Prematurity: Medication Impact on the Fetal Heart Rate

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Objectives

• Discuss normal physiologic characteristics of preterm fetal heart rate tracings
• Recognize common pharmacologic effects of medications on the preterm fetal heart rate tracing
• Describe current assessment guidelines for the preterm fetus

Preterm birth

US, 1998-2008

March of Dimes 2010 Prematurity Birth Report Card

Monitoring the Preterm Fetus

• Unique challenges
• Limited research
• EFM implemented to establish fetal well being
  – Physiologic differences dependent on fetal development stage
  – Response and/or tolerance to interruptions in oxygenation pathway differ from those of the term fetus

Influence on FHR Regulation

• Autonomic nervous system
  – Parasympathetic
    • Vagus Nerve
      – Medulla Oblongata
  – Sympathetic
    • Nerve fibers of myocardium
• Baroreceptors
• Chemoreceptors
Parasympathetic Nervous System

- Vagal nerve fibers stimulate the SA/AV nodes
  - Regulates fetal heart rate
- Stimulation of the SA node
  - Decreases rate of firing/transmission of impulses
    - Atrium to the ventricle
    - Lowers the heart rate and variability
- Transmits impulses causing BTB variability
- PNS activity increases with gestational age

Sympathetic Nervous System

- Distributed in the heart muscle
- Stimulation of nerves
  - Release of epinephrine/norepinephrine
    - Increases
      - Fetal heart rate
      - Contractility force
      - Cardiac output
    - More dominant in preterm gestations

Baroreceptors

- Location: Aortal arch and carotid sinus
  - Small stretch receptors
  - Sensitive to blood pressure changes
- Increased blood pressure
  - Impulses sent via vagus nerve to brain and heart
  - Decrease in fetal heart rate/cardiac output
  - Protective stabilizing function to lower blood pressure

Chemoreceptors

- Location: Peripheral and central nervous systems
- Associated with control of respirations
- Increases in carbon dioxide or decreases in blood oxygen levels
  - Reflex tachycardia and increased blood pressure
  - Protective attempt to circulate more blood

FHR Interpretation

The 2008 National Institute of Child Health and Human Development Workshop Report on Electronic Fetal Monitoring: Update on Definitions, Interpretation, and Research Guidelines

- Mean FHR rounded to increments of 5 bpm during a 10 minute window
- Excludes
  - Periodic or episodic changes
  - Marked FHR variability (>25 bpm)
- Minimum of 2 minutes of identifiable baseline
  - Can be determined between contractions
  - Does not need to continuous
- Normal 110-160 bpm
Development of FHR Patterns During Normal Pregnancy
Pillai & James, 1990

- 43 low risk women in 2nd/3rd trimester
- Synchronized recordings in 4 week intervals
  - EFM for 90-100 minutes
    - 9 am and 6 pm
  - Ultrasound
    - Fetal eye movement, limb/body movement, fetal breathing, and mouthing movements

Is there an inverse relationship between EGA and FHR baseline?

Results: Baseline Rate
- Negative correlation with gestational age
- Mean fall in baseline: 16 weeks to “term”
  - 24 bpm
  - 1 bpm per week of gestational age
- Rate of fall greatest between 16-20 weeks
  - Less marked in last trimester
    - Establishment of rest/activity cycles

Variability
- Fluctuations in the baseline FHR that are irregular in amplitude and frequency
- Quantified as the amplitude of the peak and trough in bpm
- Excludes
  - Periodic or episodic changes
  - Determined in 10-minute window

Baseline Variability

<table>
<thead>
<tr>
<th>Absent: Undetectable</th>
<th>Minimal: ≤ 5 bpm</th>
<th>Moderate: 6-25 bpm</th>
<th>Marked: &gt; 25 bpm</th>
</tr>
</thead>
</table>

Is it all right to see minimal variability in the preterm fetus?
**Fetal Heart Rate Variability Reveals Differential Dynamics**

Schneider et al, 2009

- 92 singletons
- Two subgroups
  - 24+1 to 32+0 weeks
  - 32+1 to 41+6 weeks
- Magnetocardiogram sessions
  - Measurement of magnetic fields produced by electrical activity in the heart

**Magnetocardiogram**

**Results**

- Inverse relationship with gestational age
- FHR Pattern I
  - FHR with "small oscillation bandwidth" ≤5 bpm
  - 24+1 to 32+0 gestations
- FHR Pattern II
  - FHR with oscillations >5 bpm
  - >32+1 to 41+6 gestations

**Acceleration**

- Visually apparent abrupt increase in FHR
- Peak ≥ 15 bpm from baseline and lasting ≥ 15 seconds
  - **Preterm gestation** (32 weeks)
    - Peak ≥ 10 bpm from baseline and lasting ≥ 10 seconds

**Decelerations**

- Most frequent in 20-30 weeks
- Absence of uterine contractions
- Fetal movement
- Reflection of developing cardioregulatory mechanisms and CNS maturity

**Association Between FHR Patterns and Fetal Movements Between 20-30 Weeks Gestation**

Sorokin et al, 1982

- Low risk patients
  - 20-22 weeks (10 patients)
  - 28-30 weeks (10 patients)
- Fetal monitoring
  - Day sessions lasting 1-2 hours in quiet room
  - 1-2 hours after a meal
  - Semi-fowlers with lateral tilt
FHR Change Frequency

<table>
<thead>
<tr>
<th>EGA</th>
<th>Minutes monitored</th>
<th>Accels</th>
<th>Decels</th>
<th>Accels/Decels</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-22 weeks</td>
<td>964</td>
<td>1.3%</td>
<td>97.1%</td>
<td>1.6%</td>
</tr>
<tr>
<td>28-30 weeks</td>
<td>1012</td>
<td>35.8%</td>
<td>33.9%</td>
<td>30.3%</td>
</tr>
</tbody>
</table>

FHR Changes with Fetal Movement

<table>
<thead>
<tr>
<th>EGA</th>
<th>Accels</th>
<th>Decels</th>
<th>Accels/Decels</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-22 weeks</td>
<td>62.5%</td>
<td>62.8%</td>
<td>40%</td>
</tr>
<tr>
<td>28-30 weeks</td>
<td>94.6%</td>
<td>60.3%</td>
<td>90.6%</td>
</tr>
</tbody>
</table>

Conclusion

Criteria for evaluating fetal well being in the preterm fetus is different than criteria for advancing gestational age.

Medications and Preterm FHR

- **Magnesium sulfate**
  - Decreases variability
  - Decrease acceleration amplitude

- **Prostaglandin inhibitors and calcium channel blockers**
  - Minimal effects

- **Corticosteroids**
  - Decrease variability
  - Decrease biophysical characteristics

- **Beta sympathomimetics**
  - Tachycardia
  - Mother and fetus

FHM in the Preterm Fetus

- **FDA Drug Safety Communication: New warnings against use of terbutaline to treat preterm labor**
  - Safety Announcement
    - Additional Information for Patients
    - Additional Information for Healthcare Professionals
  - Safety Announcements
    - FDA Drug Safety Communication: New warnings against use of terbutaline to treat preterm labor
  - The U.S. Food and Drug Administration (FDA) is warning the public that terbutaline should not be used in pregnant women for prevention of preterm labor because of the potential for serious maternal heart problems and death. The agency is requiring the addition of a boxed warning and Contraindication to the terbutaline label to warn against this use. In addition, vaginal terbutaline should not be used for prevention or treatment of preterm labor because it is has not been shown to be effective and has serious safety concerns. The agency is requiring the addition of a boxed warning and Contraindication to the terbutaline label to warn against this use.
Antenatal Corticosteroid Therapy for Fetal Lung Maturation

- 24-34 weeks gestation
  - At risk for preterm delivery within 7 days
- Single course
- Betamethasone
  - 12 mg IM 24 hours apart x 2 doses
- Dexamethasone
  - 6 mg IM q12 hours x 4 doses

ACOG, 2011

Does corticosteroid administration suppress FHR characteristics and biophysical activities?

Effects of Maternal Betamethasone Administration on the Fetus
Derks et al, 1995

- 31 women who had received 2 doses for PTL
  - Gestational age: 26-32 weeks
- EFM for 5 successive days (0-4)
- Ultrasound (Days 0, 2 and 4)
  - Fetal body movement
  - Fetal breathing
  - Eye Movements

Results

- FHR variability below normal range for EGA
  - 1/3 cases
- Body movement
  - Reduced by 50% on Day 2
- Breathing movement
  - Absent on Day 2
- Eye movements: unchanged
- Day 4: return to normal state

Conclusion

- Considerable decrease in biophysical characteristics
  - Except eye movement
- Transient reduction in movements/activity
- ? Glucocorticoid receptor mediated process

Effect of Dexamethasone and Betamethasone on FHR Variability
Senat et al, 1998

- 82 patients with preterm labor
  - 25-33 weeks (median 29)
  - Singleton, twins, triplets
- Randomly assigned
  - Betamethasone: 42
  - Dexamethasone: 40
- FHR tracings reviewed (30 minutes)
  - Before, during and after treatment
Betamethasone Group

- Increase in FHR baseline
  - 2.6% (145 bpm to 147-148 bpm)
- Variability decreased by 28%
  - Returned to baseline or above baseline
  - 96 hours
- Accelerations
  - Gradual increase after treatment stopped
- No change in decelerations or contractions

Dexamethasone Group

- No “significant” changes
  - Baseline
  - Variability
  - Accelerations

Result

- Reduced biophysical characteristics
  - Movement, fetal breathing and reactivity
- Amniotic fluid index unchanged
  - Not volume
- Fetal tone unchanged

Conclusion

Dexamethasone preferred steroid
Less alteration in FHR variability

Effect of Steroids on Biophysical Profile And Doppler Indices

- 35 singleton pregnancies
  - 28-34 weeks
  - Betamethasone
- Biophysical profile and dopplers
  - Pre-steroid
  - 24, 48, 72, 96 and 120 hrs after administration of 1st dose

Specific Biophysical Scores

- Pre steroid: 10
- 24 hours: 8
- 48 hours: 6 (maximum peak of steroid)
- 72 hours: 8
- 96 hours: 10
- 120 hours: 10
Dopplers
- Umbilical artery & middle cerebral artery
  - Peak systolic velocity
  - Pulsatility index
  - Resistance index
  - End diastolic velocity
  - S/D ratios
- Unchanged!

Conclusion
Doppler flow studies in conjunction with biophysical profiles may assist with interpretation of post-steroid depression in the fetus and avoid an unwarranted delivery.

Magnesium Sulfate
- Tocolytic (Mercer et al, 2009)
  - 4-6 gram loading dose over 30 minutes
  - Continuous infusion
    - 2 grams/hr up to 5 grams/hour
- Neuroprotection prior to preterm birth
  - ACOG, 2010
  - Variety of protocols
    - Crowther: 4 gram load, 1 gram/hour x24 hours
    - Rouse: 6 gram load, 2 grams/hr up to 12 hours

The Effect of Magnesium Sulfate On FHR Parameters
Hallack et al, 1999
- 34 patients
- > 30 weeks EGA (nonlaboring)
- 800 kcal meal
- Randomized
  - Magnesium Sulfate (6 gram load and 2 gram/hr)
  - Placebo
- One hour monitoring sessions
  - Baseline, 1 hour and 3 hours of infusion

Results

<table>
<thead>
<tr>
<th></th>
<th>FHR</th>
<th>Group</th>
<th>0 hour</th>
<th>1 hour</th>
<th>3 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Placebo</td>
<td>134.4 ± 6.3</td>
<td>134.4 ± 7.1</td>
<td>134.6 ± 7.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mag Sulfate</td>
<td>136.6 ± 6.4</td>
<td>135.1 ± 6.6</td>
<td>132.3 ± 7.6</td>
<td></td>
</tr>
<tr>
<td>Variability</td>
<td>Placebo</td>
<td>2.75 ± 0.33</td>
<td>2.81 ± 0.30</td>
<td>2.71 ± 0.52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mag Sulfate</td>
<td>2.82 ± 0.29</td>
<td>2.84 ± 0.28</td>
<td>2.67 ± 0.36</td>
<td></td>
</tr>
<tr>
<td>Accels</td>
<td>Placebo</td>
<td>10.2 ± 8.3</td>
<td>10.3 ± 8.2</td>
<td>10.4 ± 6.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mag Sulfate</td>
<td>11.1 ± 6.2</td>
<td>10.3 ± 8.2</td>
<td>7.4 ± 4.1</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion
Administration of magnesium sulfate was associated with FHR changes but the clinical significance is questionable.
Effects of Magnesium Sulfate On Cerebral Blood Flow
Twickler et al, 2010

- 38 patients
  - Singletons/twins (24-31 weeks EGA)
  - 18 Magnesium Sulfate (Rouse protocol)
  - 10 Placebo
- Middle cerebral artery measurements
  - Before medication administration
  - 1, 2, 3, and 4 hour intervals

Results

- Decrease in FHR baseline (doppler waveforms)
  - 8-10 bpm
  - Confirmed results in Hallack trial
- No significant difference
  - Peak systolic velocity
  - Vessel diameter
  - Volume flow

Conclusion

Magnesium sulfate has no significant effects on fetal cerebral blood flow

Assessment Guidelines

High Risk Antepartum Care

- 1 nurse to 3 women if “stable condition”
  - 1:1 if not stable
- Magnesium sulfate administration
  - 1 nurse in continuous bedside attendance
    • First hour of administration
  - 1:1 ratio continues until the patient is no longer contracting to “the degree that preterm birth is an imminent concern”
  - 1 nurse to 2 women when no longer contracting...

Fetal Assessments

- Rate
- Variability
- Periodic and Episodic Changes
- Uterine Activity
- Pattern Evolution
- Associated Clinical Findings
- Communication

Guidelines for Professional Registered Nurse Staffing for Perinatal Units
Frequency of Assessments

- Guidance on preterm labor patients
  - AWHONN
  - “Expert opinion”
- Refer to unit policies

“When EFM is used to record FHR data permanently, periodic documentation can be used to summarize evaluation of fetal status at the frequencies recommended by AAP/ACOG...A summary note including findings of the fetal status may be documented in the medical record frequently.”

AWHONN, 2009