Objectives

- Explain the rationale for antenatal testing
- Review the physiology of fetal biophysical parameters
- Discuss the fetal response to hypoxemia and acidemia
- Describe the types of antenatal testing
- List indications for testing
Why test?

- Part of obstetrical practice since 1970’s
- Goals
  - Identify fetus at risk of stillbirth and other complications of intrauterine asphyxia (neurologic injury)
  - Intervene to prevent adverse outcomes
- Limited high quality data supporting use, timing, frequency, indication, and effects of gestational age on testing
- ACOG practice bulletin #145: antepartum testing for “pregnancies in which the risk of antepartum fetal demise is increased” (1C evidence)

Why test?

- Efficacy on two lines of evidence

1. Observational studies report lower rates of stillbirth in pregnancy with testing than historical controls with same indication but no testing

2. Same or lower rates of stillbirth in high risk pregnancies than in a contemporary low risk untested pregnancies

Rationale

- Acidemia is most common cause of fetal death or damage
- 70-90% of late fetal deaths show evidence of chronic or acute and chronic compromise
- Detection of signs of compromise can lead to intervention
Rationale

- Fetus responds to hypoxemia and acidemia in a detectable sequence of biophysical changes
  - Physiologic adaptation
  - Physiologic decompensation
  - Animal models show biophysical activities (heart rate & movement), change in response to fetal oxygenation and pH levels
  - Also sensitive to EGA, maternal medications, smoking, sleep wake cycles, fetal diseases, and anomalies
- Antepartum testing does not identify risk of stillbirth from sudden insult
Fetal Biophysical Development

- Cell differentiation with local regulation
- Progression from local → regional → central neuronal regulation
- Brain modulation
  - Short sleep-wake cycles
  - Circadian cycles
  - Consciousness cycles
- Neurons are sensitive to hypoxia and ischemia due to high metabolic rate and demand
Response to hypoxemia

- Oxygen transport through maternal, placental, and fetal compartments
- Compensatory
  - Increased oxygen extraction
  - Elevated fetal hemoglobin with increased O$_2$ carrying capacity
  - Blood flow redistribution to brain
  - Due to compensation, testing variables may disappear or reappear
Response to hypoxemia: cardiovascular

- Hypoxia (arterial paO$_2$ <20mm Hg)
- Transient/mild (contractions)
  - Chemoreceptors $\rightarrow$ increase FHR and variability
  - Persists $\rightarrow$ peripheral vasoconstriction/ hypertension $\rightarrow$ baroreceptors slow heart rate (decelerations)
- Vasoconstrictors from adrenal gland
  - Abolished sympathetic response to fetal movement $\rightarrow$ loss of accelerations
- Myocardial depression seen as decelerations, bradycardia with loss of variability
How to test?

- Maternal assessment of fetal movement
- Contraction stress test
- Nonstress test
- Biophysical profile
- Amniotic fluid volume
- Doppler Velocimetry
  - Umbilical artery
  - Middle cerebral artery
  - Ductus venosus
Fetal Kick Counts

- Fetal movement decreases in response to hypoxemia
- No evidence based threshold
  - Objective count
  - Subjective perception
- Perception of decreased movement should be assessed by further testing
Contraction Stress Test

- Based on fetal response to transient decreased oxygen delivery during contractions

- Disadvantages
  - Oxytocin administration
  - Relative contraindications
    - PTL, increased PTD risk, PPROM, previa, previous classical
  - High false positive rate

- Rate of stillbirth within 1 week of negative test (false negative rate) is low

- Assume adequate fetal oxygenation after a negative result
CST

- Positive (Non-reassuring)
  - Late decelerations in 50% or more of contractions, even if less than 3 in 10 minutes
CST

- Negative
  - No late or significant variable decelerations with 3 contractions in 10 minutes
CST

- Positive (Non-reassuring)
  - Late decelerations in 50% or more of contractions, even if less than 3 in 10 minutes

- Negative
  - No late or significant variable decelerations with 3 contractions in 10 minutes

- Equivocal
  - Intermittent late or significant variable decelerations

- Unsatisfactory
  - Fewer than 3 contractions in 10 minutes
  - Tracing uninterpretable
CST

- Positive
  - Decreased fetal reserve
  - 20-40% incidence of abnormal FHR pattern in labor
- False positive
  - 50% of reactive positive CST were false positive
  - 100% of non-reactive positive CST were true positive
- Stillbirth rates per 1,000 births
  - Negative 0.3
  - Reactive positive 0
  - NR positive 88
Nonstress test

- 1 or 2 accelerations during CST predicted a negative CST
- Absence of accelerations on baseline FHR tracing is associated with adverse perinatal outcome*
- Indicates normal fetal autonomic function and the absence of acidosis or neurologic depression
- High false positive rate of 50-60%

Nonstress test

- Reactive: Two 15x15 accelerations in 20 minutes  (can wait up to 120 minutes)
- Nonreactive: No accelerations over 40 minute period
- Vibroacoustic stimulation reduces the number of nonreactive tests and testing time without compromising predictive values
- 50% of NST are nonreactive from 24-28 weeks gestation
- Smoking decreases reactivity
NST

- FHR
  - Chemoreceptors, baroreceptors
  - Arousal/sleep
  - Hormones
  - Blood volume

- Parasympathetic input
  - Chronotropic $\rightarrow$ slows heart rate
  - Oscillatory effect $\rightarrow$ variability (24-28 weeks)
  - Greater influence as gestational age increases

- Sympathetic input
  - Norepinephrine $\rightarrow$ accelerations, increased baseline
  - Increased amplitude and frequency of accelerations as gestational age increases
Biophysical Profile

- Assessment of oxygenation
  - Acute: Movement, Tone, Breathing, NST
    - Not essential for life, expend oxygen and energy
    - 15-20% reduction in $O_2$ demand with cessation sheep model
  - Chronic: AFI

- Direct linear correlation with fetal pH

- Presence of these variables implies absence of significant central nervous system hypoxemia or acidemia at the time of testing

- Normal is reassuring, not normal requires differential diagnosis
BPP Criteria

- Nonstress test (reactive, nonreactive)
- Fetal breathing movements (1 or more episodes of rhythmic breathing movements of ≥ 30 seconds in a 30 minute period)
- Fetal tone (one or more episodes of extension of a fetal extremity or spine with return to flexion)
- Fetal Movement (three or more discrete body or limb movements within 30 minutes of observation. An episode of active continuous movement is counted as one movement)
- Amniotic Fluid (single pocket of fluid – 2x2, 2x1, AFI)
- Typical time to complete is 5 minutes, 30 minutes allowed (fetal sleep 20-40 minutes)
<table>
<thead>
<tr>
<th>Biophysical Variable</th>
<th>Normal Score (Score = 2)</th>
<th>Abnormal (Score = 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal breathing movements</td>
<td>At least 1 episode of FBM of at least 30 s duration in 30 min observation</td>
<td>Absent FBM or no episode of &gt;30 s in 30 min</td>
</tr>
<tr>
<td>Gross body movement</td>
<td>At least 3 discrete body/limb movements in 30 min (episodes of active continuous movement considered as single movement)</td>
<td>2 or fewer episodes of body/limb movements in 30 min</td>
</tr>
<tr>
<td>Fetal tone</td>
<td>At least 1 episode of active extension with return to flexion of fetal limb(s) or trunk</td>
<td>Either slow extension with return to partial flexion or movement of limb in full extension</td>
</tr>
<tr>
<td></td>
<td>Opening and closing of hand considered normal tone</td>
<td>Absent fetal movement</td>
</tr>
<tr>
<td>Reactive fetal heart rate (FHR)</td>
<td>At least 2 episodes of FHR acceleration of &gt;15 beats/min and associated with fetal movement in 30 min</td>
<td>&lt;2 episodes of acceleration of FHR or acceleration of &lt;15 beats/min in 30 min</td>
</tr>
<tr>
<td>Qualitative amniotic fluid volume (AFV)</td>
<td>At least 1 pocket of AF that measures at least 2 cm in 2 perpendicular planes</td>
<td>Either no AF pockets or a pocket &lt;2 cm in 2 perpendicular planes</td>
</tr>
</tbody>
</table>

FBM = fetal breathing movement; FHR = fetal heart rate; AFV = amniotic fluid volume; AF = amniotic fluid.
BPP

- Loss of variables based on oxygen sensitivity
- Most sensitive
  - Cardioregulatory (FHR accelerations)
  - Breathing center
- Fetal movement
- Fetal tone
- May not be as accurate in terms of negative predictive value with early < 32 week fetal growth restriction
Fig. 3. Mean umbilical vein pH (±2 SD) per fetal biophysical profile score category. Mean pH did not vary significantly between biophysical profile scores of 10 and 8 of 10 but fell significantly and progressively for a biophysical profile score of ≤6 of 10. Significant linear correlation between mean pH per biophysical profile score was observed ($R^2$ was 0.912, $p < 0.01$). Asterisk, Significantly lower than mean pH value for immediately higher biophysical profile score ($p < 0.01$, Student $t$ test).
FIG. 5. (A) The relationship between the fetal BPS result and the occurrence of various perinatal morbidity. The incidence of fetal distress in labor (FD) cesarean section for fetal distress (LSCS-FD), low 5-minute Apgar score, and venous cord blood acidemia exhibit a very significant linear inverse relationship to test score. These data are based on observations made in more than 26,000 high-risk fetuses. (B) The relationship between the fetal BPS and perinatal death, both gross and corrected for fatal anomalies. Unlike morbidity, the mortality rate increases in an inverse exponential fashion as the BPS score decreases. (Reproduced from Manning and colleagues56 with permission of the publisher.)
**Fig. 2.** Relationship between last fetal biophysical profile score (BPS) and incidence of cerebral palsy (CP). An inverse, exponential, and highly significant relationship is observed ($r^2 = -0.965$, $p < 0.001$).
Interpretation of BPP

- Normal: ≥ 8/10 or 8/8
- Equivocal: 6/10
- Abnormal: ≤ 4/10
BPP abnormal results

- Fetal sleep
  - Unusual to observe loss of 2 variables due to sleep alone
  - The longer the variable is absent, the more likely it is related to pathology
- Maternal health or substances
- Steroids (for 4 days after administration)
  - Decreased variability
  - Reduced fetal breathing and body movements
- Preterm labor (reduced breathing)
<table>
<thead>
<tr>
<th>Test Score Result</th>
<th>Interpretation</th>
<th>PNM within 1 Week without Intervention</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 or 10</td>
<td>Risk of fetal asphyxia extremely rare</td>
<td>1 per 1,000</td>
<td>Intervention only for obstetric and maternal factors</td>
</tr>
<tr>
<td>8 of 10 (normal fluid)</td>
<td>8 of 8 (NST not done)</td>
<td></td>
<td>No indication for intervention for fetal disease</td>
</tr>
<tr>
<td>8 of 10 (abnormal fluid)</td>
<td>Probable chronic fetal compromise</td>
<td>89 per 1,000</td>
<td>Determine that there is functioning renal tissue and intact membranes</td>
</tr>
<tr>
<td>6 of 10 (normal fluid)</td>
<td>Equivocal test, possible fetal asphyxia</td>
<td>Variable</td>
<td>If so, deliver for fetal indications</td>
</tr>
<tr>
<td>6 of 10 (abnormal fluid)</td>
<td>Probable fetal asphyxia</td>
<td>89 per 1,000</td>
<td>If the fetus is mature, deliver</td>
</tr>
<tr>
<td>4 of 10</td>
<td>High probability of fetal asphyxia</td>
<td>91 per 1,000</td>
<td>In the immature fetus, repeat test within 24 hr</td>
</tr>
<tr>
<td>2 of 10</td>
<td>Fetal asphyxia almost certain</td>
<td>125 per 1,000</td>
<td>If &lt;6/10, deliver</td>
</tr>
<tr>
<td>0 of 10</td>
<td>Fetal asphyxia certain</td>
<td>600 per 1,000</td>
<td>Deliver for fetal indications</td>
</tr>
</tbody>
</table>

PNM = perinatal mortality.
Amniotic Fluid Volume

- Hypoxemia
  - Redirection of blood flow (heart, brain, adrenals)
  - Renal hypo perfusion
  - Decreased urine production
  - Oligohydramnios

- Typically takes 15 days to go from normal to oligohydramnios

- Oligohydramnios correlated with adverse pregnancy outcome
Amniotic Fluid Volume

- AFI ≤ 5 is 2 SD below mean
  - 7 is 5%tile
  - Most studies reporting adverse outcome used 5 rather than 5%tile for EGA
- SDP vs AFI
  - Equivalent prediction of adverse outcome
  - Use of AFI results in more IOL and CD
Modified BPP

- NST and AFI
- Focuses on components most predictive of outcome
- False negative is same as BPP
<table>
<thead>
<tr>
<th>Test</th>
<th>False negative rate</th>
<th>False positive rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST</td>
<td>0.04%</td>
<td>35-65%</td>
</tr>
<tr>
<td>NST</td>
<td>0.2-0.7%</td>
<td>55-90%</td>
</tr>
<tr>
<td>BPP</td>
<td>0.07-0.08%</td>
<td>40-50%</td>
</tr>
<tr>
<td>Modified BPP</td>
<td>0.08%</td>
<td>60%</td>
</tr>
</tbody>
</table>

- False negative: antepartum stillbirth within 1 week
- False positive: reassuring back up test

Umbilical Artery Doppler

- Compromise of placental vascular tree
  - 30% results in increased umbilical artery S/D ratio
  - 60-70% results in absent/reversed EDF
  - Examines fetal cardiac afterload
- Most useful in FGR due to placental insufficiency
  - Absent or reversed is associated hypoxemia, acidemia and increased perinatal morbidity and mortality
- Steroids may transiently improve blood flow (catecholamine inotropy)
- Abnormal result leads to increased risk of FHR tracing abnormalities in labor (consider CD in AEDF)
- Perform during fetal apnea

Fetal Growth Restriction

- Perinatal mortality (GRIT)
  - FGR, forward flow: 5.6%
  - FGR, A/R EDF, normal venous Doppler: 11.5%
  - FGR, A/R EDF, abnormal venous Doppler: 38.8%
- Adverse outcome (PORTO)
  - 3-10%tile: 2%
  - <3%tile: 6.2%
  - <3%tile and abnormal Doppler: 16.7%
- Use of umbilical artery Doppler in antenatal testing of FGR can significantly reduce perinatal death (29%) as well as unnecessary IOL in preterm FGR*
- Should be complemented by BPP or NST

Middle cerebral artery Doppler

- Monitor fetal anemia
- FGR with brain sparing
  - Low prognostic value
Venous Doppler

- Umbilical vein enters fetal liver, turns right, joins transverse portion of left portal vein
- Ductus venosus originates at turn, but joins IVC just below level of right atrium – shunts oxygenated blood across FO
- 30-40% blood bypass in the high flow rate ductus venosus
  - Modulated in setting of chronic hypoxemia
  - Compromised liver blood supply → elevated transaminases and metabolic deterioration
- Decreased liver size causes AC lag, the first biometric sign of FGR
Venous Doppler

- Blood flows antegrade throughout cardiac cycle
- Absent or reversed a-wave indicates cardiovascular instability and can be sign of impending acidemia and death
When to test?

- When increased risk for demise is identified and perinatal benefit for delivery exists if test is abnormal
- Based on expert opinion, clinical experience, community standards
- 32 weeks in non-growth restricted fetuses (observational data)
- Weekly but can be increased with worsening status

Who to test?

- Pre-gestational diabetes
- GDM treated with medication
- GDM poorly controlled on nutritional therapy
- Hypertension
- Fetal growth restriction
- Mo-Di or Mo-Mo twin gestation
- Post-term gestation
- Decreased fetal activity
- SLE
- Antiphospholipid Antibody Syndrome

- Sickle Cell Disease
- Isoimmunization
- Oligohydramnios
- Polyhydramnios
- Prior stillbirth
- PPROM
- Maternal cyanotic heart disease
- Poorly controlled hyperthyroidism
- Maternal vascular disease
Risk factors for stillbirth

- Congenital / karyotypic anomalies
- IUGR/ placental abnormalities
- Maternal comorbidities:
  - DM, SLE, renal dz, thyroid dz, cholestasis
- Hypertensive disorders, preeclampsia
- Multiple gestation
- **Black Race**
- **Nulliparity**
- AMA
- **Obesity**
- Infection: Parvo, syphilis, streptococcal, listeria
- Modifiable: Obesity, Smoking, ETOH/illicit drug use
Risk Factors for stillbirth

- Diabetes
  - 2-5 fold increased risk
  - Preconceptional glycemic control reduces rates of stillbirth
- Multiples
  - Four times higher than singletons: 19.6 per 1,000
  - Multiples complications: TTTS, IUGR, fetal abnormalities, AMA
- Previous adverse pregnancy outcome
  - Explained and unexplained (1.7-2x) stillbirth
  - IUGR delivered < 32 weeks
  - Preeclampsia
Additional indications

- AMA
- Obesity
- Abnormal serum screening*
- Fetal structural anomalies
- Uncertain whether testing reduces risk, use on case by case basis

**Obesity**

- Modest increases in maternal BMI increased the risk of stillbirth

---

### Table. Relative Risks From Nonlinear Dose-Response Analysis for Maternal BMI and Fetal Death, Stillbirth, and Neonatal, Perinatal, and Infant Death

<table>
<thead>
<tr>
<th>Fetal Death (n = 6)</th>
<th>BMI[a]</th>
<th>17</th>
<th>20</th>
<th>22.5</th>
<th>25</th>
<th>27.5</th>
<th>30</th>
<th>32.5</th>
<th>35.0</th>
<th>37.5</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% CI)</td>
<td>1.02</td>
<td>1</td>
<td>1.02</td>
<td>1.07</td>
<td>1.17</td>
<td>1.34</td>
<td>1.59</td>
<td>1.97</td>
<td>2.58</td>
<td>3.54</td>
<td></td>
</tr>
<tr>
<td>AR (95% CI)c</td>
<td>78</td>
<td>76</td>
<td>78 (75-81)</td>
<td>82 (76-88)</td>
<td>89 (82-98)</td>
<td>102 (93-112)</td>
<td>121 (109-135)</td>
<td>150 (130-174)</td>
<td>197 (159-244)</td>
<td>270 (195-373)</td>
<td></td>
</tr>
</tbody>
</table>

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**Original Investigation**

Maternal Body Mass Index and the Risk of Fetal Death, Stillbirth, and Infant Death

A Systematic Review and Meta-analysis

Dagfinn Aune, MS; Ola Didrik Saugstad, MD, PhD; Tore Henriksen, MD, PhD; Serena Tonstad, MD, PhD
Nonlinear dose-response analysis

- Best fitting fractional polynomial
- 95% CI

Relative Risk of Fetal Death, 95% CI

Maternal BMI, Units
Risk Factors: Obesity

- Increased risk early fetal loss and stillbirth
- BMI 30-39.9: 8/1,000
- BMI > 40: 11/1,000
- Increases with increasing EGA especially after 36 weeks (5x placental dysfunction)
- Remains risk factor after controlling for smoking, DM, preeclampsia
Risk Factors: AMA

- Lethal congenital and chromosomal abnormalities
- Persists after controlling for HTN, DM, previa, multiples
- Primiparous greater than multiparous
**Maternal age and the risk of stillbirth throughout pregnancy in the United States.**

**Table I** Risk of stillbirth for women younger than 35, 35 to 39, and 40 years or older by medical condition status throughout pregnancy

<table>
<thead>
<tr>
<th>GA, wks</th>
<th>Number of stillbirths</th>
<th>Risk of stillbirths per 1000 ongoing pregnancies</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger than 35 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35-39 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 y or older</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------</td>
<td>-----------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Total population</td>
<td>20-23</td>
<td>6233</td>
<td>916</td>
</tr>
<tr>
<td></td>
<td>24-27</td>
<td>3321</td>
<td>489</td>
</tr>
<tr>
<td></td>
<td>28-31</td>
<td>2701</td>
<td>338</td>
</tr>
<tr>
<td></td>
<td>32-33</td>
<td>1463</td>
<td>197</td>
</tr>
<tr>
<td></td>
<td>34-36</td>
<td>2655</td>
<td>403</td>
</tr>
<tr>
<td></td>
<td>37-38</td>
<td>2239</td>
<td>347</td>
</tr>
<tr>
<td></td>
<td>39-40</td>
<td>1898</td>
<td>285</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>450</td>
<td>70</td>
</tr>
<tr>
<td>No medical conditions*</td>
<td>20-23</td>
<td>5417</td>
<td>749</td>
</tr>
<tr>
<td></td>
<td>24-27</td>
<td>2724</td>
<td>362</td>
</tr>
<tr>
<td></td>
<td>28-31</td>
<td>2137</td>
<td>239</td>
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<tr>
<td></td>
<td>32-33</td>
<td>1135</td>
<td>138</td>
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<td></td>
<td>34-36</td>
<td>2111</td>
<td>286</td>
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<tr>
<td></td>
<td>37-38</td>
<td>1795</td>
<td>255</td>
</tr>
<tr>
<td></td>
<td>39-40</td>
<td>1570</td>
<td>236</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>386</td>
<td>52</td>
</tr>
</tbody>
</table>

GA, Gestational age.
* Excluded pregnancies with diabetes, chronic hypertension, pregnancy-associated hypertension, eclampsia, and renal, cardiac, or lung diseases at the beginning of each gestational age interval.
Figure  Hazard (risk) of stillbirth for singleton births without congenital anomalies by gestational age, 2001-2002.
Advanced Maternal Age

- Evidence supports managing AMA as post-term earlier in gestation
- Testing at 37 weeks in women ≥ 35
  - Avoid 3.9/1,000 fetal deaths
  - Per each death avoided*
    - 863 antepartum tests
    - 71 IOL
    - 14 CD
- Offer testing > 40 (biologically post-term at 39 weeks)
- Offer testing >35 if other risk factors (obesity, AA, etc)

* Fretts RC, Elkin EB, Myers ER, Heffner LJ. Should older women have antepartum testing to prevent unexplained stillbirth? Obstet Gynecol 2004;104:56.
Management of Abnormal Results

- High False Positive rate
- Additional testing with a different test
- Correction of maternal factors influencing abnormal result
  - DKA
  - Respiratory compromise
- Consider severity of disease, progression of disease, other testing, and EGA
- IOL not contra-indicated
  - 40% of +CST will tolerate labor *

Questions?

- Why
- What
- When
- Who
- Where