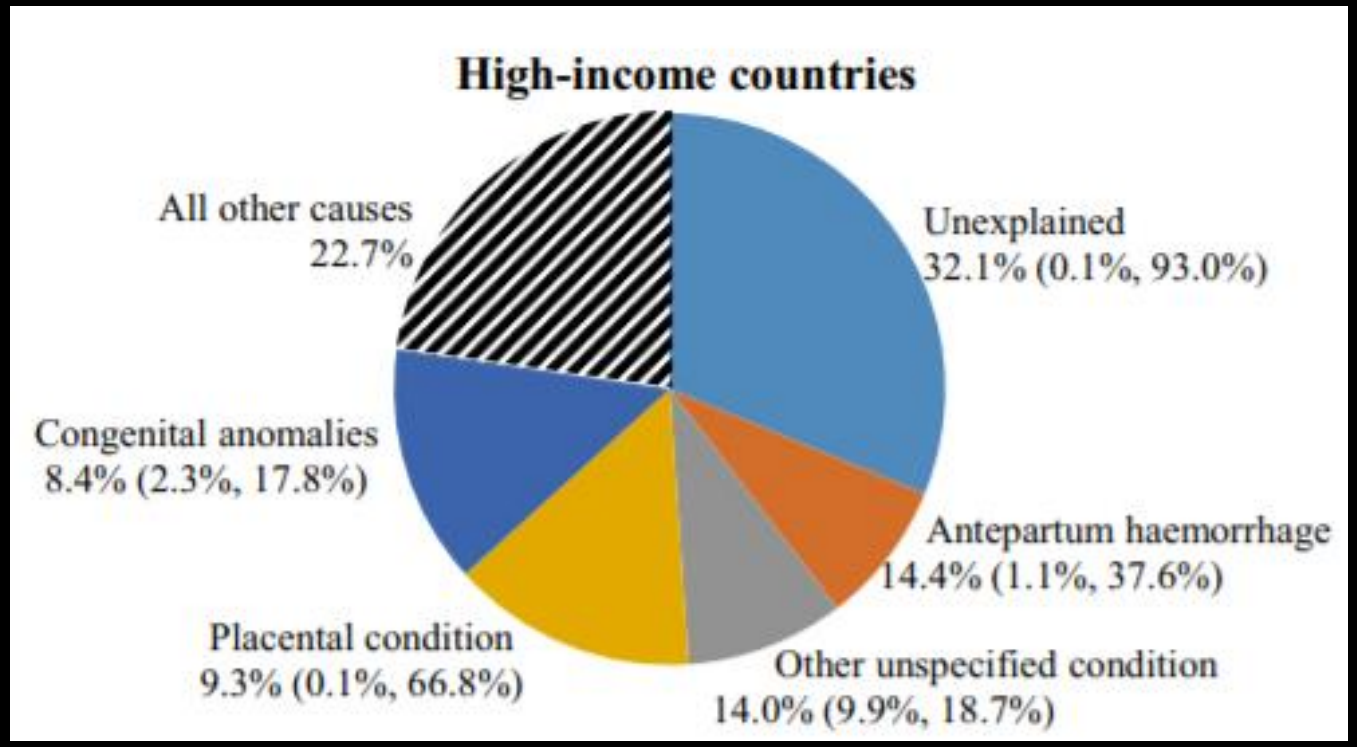
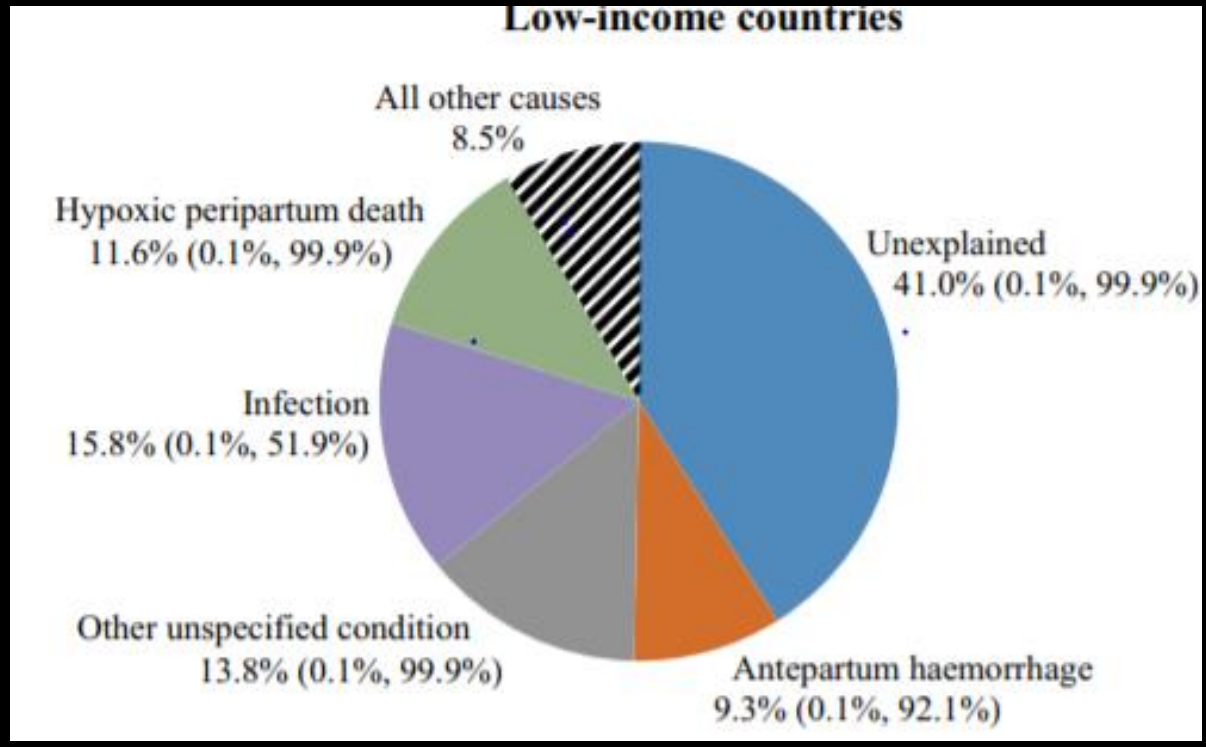
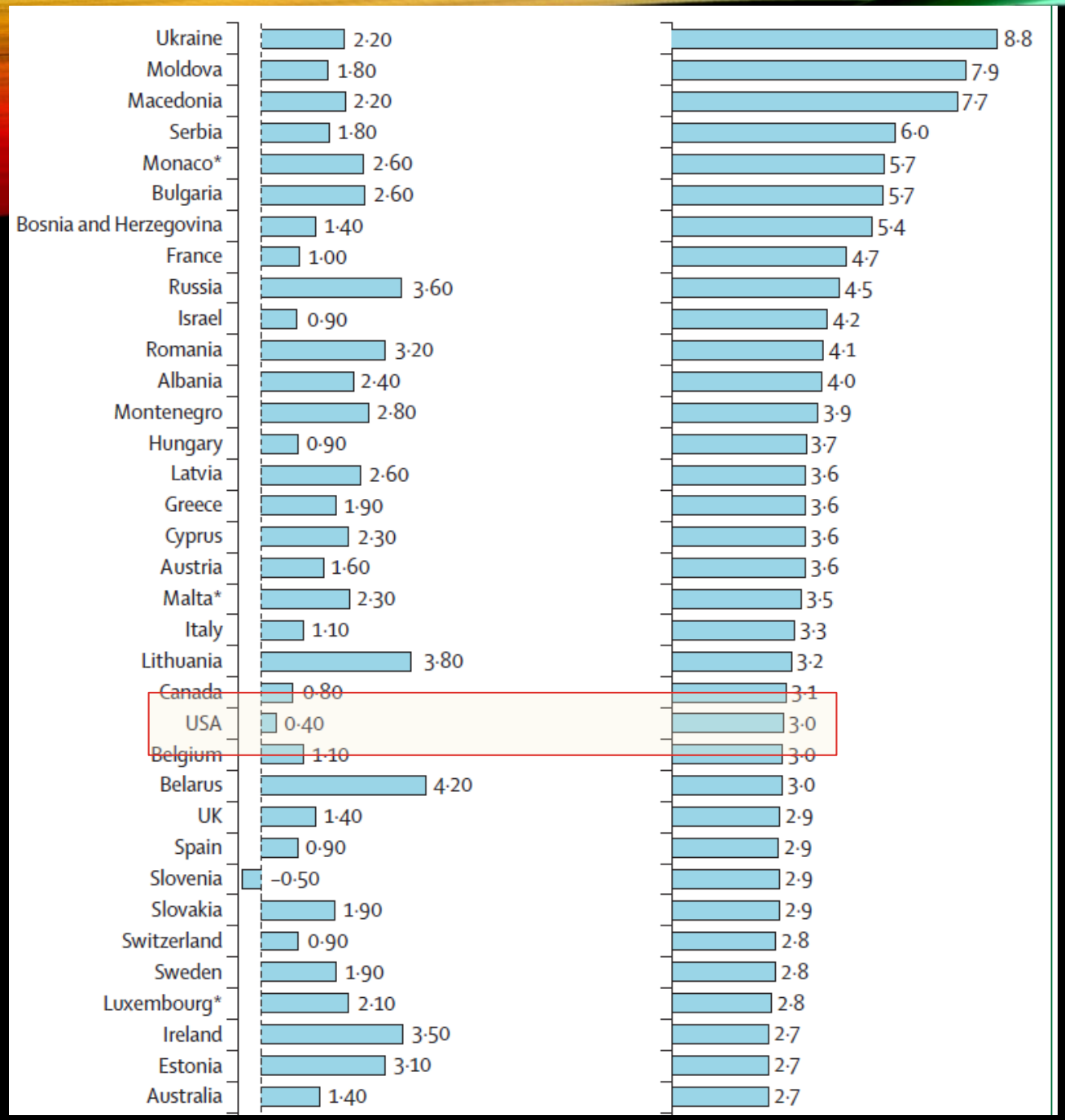
STILLBIRTH ETIOLOGIES





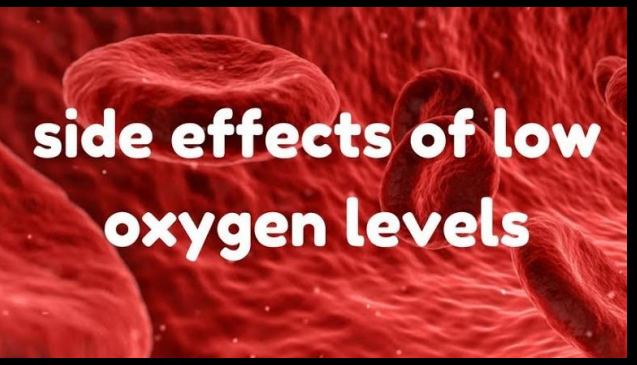
Reinebrant et al, BJOG 2017



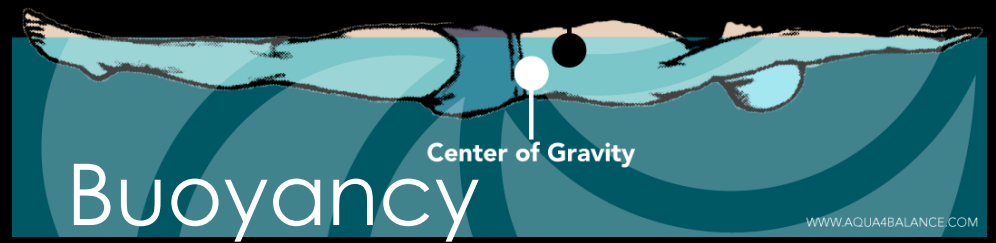
ANNUAL RATE REDUCTION AND ANNUAL RATE OF STILLBIRTH IN DEVELOPED COUNTRIES

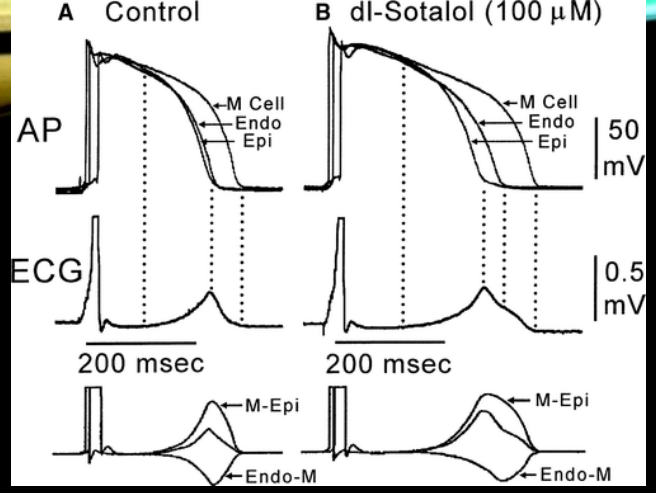
Flenady et al Lancet 2016

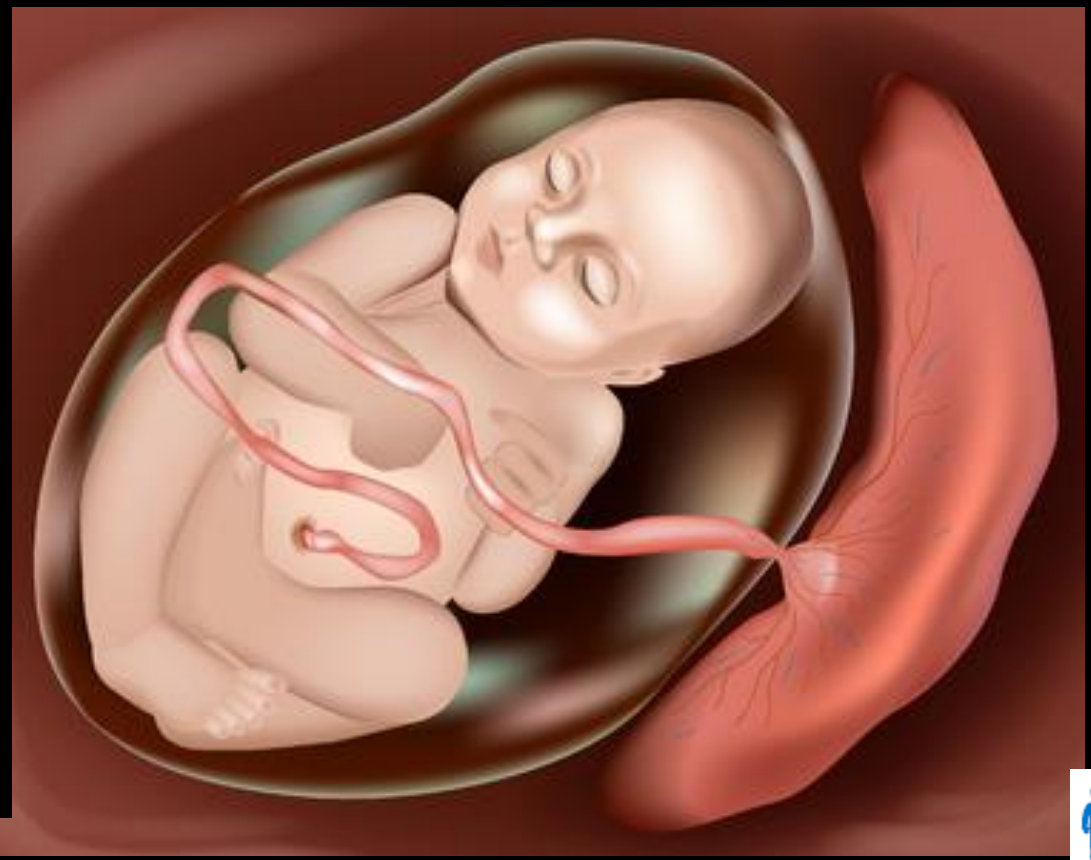
Physical and Mental Health



Genetic Makeup







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MYTHS ABOUT STILLBIRTH

- MYTH "It was inevitable, natures way, there must have been something wrong with the baby."
  - Response: If more funding and effort were placed into determining the causes of stillbirth, it would likely be cut in half. Many of the conditions leading to stillbirth are treatable if identified. An example, maternal Vit D deficiency.
- MYTH "We don't know why the fetus died."
  - Response: If the types of diagnostic procedures and treatments that are routinely used in our ICUs, such as pulse oximetry and cardiac monitoring, medications and surgery, could be used prenatally, the outcomes would be different
- MYTH "The death was likely due to a sudden event and could not have been prevented. It won't happen again."
  - Response: ECG patterns precede demise and may be present for weeks prior to fetal death. Occurrence risk for fetal demise in channelopathies is 8 time higher than for stillbirth in the normal population. 50% recurrence risk for dx. Tools such as BPPs are making a difference.

CARDIAC MONITORING

- Heart rate
- Arrhythmias
- Hypertrophy and signs of chronic strain
- STT abnormalities and ischemia
- Bundle Branch block, WPW, and other conduction disturbances
- QT prolongation, T wave alternans, J waves, and other repolarization abnormalities
- Medication effects
- Changes over time

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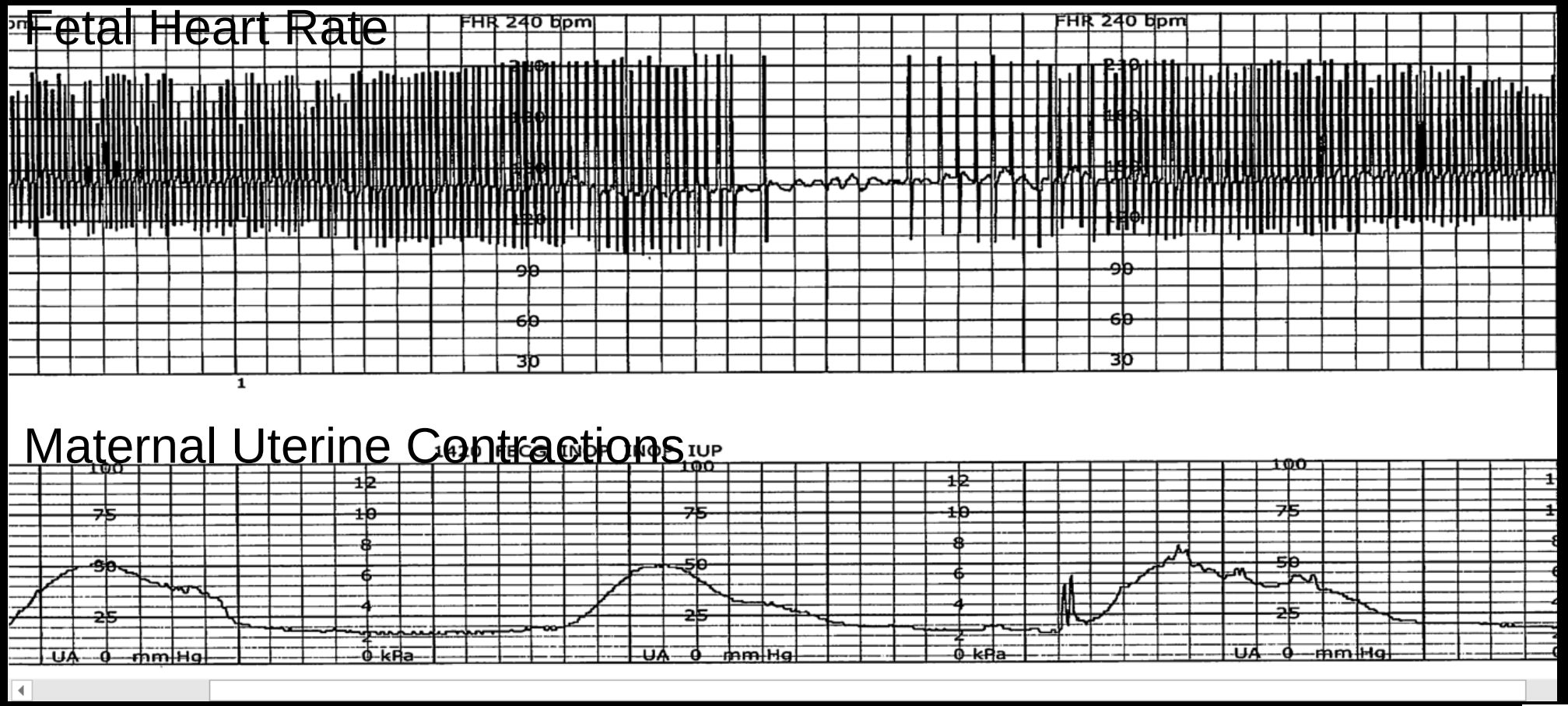
Fetal Monitoring during Labor

Fetal Heart Rate

Maternal Uterine Contractions



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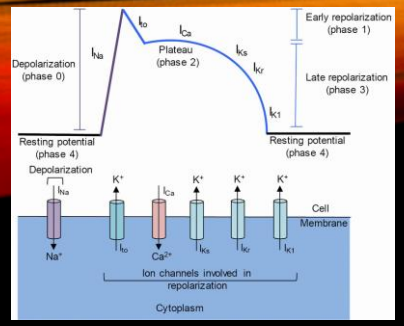

CARDIAC CAUSES OF STILLBIRTH

- Long QT syndrome (LQTS),
- Brugada syndrome (BrS),
- Catecholaminergic polymorphic ventricular tachycardia (CPVT),
- Short QT syndrome (SQTS),
- Right bundle branch block (RBBB),
- Sudden infant death syndrome (SIDS),
- Sick sinus syndrome (SSS),
- Early Repolaarization Syndrome (ERS) or J wave Syndrome
- Familial atrial fibrillation (FAF),
- Arrhythmogenic right ventricular cardiomyopathy (ARVC),
- Cardiac conduction disease (CCD),
- Paroxysmal familial ventricular fibrillation (PFVF),
- Dilated cardiomyopathy (DCM),
- Left ventricular non-compaction (LVNC),
- Hypertrophic cardiomyopathy (HCM),
- Congenital heart defects (CHD)

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INHERITED ARRHYTHMIA SYNDROMES AS A CAUSE OF STILLBIRTH

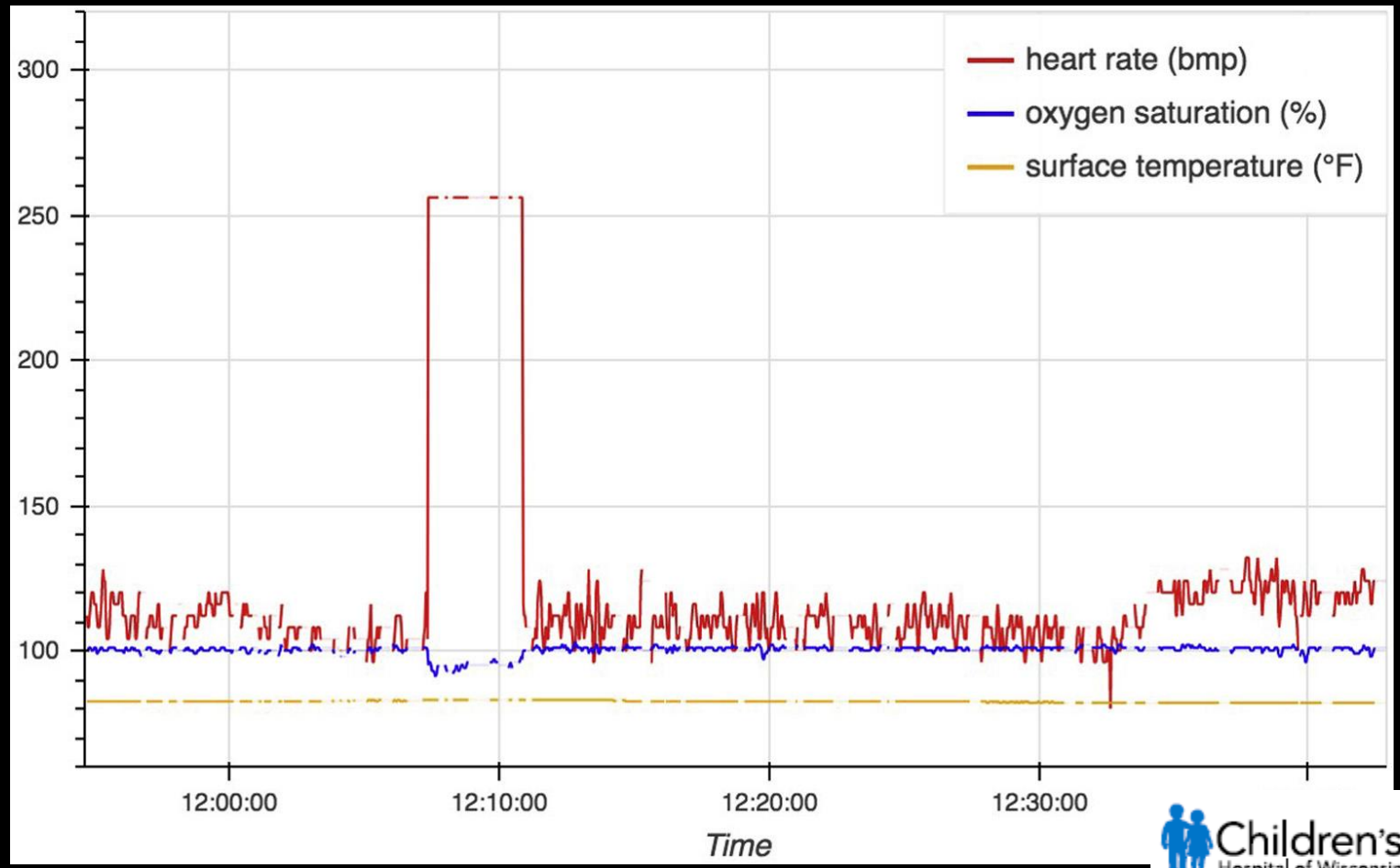
- Crotti et al, JAMA 2013
  - 3.3% of 91 cases had definite pathologic ion channel diseases
    - Long QT Syndromes (
    - 8.8% had probable pathogeni ion channel disseizes, based on functional testing of the ion channels
    - SCN5A (LQT3) over-represented in cases
- Sahley et al, Plos One 2019
  - 290 cases, 35 fetuses, 12.1% had either channelopathy or cardiomyopathy gene defect leading to stillbirth
    - 20 had Ion Channelopathy, 5 with LQT1, 4 with 2 defects
    - 15 had CM genes, 2 with both CM and channelopathy

"SMART" INFANT MONITORS

ANJEWIERDEN ET AL JPEDS 2021

- 2508 of 100,949 infants using sock monitor
- 5070 events of HR over 240 bpm in first year of life
  - 4% for Congenital Heart Dx
  - 2.5% otherwise
- 17% lasted longer than 45 min

- Hidden arrhythmias may be much more common than previously thought.
- What are these arrhythmias? SVT, A Flutter, Torsades?



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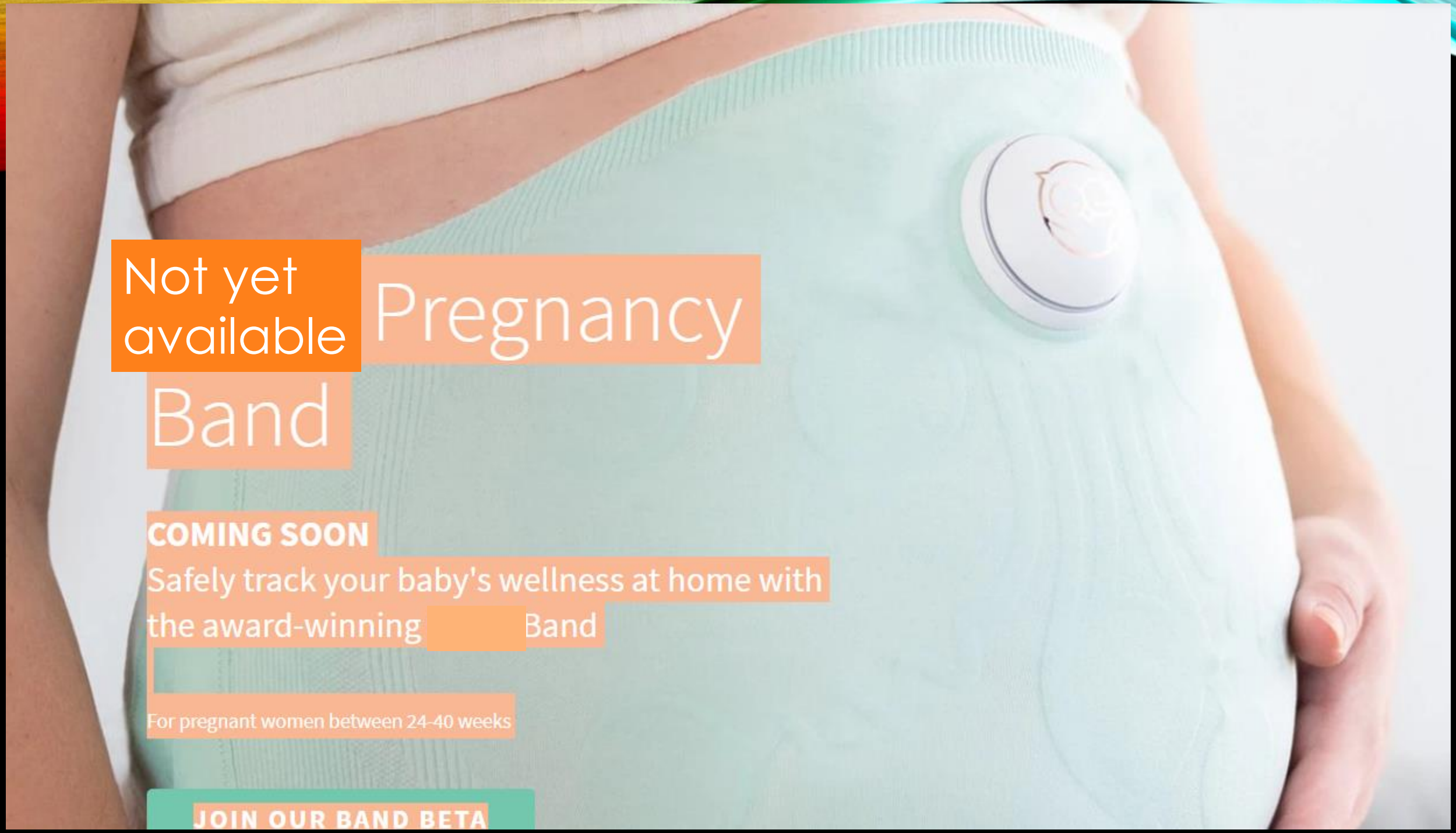
Not yet available
Pregnancy
Band
COMING SOON
Safely track your baby's wellness at home with
the award-winning Band
For pregnant women between 24-40 weeks
JOIN OUR BAND BETA

HYDROPS FETALIS – THE HIDDEN ROLE OF FETAL ARRHYTHMIAS AS A CAUSE

- 4 enrolled
- 1 had intrauterine demise
- 3 had resolution of hydrops because of treatment as the result of fMCG findings
  - Two out of the 3 survivors would have likely died without fMCG
- fMCG may provide a critical survival advantage by identifying under-recognized life-threatening arrhythmias.

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31YR/O G2P1 FEMALE AT 25 3/7 WKS GA

- Presented at 20 wks for anatomy scan-found to have HF, fetal bradycardia, first degree AVB and occasional ectopic beats. Fetal heart rate in the 90's.
- Chromosomes, and SSA, SSB were negative.
- Echocardiogram showed mild to moderate hydrops fetalis with decreased biventricular function, mitral and tricuspid regurgitation, and cardiomegaly.
- Started terbutaline 2.5 mg QID and dexamethasone 4 mg daily for presumed viral myocarditis; diclegis for nausea.
- No tachyarrhythmias had been identified.

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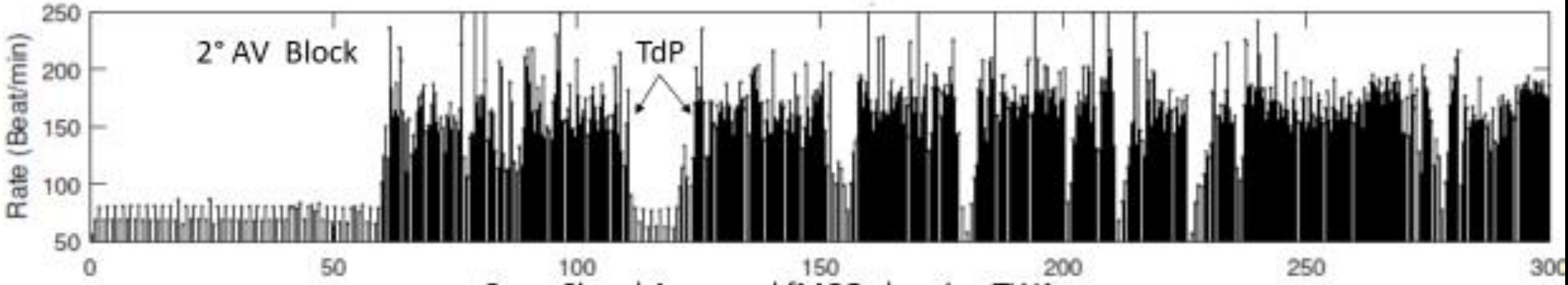
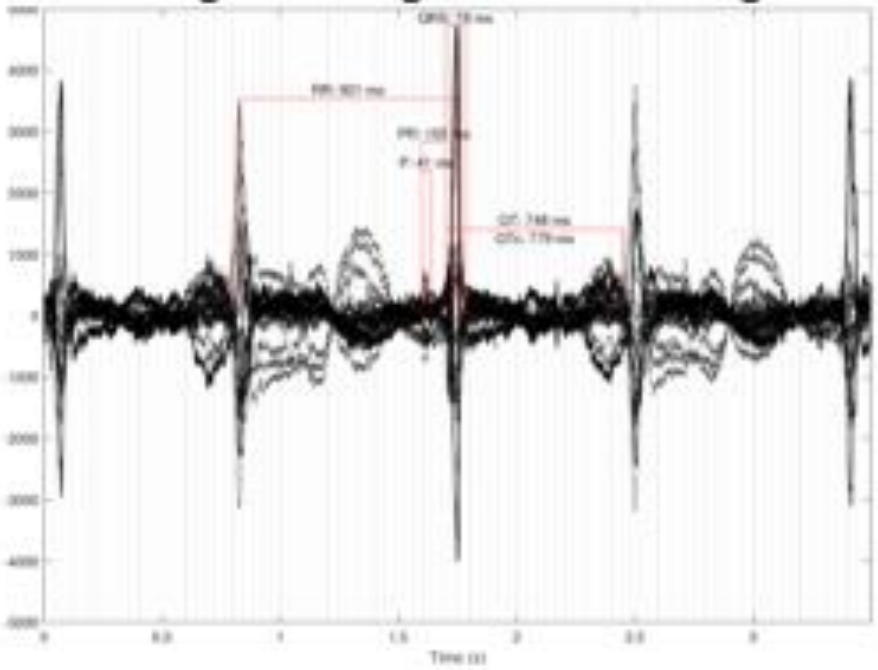
FMCG at 25 3/7: Brief periods of 3:1 second degree AV block, severe QTc prolongation with QTc of 779 ms (normal < 500 ms), T wave alternans, and Torsades de Pointes ventricular tachycardia (TdP), which had not been recognized by the referring center



3 sec Signal Averaged fMCG showing TWA



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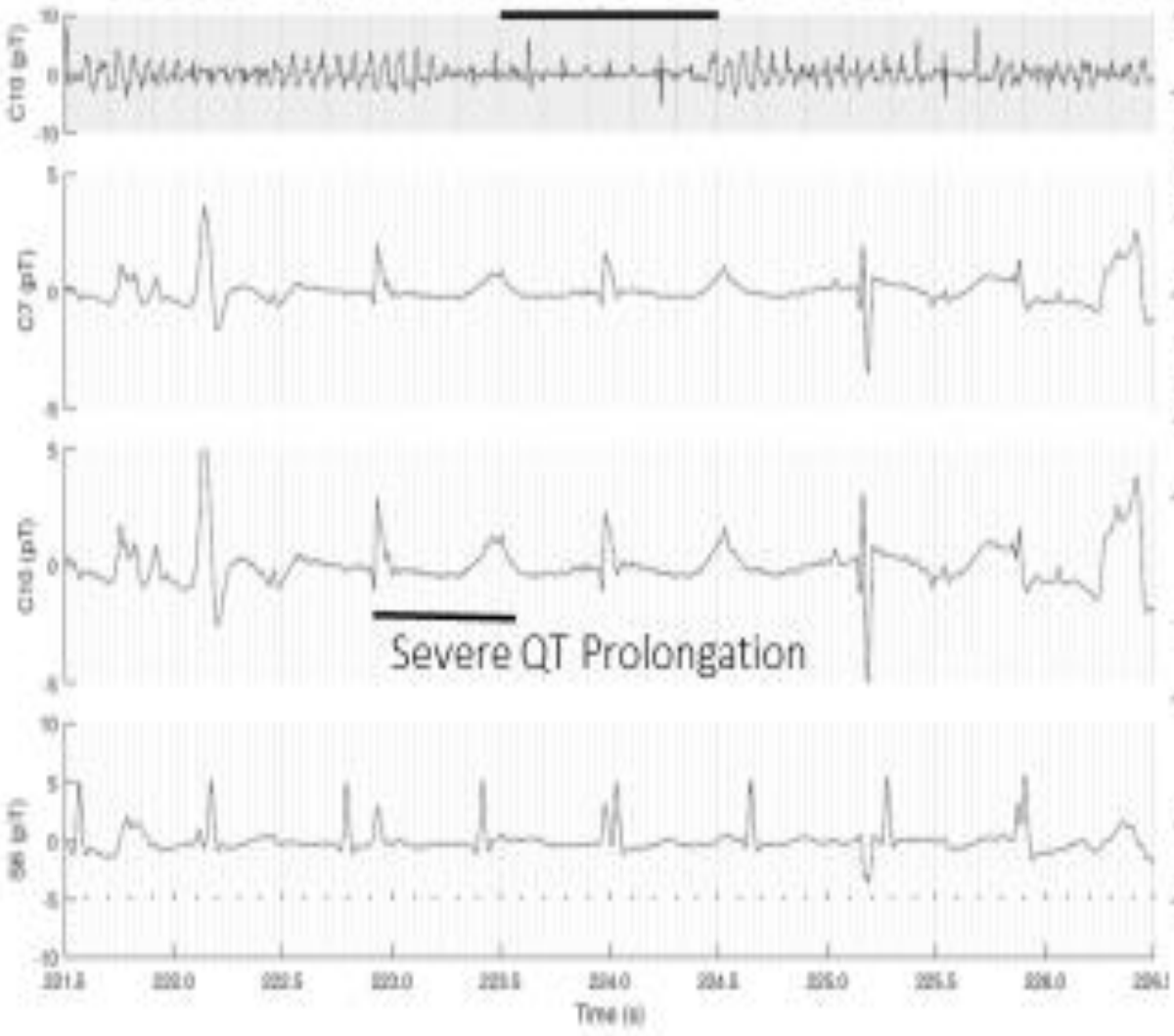
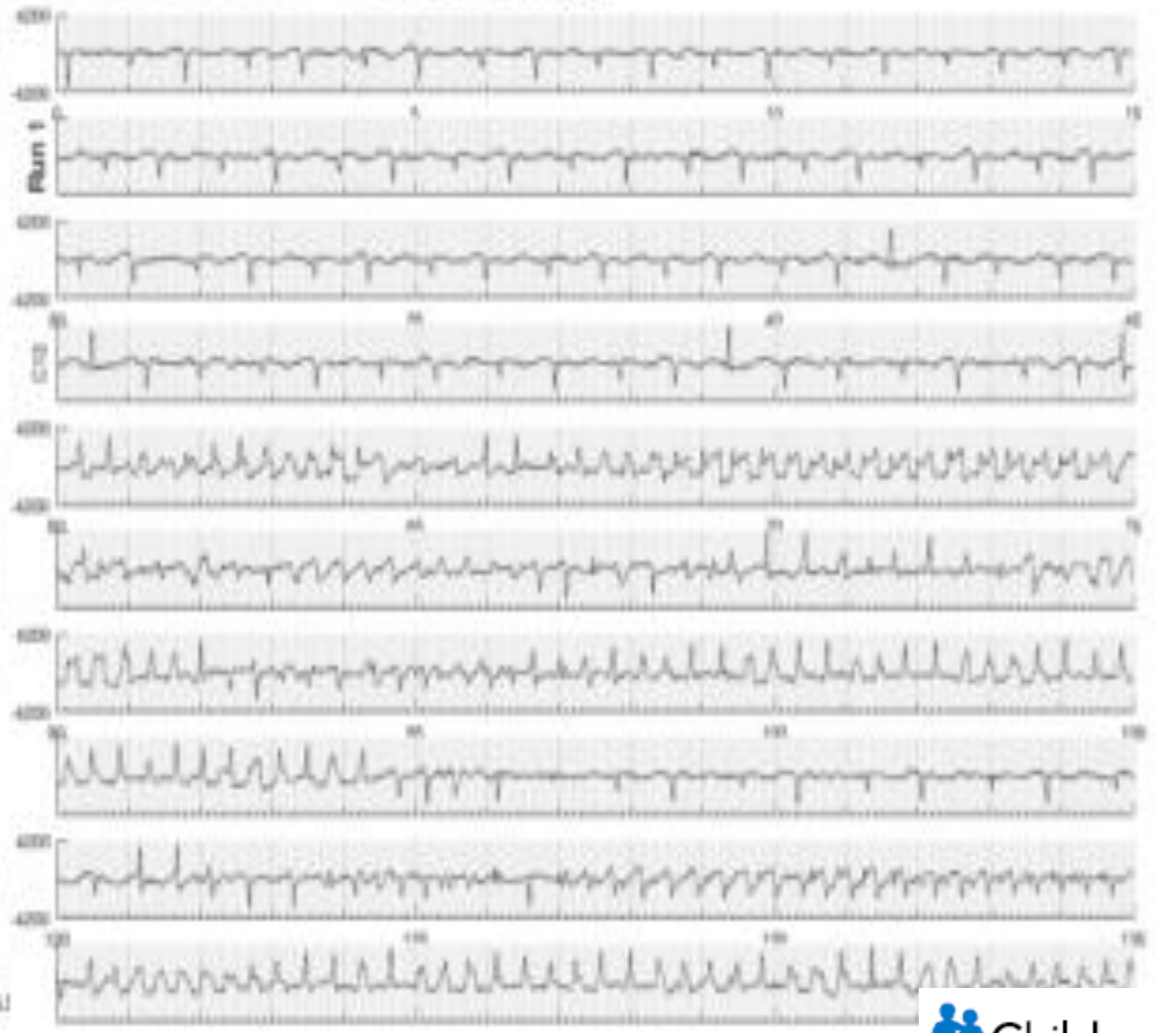
Torsades de Pointes

5 Sec rhythm and 15 Sec Inset

2 Min Holter-like Recording





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PRENATAL F/U

- We recommended discontinuation of the dexamethasone, diclegis,and terbutaline (which were likely pro-arrhythmic).
- She was admitted at her home center for initiation of magnesium sulfate and propranolol. This improved her hydrops.

- After attempting to reduce the propranolol dose from 320 mg, the fetus had breakthrough TdP and they again increased the maternal dose.

- fMCG at 30 2/7 weeks showed a QTc of 758 ms, with only sporadic brief TdP and PVCs.

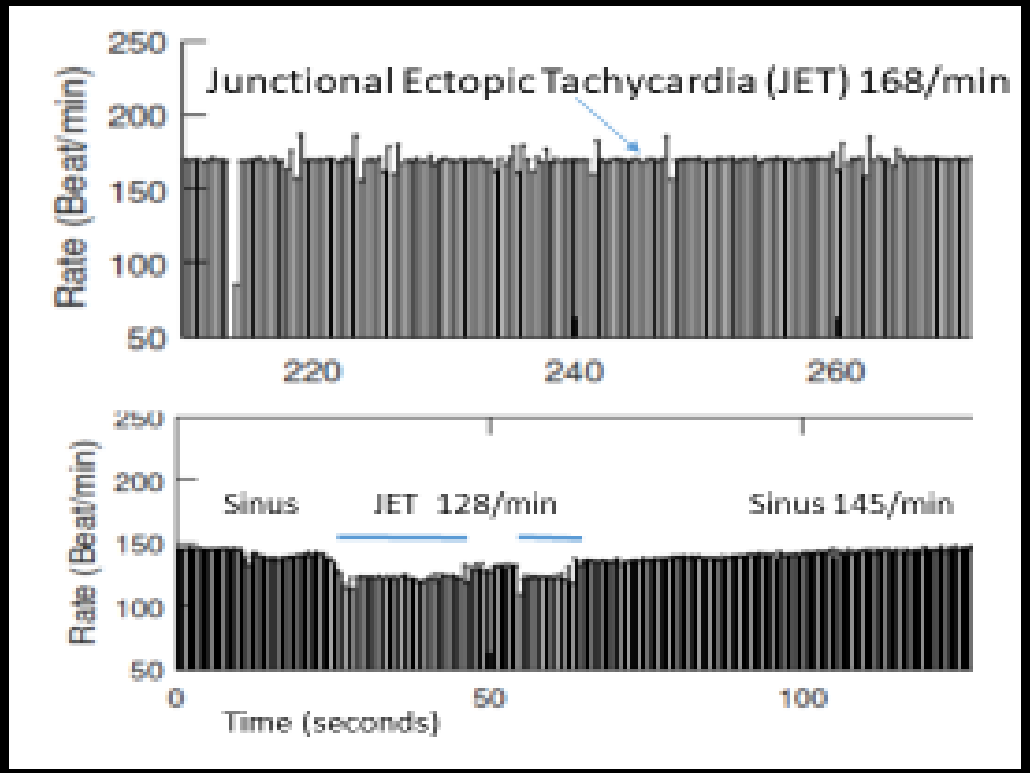
NEONATAL OUTCOME

- 2.01 kg female infant born at 36 2/7 wks d/t Pre-term Labor.
- Propranolol was started and no TdP postnatally. QTc 570 ms.
- At 5 weeks of age a permanent pacemaker was implanted, and she was discharged at 6 wks of age.
-
- Viral titers were ultimately negative, but genetic testing showed pathogenic defects in both LQTS1 and LQTS2.

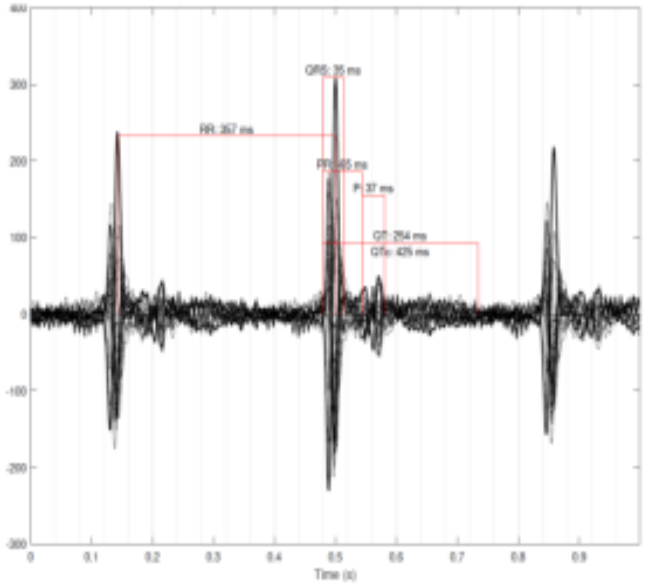
33-YEAR-OLD G1P0 FEMALE AT 19 WKS GA.

- Moderate non-immune fetal hydrops.
  - The viral titers, SSA/SSB, and amnio-genetic microarray were normal.
- Fetal echocardiogram - small pericardial and bilateral pleural effusions, normal cardiac anatomy, and a top normal sinus rate of 163/min with flow reversal in the ductus venosus.
- The fetal magnetocardiogram (fMCG) s
  - low junctional ectopic tachycardia (JET) at 168/min with ST elevation, and J wave.

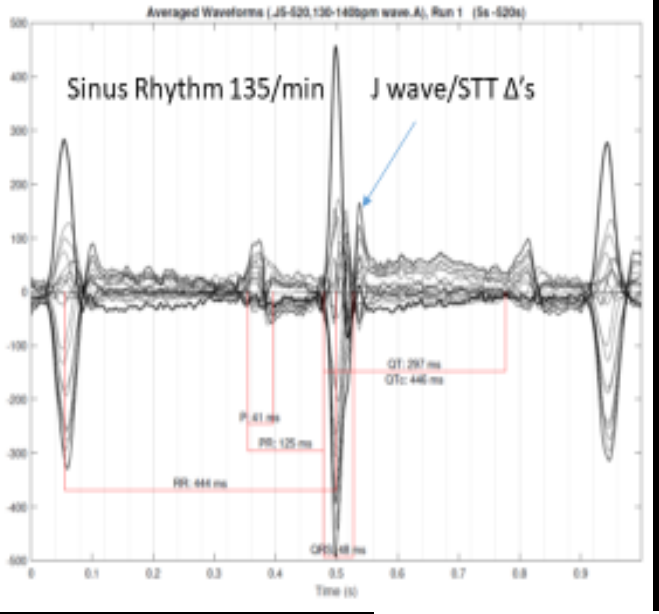
FETAL MCG



20 2/7 wks GA, JET 168 bpm, retrograde fragmented P waves



22 4/7 wks GA, Transplacental amiodarone, Sinus rhythm, J wave, STT changes



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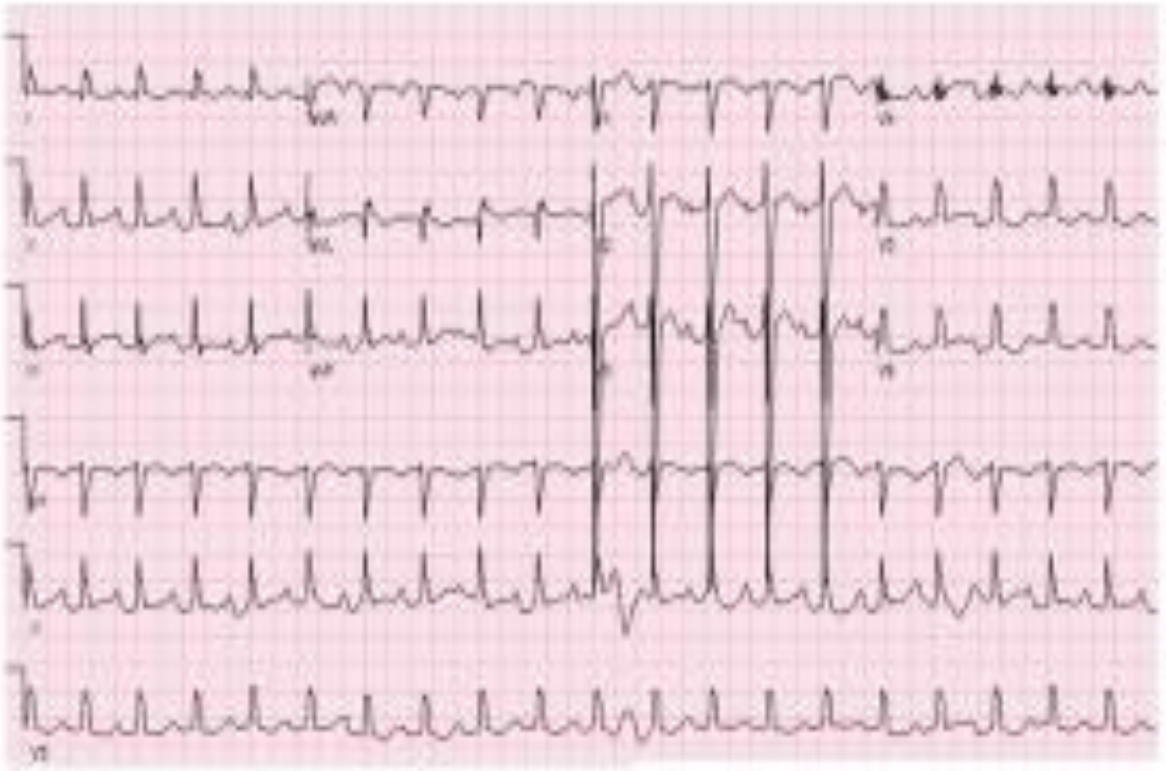
FETAL FOLLOW UP

- Transplacental antiarrhythmic therapy was started -using amiodarone. Within 5 days, the rate had slowed to 140/min
- At 22 4/7 wks she returned for follow-up fMCG. This showed sinus rhythm with 1st degree AV block, persistent J waves and STT changes. Brief JET with wide QRS was seen at rates slower than the sinus rate.
- Follow up fMCG studies were performed at 26 2/7 and 32 4/7 wks gestation due to recurrence of hydrops.

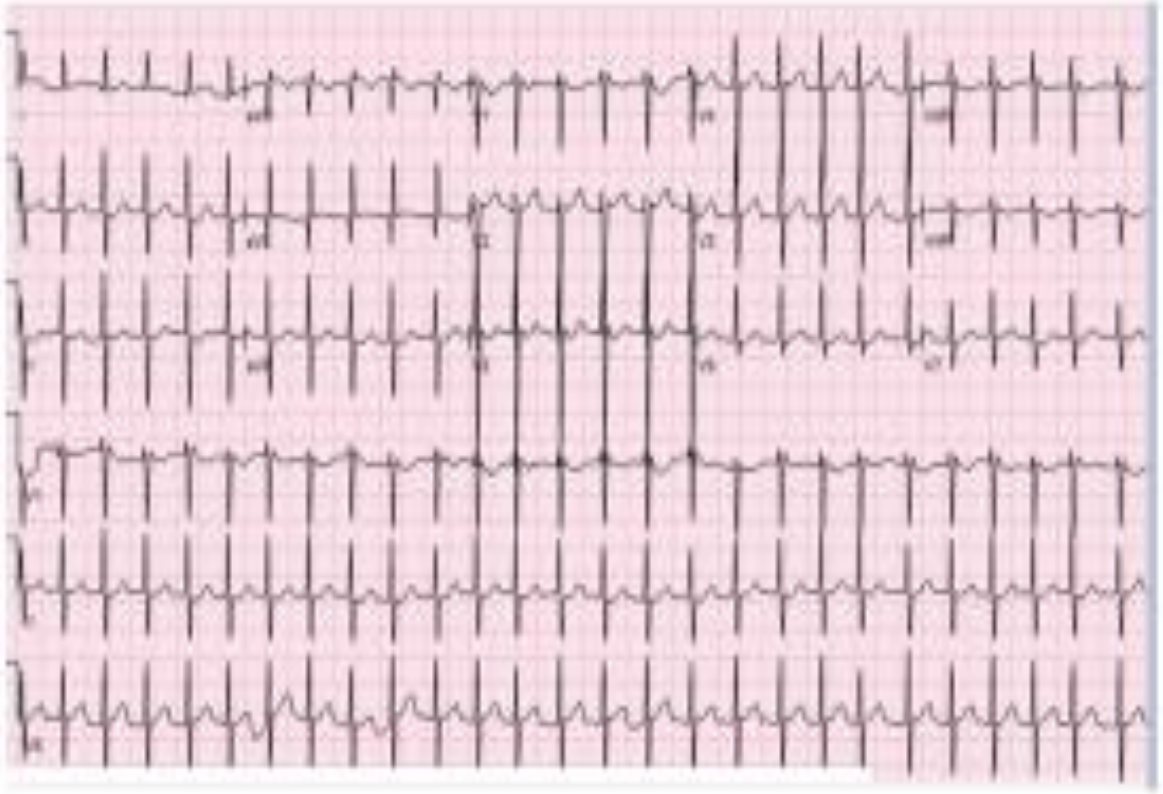
NEONATAL F/U, JET

- The infant was born at 37 1/7 due to early maternal pre-eclampsia
- ECG showed sinus rhythm with 1st degree AV block and complete left bundle branch block.
- Amiodarone was not administered postnatally. She was transitioned to
- propranolol (2 mg/kg/day) was started at 28 days of age after recurrent JET tachycardia. Plan is to treat to about 1 year of age.
- No etiology known

NEONATAL ECGS



Day 0, Sinus Rhythm 120/min, 1st AV block, LBBB

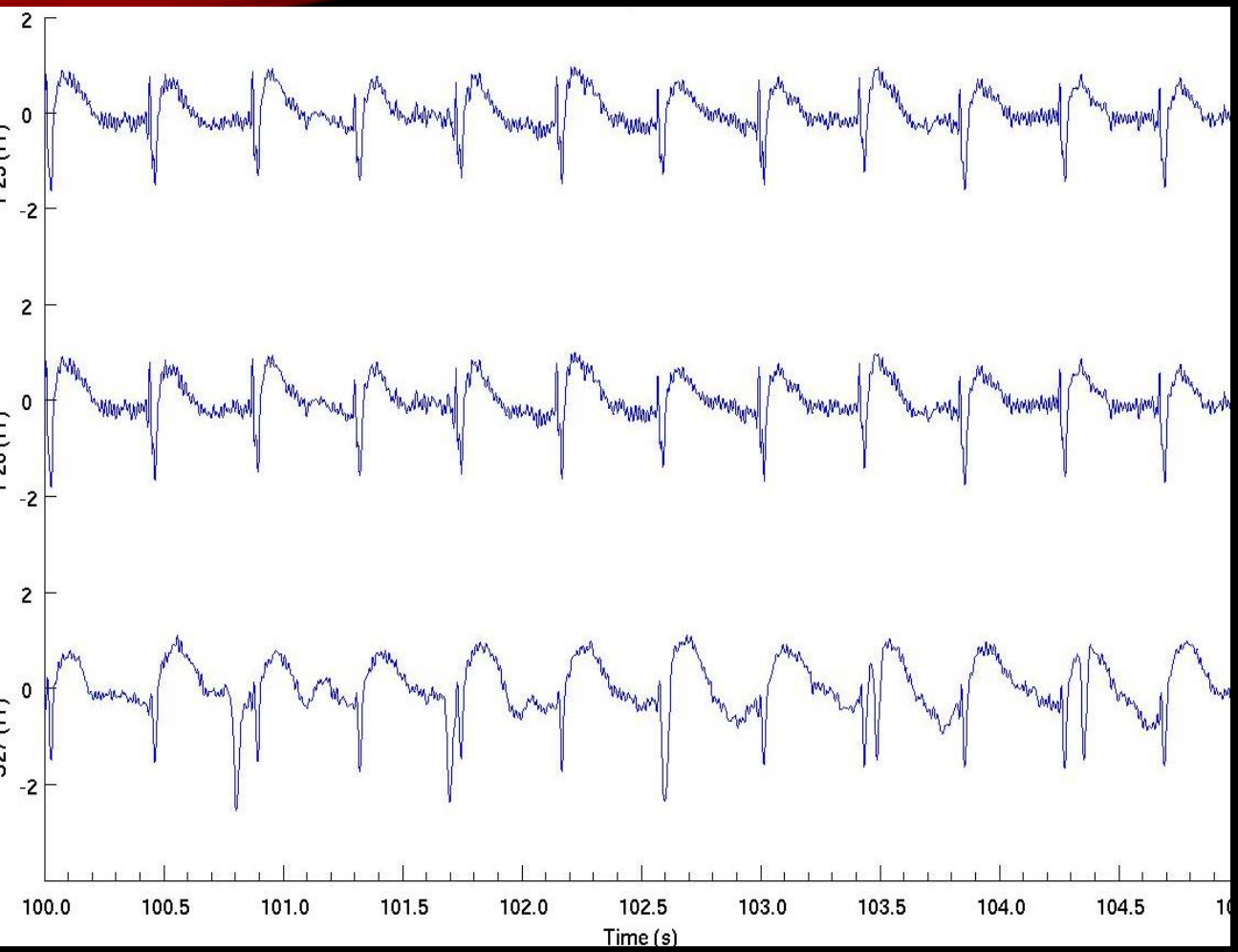


Day 28, JET 168/min, narrow QRS

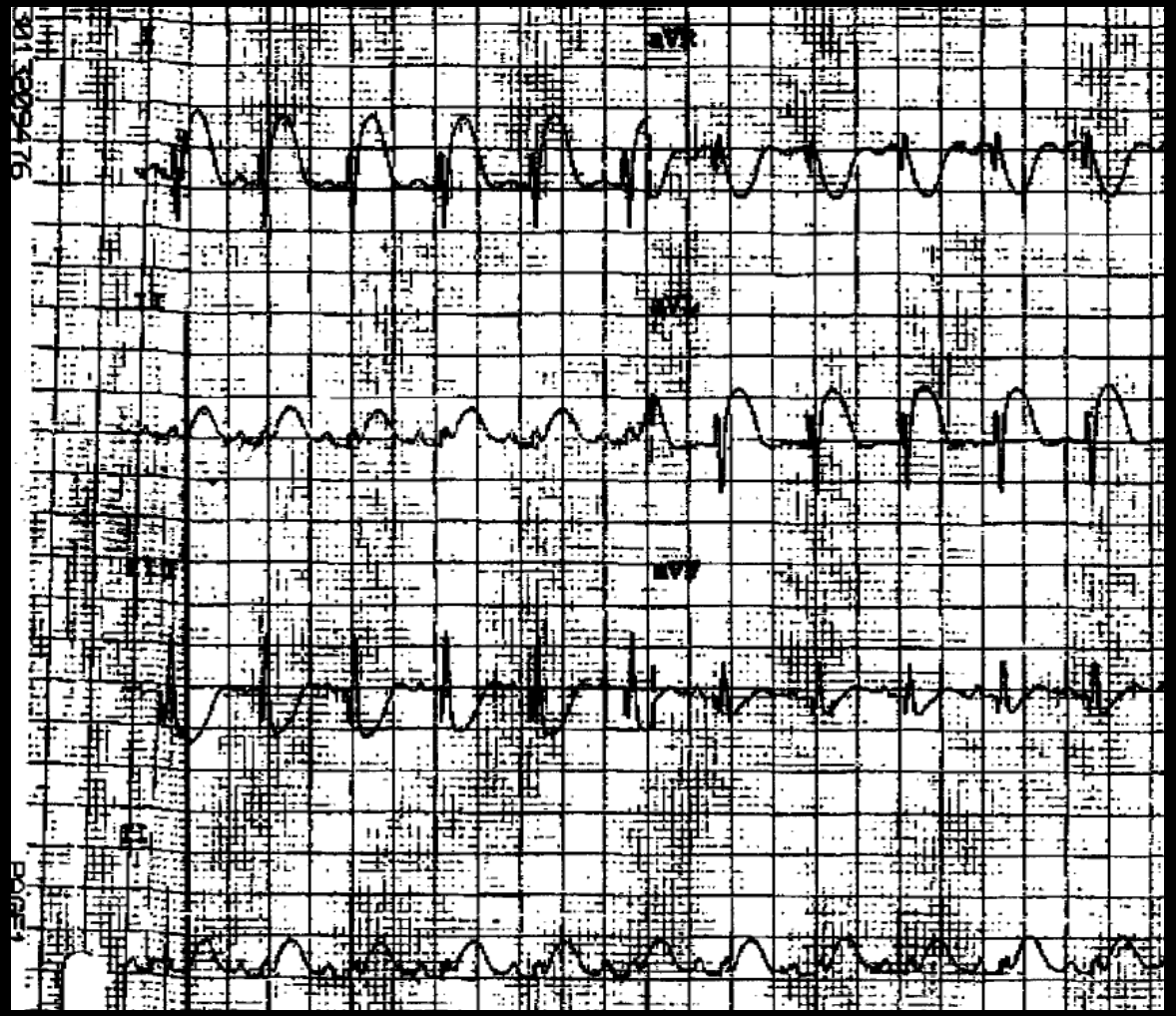
27 2/7GA FETUS WITH PRIOR SIBLING DEATHS

- Mother herself had a Hx of frequent cardiac arrests prior to 3 mo of age due to V Tach, but she "outgrew" it.
- The family lost 2 children to intractable ventricular tachycardia in the neonatal period. One of the two had undergone transplant.
  - The genetics of the heart were being assessed and an animal model developed for assessment of antiarrhythmic drugs (this was escalated after the fMCG).
- This pregnancy had been uncomplicated, but family wanted to know if this infant was likely to develop arrhythmias

fMCG Current Pregnancy



Sibling ECG @ 1 wk/o



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FOLLOW/UP

- Infant was born at term and confirmed on ECG to have same findings
- Multiple episodes of Torsades de Pointes VT in first week of life treated with defibrillation and antiarrhythmic drugs
- Meanwhile the drug testing from the prior sibling was completed, and the most effective drug was….. Erythromycin
- Since all other drugs had failed the infant was started on erythromycin, and continued it until 6 months of age. She is now 8 years old. No more arrhythmias were noted
- LESSONS LEARNED - Developmental changes in ion channels can allow long-term survival. Treatments can be determined by unique personalized medical therapy. This takes time. Therefore early amnio is needed.

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HOW ACCURATE IS FMCG IN IDENTIFYING THE FETUS AT RISK

- Of 49 cases of inherited arrhythmias, we have had 2 false negatives (1 under 27 weeks GA, 1 also false neg by neoECG) and one false positive.
- Thus far in my RO1, 4 fetuses have had stillbirth. fMCG was abnormal in all. But it was also abnormal in that did not have stillbirth. Some features are more predictive than others in preliminary assessment.
  - J waves
  - QTc > 600 ms 1
    - Torsades 0 in 1 in our series, but 5 of 11 in our recently published series (Strand et al, Circ AE 2019)
- The fact that so many fetuses in our series have had abnormal findings highlights the need to bring this technology into common use.

  Applied Physics Systems, Inc plans to commercialize fMCG

ADVOCACY TO PREVENT STILLBIRTH

- Stigmas still exist regarding pros-cons of research in pregnancy
- Broader awareness needed for the problem of stillbirth
- Faster means of developing drug testing once gene defect is established
- Improve post-mortum evaluations
  - Limited means for transferring a fetus for autopsy to a central location, and back
  - No funding for post-mortem genetic testing
  - Limited number of trained organ-specific pathologists
  - Underutilization of the post-mortum MRI
- Additional funding and investment needed
- FDA currently separates research on devices for the fetus from that of the infant

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TOTAL NUMBERS SINCE LAST RPPR (02/25/2020)						
Fetal Diagnosis	Number Screened	Number Eligible	Number Enrolled	Complete V1	Complete V2	Complete ECG
Mono Twins	0	0	0	0	0	0
Gastroschisis	1	1	0	0	0	0
CHD	7	6	5	4	0	2
Hydrops	6	6	4	4	3	3
Prior Stillbirth	2	1	1	1	0	0
TOTAL	16	14	10	9	3	5

TOTAL NUMBERS SINCE PROJECT START THROUGH 02/16/21						
Fetal Diagnosis	Number Screened	Number Eligible	Number Enrolled	Completed V1	Completed V2	Complete ECG
Mono Twins	11	7	3(1 SB)	3	1	5
Gastroschisis	21	18	1	1	1	1
CHD	11	9	7(2 ID)	6	1	4
Hydrops	9	8	4(1 SB)	4	3	2
Prior Stillbirth	5	4	3	3	2	2
TOTAL	57	46	18	17	8	14

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