Diagnosis and management of fetal arrhythmias

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CPP 2014
Venice
# Fetal Arrhythmia: Methods of Prenatal Diagnosis

<table>
<thead>
<tr>
<th>Method</th>
<th>Atrial systole</th>
<th>Ventricular systole</th>
<th>AV-relationship</th>
<th>Rate</th>
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<tbody>
<tr>
<td>Electrocardiogram</td>
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<td>Abdominal wall</td>
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<td>Doppler (Doptone)</td>
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<td>Echocardiography:</td>
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<td>Two-dimensional</td>
<td>X(?)</td>
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<td>M-mode</td>
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<tr>
<td>Doppler-mode</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</table>
M-Mode Echocardiography

• Cardiac motion vs. Time
  Cursor locates through anatomic structures
• Choose structures that reflect atrial vs. ventricular activation
  - Chamber walls
  - AV valves
  - Semilunar valves
How is the Diagnosis Established?

- **Spectral Doppler**
  Detect mechanical / flow consequences of electrical activity
  intracardiac
  fetal artery and vein
  umbilical vessels

SVES with AV conduction
Long QT Syndrome – Bigeminus
Long QT syndrome – Bigeminus
Simultaneous Doppler of arterial and venous blood flow in differentiation of fetal arrhythmias and measurement of cardiac time intervals

- mitral flow – LVOT
- ascending aorta – superior caval vein
- aortic arch – brachiocephalic vein
- descending aorta – inferior caval vein
- pulmonary artery – pulmonary vein
- renal artery – renal vein
- descending aorta – vena azgos continuity in left isomerism
Diagnosis of arrhythmia

Doppler in DAo and V. azygos
Extrasytoles
ectopic beat
premature ectopic beats
Extrasystoles I (ES)

Extrasystoles most frequently
Mostly isolated SVES
Mostly no clinical importance
Cardiac malformations rarely in ES
Extrasystoles II (ES)

ES sometimes trigger of reentry-tachycardia

However, rare occurrence of SVT (in about 1% of cases with ES)
Fetal Tachyarrhythmia
Fetal Tachyarrhythmia

- Electrophysiology
  - Pathophysiology
  - Antiarrhythmic drugs
- Antiarrhythmic therapy
Fetal Tachyarrhythmias

sustained rhythmic ventricular rate > 190 /min

**Supraventricular Tachycardia**
- Ventricle tachycardia
- Atria tachycardia
  - 240-280 /min
- 1:1 AV conduction

**Atrial flutter**
- Ventricle tachycardia
- Atria tachycardia
  - 380-480
- 2:1 AV conduction / 3:1 AV conduction

**Ventricular Tachycardia**
- Ventricle tachycardia
- Atria normofrequent
- Dissociation
Atrioventricular Reentry by an accessory pathway accounts for 93% of fetal SVT with 1:1 AV conduction (Naheed et al, 1996)

Initiation

AV Reentry Tachycardia
Clinical Reentrant SVT

- Sudden Onset and Termination of SVT
- 1:1 atrioventricular conduction
- Rate 240-260 beats/minute
- Hydrops fetalis common
- Structural CHD rare
- Postnatal recurrence in approx. 50% of cases
SVT
Electrophysiology of Atrial Flutter

- Intraatrial macro-reentry
- Variable atrioventricular block
- AV node is not part of the reentry circuit
Fetal Tachyarrhythmia

- Electrophysiology
- Pathophysiology
- Antiarrhythmic drugs
- Antiarrhythmic therapy
Fetal sheep studies about SVT

Therapeutic considerations

Hydrops in fetal SVT is caused by an increase of venous pressure and reduced lymphatic flow rate.

There are primarily no hyoxemia and no hypoxia-induced alteration of membrane permeability or hepatic function.

Non irreversible damages - therefore an intrauterine therapy is indicated, especially in order to avoid the negative consequences of preterm delivery.

Gest AL et al., 1993
SVT-induced CM after long-term SVT
Fetal Tachyarrhythmia

- Electrophysiology
- Pathophysiology
- Antiarrhythmic drugs
- Antiarrhythmic therapy
In utero treatment

*Digoxin*

- Drug of first choice
- Fetal/ maternal ratio: 0.8- 1.0, but impaired if hydrops !!!
- High Serum levels (2.0- 2.5 ng/ ml) are needed
- High dosages p.o. or i.v. in pregnancy (high GFR and impaired absorption of p.o. digoxine)
- Increasing serum level if you add verapamile, amiodarone, flecanide and sotalol
- Theoretically: Atrial and ventricular flutter dependent on the refractoriness of accessory pathway, e.g. Kent's bundle
In utero treatment

Flecainide

- class IC antiarrhythmic agent
- prolongation of conduction in all parts of heart (accessory pathway, sinus and AV-nodes, ventricular myocardium)
- fetal/maternal ratio: 0.8
- negative inotropic effect
Results of a meta-analysis
Intrauterine treatment (n=420)

• Digoxin as 1st choice in 67.6 % (75/111) of cases with AF (success rate: 45.1 % (34/73))
  – Success rate in hydropic fetuses: 6.1 %
  – Success rate in non-hydropic fetuses: 51.7 % (p = 0.05)

• Digoxin as 1st choice in 63.4 % (199/314) of cases with SVT (success rate: 51.5 % (102/198))
  – Success rate in hydropic fetuses: 24.6 %
  – Success rate in non-hydropic fetuses: 65.4 % (p < 0.0001)

• Success rate of Digoxin in all fetuses:
  – Hydropic fetuses: 19.5 %
  – Non-hydropic fetuses: 63.3 % (p < 0.00001)

Krapp M et al. Heart 2003;89:913-17
Fetal response to transplacental therapy was significantly associated with tachycardia mechanism and fetal state

*Jaeggi E et al. Circulation 2011;124:1747-54*

**AF responds more slowly than SVT (cardioversion at day 5 and 10 was reached in 25% and 41% with AF and in 50% and 63% with SVT); in hydropic fetuses cardioversion was reached in 50% after 9 days (vs. 4 days)(21% died).**
Fetal response to transplacental therapy was significantly associated with the choice of antiarrhythmic drug.  
Jaeggi E et al. Circulation 2011;124:1747-54

Fig 3. Freedom from termination of fetal AF (n=36): 1st line agents

- Digoxin
- Flecainide
- Sotalol

Days
Percent of Fetuses

Fig 4. Freedom from termination of fetal SVT (n=75): 1st line agents

- Digoxin
- Flecainide
- Sotalol

Days
Percent of Fetuses

In AF, first-line sotalol was better than the other drugs; time for cardioversion in 50% of cases was 12 days with sotalol. In SVT, with first-line use of flecainide, digoxin and sotalol the time for cardioversion in 50% was 3, 4, and 12 days.
Fetal SVT – Treatment Algorithm

Fetal SVT

PSVT without hydrops
- Observe
- Maintain po Digoxin
- Maintain po Digoxin + po Flecaïnide
- Maintain po Digoxin + po Amiodarone

SVT with hydrops
- Maternal iv Digoxin Load
- Observation
- Maintain po Digoxin
- Maintain po Digoxin + po Flecaïnide
- Maintain po Digoxin + po Amiodarone
- Maintain po Digoxin add po/iv Amiodarone and via umbilical vein

Sustained SVT
- Persistent SVT
- Persistent SVT > 210 bpm with increasing hydrops (after 72 h)
- Persistent SVT with hydrops
- C/S Delivery
Complete Heart Block

- A-V dissociation
- Faster atrial than ventricular rate
- No fixed relationship
Color –Encoded M-Mode of Complete Heart Block

- A-V dissociation
- Faster atrial than ventricular rate
- No fixed relationship
- ~50% have complex CHD
- ~50% have maternal antibodies
- Rare case with long QTc
AV block with left isomerism
Findings of left isomerism in prenatal life

<table>
<thead>
<tr>
<th>Left isomerism</th>
<th>Incidence in prenatal series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interrupted V. cava inferior</td>
<td>~ 90 %</td>
</tr>
<tr>
<td>AVSD</td>
<td>~ 70 %</td>
</tr>
<tr>
<td>Viscerocardiac heterotaxia</td>
<td>~ 55 %</td>
</tr>
<tr>
<td>AV block</td>
<td>~ 40 %</td>
</tr>
<tr>
<td>Bradycardia (junctional escape)</td>
<td>~ 15 %</td>
</tr>
<tr>
<td>RVOT obstruction</td>
<td>~ 35 %</td>
</tr>
<tr>
<td>LVOT obstruction</td>
<td>~ 20 %</td>
</tr>
<tr>
<td>DORV</td>
<td>~ 23 %</td>
</tr>
<tr>
<td>TAPVC</td>
<td>~ 5 %</td>
</tr>
<tr>
<td>Bilateral Vv. cavae superior</td>
<td>~ 45 %</td>
</tr>
</tbody>
</table>

*unspecific and difficult to detect in early gestation*

AV-Block II.°, LAI, AVSD, V. azygos continuity; 13+5 w.; NT: 6.8 mm
Outcome of 59 fetuses with heart block

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>TOP</th>
<th>IUFD</th>
<th>PPD</th>
<th>alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac malformations</td>
<td>31</td>
<td>22</td>
<td>3</td>
<td>4</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Anti-Ro-antibodies</td>
<td>20</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>16 (80%)</td>
</tr>
<tr>
<td>Isolated heart block</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3 (40%)</td>
</tr>
</tbody>
</table>
Complete heart block by maternal autoantibodies

- Maternal autoantibodies (IgG against ribonucleoproteins; anti-SSA (Ro), anti-SSB (La)) in over 95% of cases without CHD
- irreversible fibrotic destruction of fetal AV node; myocarditis
- manifestation: 18th - 24th week
- risk for mother with anti-SSA: 1% - 2%
- recurrence-risk, if anti-SSA present: 16%
CHB associated by maternal autoantibodies in dichorionic twins
CHB by maternal antibodies

- Fetal hydrops in autoantibody induced CHB (approx. 25-30%) (Groves et al, Heart 1996)
- "Critical" ventricular rate: 50-55 bpm
- Congestive heart failure sometimes not until third trimester
- High pre- and postnatal mortality and morbidity by carditis and dilated cardiomyopathy (DCM)

Total mortality of antibody-induced fetal CHB: 19%, of whom 27% died in utero and 45% died within the first 3 month of life (Buyon J et al, 1998)

Pacing in newborn: 53%, later 40%; DCM was found in 23%, of whom 62% died (Eronen M et al, 2000)
Prevention of antibody-induced complete heart block
Prophylactic application of dexamethasone (4 - 8mg / day) for avoidance of complete heart block?

- Effectivity for avoidance of CHB is not proved
- Side effects are oligohydramnios, preterm birth (?), disturbances of growth and neurologic development
- Severe maternal side effects are possible (osteoporosis)

- No indication in women with anti-Ro/La-Ab, because the risk for fetal CHB is low (1% - 2%)
- Maybe indicated in women with anti-Ro/La-Ab and a previous child with CHB (risk of recurrence: 16%) under study conditions
Prophylactic application of dexamethason (4 - 8mg / day) for avoidance of complete heart block in pregnant women with autoantibodies (anti-SSA/-SSB)?

• Is the treatment indicated, if a prolongation of AV- (PQ-) interval is registered in serial echocardiographic exams during critical period of pregnancy (16 - 24 w.o.g.)?
Mechanical AV time interval

Aortic arch – V. anonyma

Mitral valve - LVOT
Outcome of fetuses with congenital AV block exposed to maternal anti-SSA/Ro antibodies

n = 95 fetuses, 18-24 weeks’ gestation

Bergman G et al. UOG 2010;36:561-566
The PR Interval and Dexamethasone Evaluation (PRIDE) prospective study

Conclusions:

- Prolongation of the PR interval was uncommon and did not precede more advanced block.
- Advanced block and cardiomyopathy can occur within 1 week of a normal echocardiogram without first-degree block.
- Echodensities and moderate/severe tricuspid regurgitation merit attention as early sign of injury.

The PR Interval and Dexamethasone Evaluation (PRIDE) prospective study

Conclusions:

A CHB is irreversible despite DEX
Progression of AV block II° to CHB despite DEX
Reversing of AV block I° and II° in rare cases by DEX

Possible side effects of DEX such as FGR, neurologic impairment etc. should be weighed

Friedman DM et al: Am J Cardiol 2009;103:1102-1106
Conclusions and recommendations for fetuses exposed to maternal anti-Ro/La antibodies

- AV prolongation did not predict progression to complete heart block to birth
- AV block I° mostly spontaneously resolves,
- severe AV prolongation may persist in neonatal life, but no progression

- Preventive Dexamethason treatment only if
  - progressive AV block
  - other Ab-mediated pathology, as EFE or effusions
- Isolated AV prolongation >6 $z$-scores: close monitoring for disease progression without treatment

IVIG for prevention of fetal CHB

- USA (PITCH study): multicenter, prospective, open-label
  - Inclusion: presence of anti-SSA/Ro ab, previous child with CHB/neonatal lupus rash, current treatment with $\leq 20$ mg/day prednisone, and $<12$ weeks pregnant
  - Protocol: IVIG (400 mg/kg) every 3 weeks from week 12 to week 24 (12, 15, 18, 21, 24 w.o.g.)
  - 20 mothers completed the study before the study was stopped, because 3 cases of CHB (at 19, 20, and 25 weeks) was reached

IVIG for prevention of fetal CHB

  - Inclusion: presence of anti-SSA/Ro ab, previous child with CHB, <12 weeks pregnant
  - Protocol: IVIG (400 mg/kg) every 3 weeks from week 12 to week 24 (12, 15, 18, 21, 24 w.o.g.)
  - CHB in 3/15 fetuses in the treatment group (20%) at 18, 23, and 26 weeks, resp., and 1/9 fetuses (11%) in the control group at 21 weeks

Maternal use of hydroxychloroquine (HCQ) may reduce the risk of cardiac neonatal lupus

- Retrospective analysis of 3 databases
- Inclusion: birth of a previous child with cardiac NL and anti-SSA and/or anti-SSB-AB
- 257 pregnancies
  - 40 exposed to HCQ initiated before 10 w.
  - 217 unexposed to HCQ

Izmirly PM et al. Circulation 2012;126:76-82
Maternal use of hydroxychloroquine (HCQ) may reduce the risk of cardiac neonatal lupus

- Recurrence rate of cardiac-NL (AV block II and III, EFE, CM)
  - Exposed to HCQ: 3 of 40 (7.5%)
  - Unexposed to HCQ: 46 of 217 (21.2%)(p=0.050)
  - (OR: 0.23; 95% CI: 0.06-0.92; p=0.037)

- No death in cases exposed to HCQ
- Overall fatality of 21.7% (47/217) in cases unexposed to HCQ

Izmirly PM et al. Circulation 2012;126:76-82
Treatment after manifestation of CHB
In utero treatment of CHB
Therapy with Sympathomimetics

- Salbutamol infusion (4 µg/min, increased by 4 µg at a time to a total of 64 µg/min) (Grooves et al, Circulation 1995; 92: 3394-96)
- Increase of ventricular escape rate
- Improvement of cardiac function (β-receptors in the fetal myocardium may result in increase of contractility and stroke volume)
## Transplacental Salbutamol treatment of a fetus with CHB and hydrops

<table>
<thead>
<tr>
<th>GA (w+d,time)</th>
<th>Salbutamol infusion dose (µg/min)</th>
<th>VR</th>
<th>AR</th>
<th>AAO vmax (m/s)</th>
<th>MPA vmax (m/s)</th>
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<td>31+1 12:50</td>
<td>0</td>
<td>48</td>
<td>138</td>
<td>1.30</td>
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<td>12</td>
<td>49</td>
<td>138</td>
<td>1.62</td>
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<tr>
<td>31+1 14:15</td>
<td>24</td>
<td>55</td>
<td>154</td>
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<tr>
<td>31+1 15:20</td>
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<td>54</td>
<td>158</td>
<td>2.36</td>
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<td>31+3</td>
<td>13.33</td>
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<td>35+5</td>
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<td>60</td>
<td>148</td>
<td>1.77</td>
<td>1.96</td>
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</table>
CHB caused by anti-SSA and anti-SSB Ab's (23+1 w.)
In utero therapy with salbutamol, digoxine and steroids were unsuccessful
In utero fetal death at 28+2 w.o.g.

„Cardiomyopathy“
Ascites
In utero treatment of CHB
Anti-inflammatory therapy with flurinated corticosteroids

• Dexamethasone or betamethasone in high doses, e.g. 4 mg dexamethasone orally each day (Copel et al, AJOG 1995; 173: 1384-90)
  (prednisolone is metabolized by placenta to prednisone)
• (Improvement in degree of AV block, but no CHB reversed to AV block II$^\circ$ or I$^\circ$; (Breuer et al; 2004; UOG))
• Improvement of contractility by diminished myocardial inflammation
• Reduction of effusions by inhibiting general inflammation, e.g. hepatitis, pleuritis
Transplacental treatment in fetuses with CHB without structural heart disease

Better postnatal survival of newborns with CHB after intrauterine treatment with dexamethasone – possibly resulting from an impairment of antibody-related myocardial inflammation.

Jaeggi ET et al; Circulation 2004;110:1542-8
Treatment with steroids, Toronto
n = 42, 1997-2010

• The survival rate of > 95% in the group of dexamethasone treated fetuses is higher than in all historical studies

• There are longterm consequences not only of steroids but also of fetal bradycardia and of high anti-Ro antibody exposure on fetal development, in particular on neurodevelopment

• The pro and contra need to be prospectively explored in a larger study

Thank you for your attention
In utero treatment of CHB

Indication:
Isolated CHB with hydrops before 32 weeks' gestation

• Medical therapy:
  1.) Increase of ventricular escape rate
     a) sympathomimetic drugs
     b) anticholinergic drugs
  2.) Transplacental and/or direct anticongestive therapy with digoxin and furosemide
  3.) Anti-inflammatory therapy with corticosteroids, immunoglobulin, and plasmapheresis

• Fetal cardiac pacing
Future aspects of the treatment of fetal arrhythmias

- Better assessment of the electrophysiological etiology of fetal tachycardia (ventriculo-atrial time interval by simultaneous venous and arterial Doppler registration (Jaeggi, 1998; Fouron, 2003), magnetocardiography (Schneider, 2005; Wakai, 2003), tissue velocity imaging (Rein, 2002; Tutschek, 2003; Steinhard, 2007) may help in choice of medication:
  - class III antiarrhythmic agents may be preferred for the rare cases with long VA tachycardia (AET, PJRT)

- New antiarrhythmic agents, especially for fetuses with atrial flutter, e.g. dronedarone

- New concepts for fetuses with CHB causing hydrops fetalis:
  - continuous medical treatment
  - in utero application of pacemaker by minimal invasive fetal surgery
Thank you for your attention
Fetal Magnetocardiography (fMCG)

higher signal quality than fECG allows measurements of cardiac time intervals (P-QRS-T)
Only few centres worldwide because the technique is too expensive and need a shield room

Differentiation of fetal arrhythmias:

- Long QT syndrome (Hamada et al. 1999; Schneider et al. 2005; Zhao et al. 2006)
- SVES vs. VES
- Preexcitation (Hosono et al. 2001; Kähler et al. 2001; Wakai et al. 2003)
- Electrophysiologic studies in fetal arrhythmias (Wakai et al. 2003)

Fetal WPW syndrome

Courtesy of U. Schneider, Jena
Fetal TEE

• Fetal surveillance and monitoring during fetal surgery
• Understanding of the underlying electrophysiological mechanism of tachycardia
• Electric stimulation in therapy-refractory supraventricular tachycardia, particularly atrial flutter
Kohl & Herberg, 2010
Fetal TEE

3 French bipolar transvenous pacing catheter (BI-PACING-BALL - 1.0 x 110 cm, Vygon Company, Aachen, Germany)

Kohl & Herberg, 2010