Natural disease progression:
The 3 phases of FGR

Preclinical: Venous redistribution & evolving growth delay
Clinical: Growth delay and arterial redistribution
Deterioration: fetal decompensation

Placental failure & neurodevelopment

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Professor of Pediatric Surgery
Dept. Gynecology & Obstetrics
Johns Hopkins University School of Medicine

Placental nutrient transport

Fetal circulation - nutrient streaming

Maternal perfusion

VENOUS REDISTRIBUTION

Steady state versus shifting in growth restricted fetuses and the role of umbilical vein oxygenation

Sites of vascular adaptation

UV

60-70%

Ductus arteriosus
Ductus venosus
Foramen ovale
Aortic isthmus
Ductus venosus
Sites of vascular adaptation

Venous redistribution
Metabolism

Circulation

Growth

AC is most sensitive for Di of Fetal

maternal Compartment

fetal Compartment

Assessment Of The Fetal PO2 Changes By Cerebral & Umbilical Doppler On Lamb Fetuses During Acute Hypoxia

Middle cerebral artery

Abnormal MCA findings

Abnormal MCA findings

REFERENCES


**OBJECTIVE:**

The purpose of this study was to evaluate the surveillance characteristics that precede stillbirth in growth-restricted fetuses that receive integrated Doppler and biophysical profile scoring (BPS). Surveillance findings were that were complicated by fetal growth restriction had multivessel Doppler scans (umbilical and middle cerebral arteries [MCA], ductus venosus, and umbilical vein) and BPS. Surveillance findings were assessed.

**CONCLUSION:**

Fetal deterioration occurs following highly abnormal metabolic, circulatory, and growth characteristics that precede stillbirth. Therefore, surveillance is at greatest risk.

**METHODS:**

Nine hundred eighty-seven singleton pregnancies that were monitored with a prospectively defined standard integrating Doppler and BPS. Surveillance findings were compared to clinical deterioration when only dyed-ink Doppler and biophysical parameters were assessed.

**STUDY DESIGN:**

This was a retrospective, institutional review board-approved study of fetal growth restriction. The criteria that were complicated by fetal growth restriction had multivessel Doppler findings of abnormal venous redistribution, cardiac dysfunction, acidemia, absent a-wave, placentation resistance, ductus venosus Doppler, and reversed a-wave. These findings were compared to clinical deterioration when only dyed-ink Doppler and biophysical parameters were assessed.

**Key words:** Doppler; biophysical; surveillance; fetal growth restriction.
Fetal neurodevelopment

Dynamic fetal variables
7.5 - 9 wks  Movement & Tone
12-14 wks  Breathing
18 - 20 wks  Accelerations

Fetal heart rate control
CARDIAC OUTPUT IS ADJUSTED TO BODY NEEDS

Surveillance tests & fetal pH by cordocentesis

Evolution over 4-6 weeks
Early onset FGR
Birth asphyxia

Evolution over 6-9 weeks
Late onset FGR
Brain sparing

Individual movement  coupling  Rest  activity  Behavioral states
1st trimester  2nd trimester  3rd trimester

Nonreactive CTG
Late decelerations
diminishing variable fetal heart rate
Loss of breathing
Loss of movement
Loss of tone

Elevated Doppler index
Normal umbilical artery
Absent    /     reversed end-diastolic velocity
Normal middle cerebral artery

Nonreactive FHR
Declining AFI
Loss of breathing
FHR variation loss
Late decelerations
Declining amniotic fluid volume
Loss of breathing
Loss of movement
Loss of tone

Elevated Doppler index
Normal umbilical artery
Absent / reversed a wave
Normal ductus venosus

Elevated Doppler index
Normal umbilical artery
Absent / reversed end-diastolic velocity
Normal middle cerebral artery

Brain sparing

Nonreactive CTG
Abnormal UA
Anhydramnios ( < 2 cm)
Abnormal DV
STV < 3.5
Absent tone & movement

STV
pH < 7.20
pH < 7.10
**Behavioral states**

<table>
<thead>
<tr>
<th>FHR</th>
<th>REM</th>
<th>Movement</th>
<th>Time to complete BPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1F</td>
<td>Quiet</td>
<td>Absent</td>
<td>26 min</td>
</tr>
<tr>
<td>2F</td>
<td>Active</td>
<td>Present</td>
<td>3 min</td>
</tr>
<tr>
<td>3F</td>
<td>Quiet</td>
<td>Present</td>
<td>14 min</td>
</tr>
<tr>
<td>4F</td>
<td>Active</td>
<td>Absent</td>
<td>2 min</td>
</tr>
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</table>

- Established by 34 wks
- In 2 hours characteristic:
  - Concurrence
  - Organized transition

**Evidence of abnormal fetal neurodevelopment in FGR**

- Abnormal organization of fetal behavior
  - Decreased percentage of coincidence
  - Abnormal state transition
  - Abnormal state organization
  - Delayed achievement of stable behavioral states

- Abnormal central integration of FHR control
  - Decreased accelerations – 80% nonreactive at 32 weeks
  - Increased baseline
  - Decreased variability and variation

**Conclusions**

- Early onset FGR develops prior to the establishment of fetal behavioral states
- Early onset FGR results in delayed establishment of fetal neurodevelopmental milestones

**Fetal growth and neurodevelopment**

**Growth in late onset FGR**

Outcome in preterm small for gestational age infants compared to appropriate for gestational age neonates at the age of 2 years: a prospective study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Preterm SGA (n=100)</th>
<th>AGA (n=200)</th>
<th>Effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head size (cm)</td>
<td>14.9 (14.8-15.1)</td>
<td>15.1 (15.0-15.2)</td>
<td>-0.2 (0.009-0.011)</td>
</tr>
<tr>
<td>Body length (cm)</td>
<td>41.5 (41.4-41.6)</td>
<td>42.0 (41.9-42.0)</td>
<td>-0.5 (0.006-0.007)</td>
</tr>
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<td>Fracture index (cm)</td>
<td>10.6 (10.5-10.7)</td>
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Delivery for: pre-eclampsia (34%)

Oligohydramnios (27%)

Average GA: 34 weeks

GA correlated with:
- Motor, social & adaptive scales (p<0.001).
Conclusions

- Early onset FGR develops prior to the establishment of fetal behavioral states.
- Early onset FGR results in delayed establishment of fetal neurodevelopmental milestones.
- Lagging head growth has the greatest impact on neurodevelopment; gestational age is an independent cofactor.
- Lagging head growth is associated with:
  - lower perceptual performance
  - motor disability
  - poor cognition
  - poor concentration
  - deficient short-term memory
  - poorer school achievement
  - i.e. all brain areas are affected.

Umbilical Doppler & neurodevelopment

- Early onset FGR (n=87) retrospectively stratified by UA EDV
  - Mild & moderate 2 year disability in 18% of AREDV vs 3% PEDV
  - Gestational age was main determinant of outcome.

UA Doppler & early onset FGR

- Brodzski et al., UOG 2000
  - 40 AREDV & 40 gestational age matched controls delivered < 30 weeks
  - Identical rate of cerebral palsy in cases and controls (14 vs 11%)
- Padilla et al., Acta Paediatr 2010
  - AREDV vs gestational age matched controls delivered at 30 weeks
  - Identical 1 year testing in cases and controls
  - FGR had smaller HC & trend to lower PDI
  - Birthweight & gestational age correlated with motor development index
  - HC & cephalization index correlated with psychomotor development

- Shand et al., Austr N Z J Obstet Gynaecol 2009
  - Early onset FGR (n=87) retrospectively stratified by UA EDV
  - Mild & moderate 2 year disability in 18% of AREDV vs 3% PEDV
  - Gestational age was main determinant of outcome.

UA Doppler & Childhood development

- Wienerroither et al., Obstet Gynecol 2001
  - 35 AREDV vs gestational age matched controls delivered 33 weeks
  - 6 year Kaufmann ABC - no single determinant identified

Morsing et al., Pediatrics 2011

- AREDV had lower verbal and global IQ compared to controls
- Boys at greater risk for developmental delay
UA Doppler & Adolescent development

Schreuder et al., Arch Dis Child 2002
- Cohort of 76 FGR adolescents stratified by UA EDV
- Average GA at delivery 32 weeks
- Intelligence, neurological, cognitive & school performance testing

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<tr>
<th>UA Doppler &amp; Adolescent development</th>
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Table 2: Results of mental development using the Wechsler Preschool 
and Primary Scale: 

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<th>Test</th>
<th>Control</th>
<th>ARED</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Full Scale</td>
<td>100</td>
<td>85</td>
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<td>Verbal</td>
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Table 3: School performance by maternal education:

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<tr>
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Conclusion – UA Doppler

- Gestational age overrides effects of UA Doppler until early 3rd trimester
- Compared to PEDV – AREDV have worse motor development at age 2
- Childhood intelligence, psychomotor, speech development worse with AREDV
- In adolescence and worst intelligence, and motor development with REDV

Cerebral Doppler & neurodevelopment


|-----------------------------------------|-----------------------------------|

Early on set FGR

Kutchera et al., EJOBG 2002
- 16 ARED matched with abnormal CPR & Controls delivered at 32 weeks
- 3-6 year Kaufman ABC

Table 1: Results of the Kaufman Assessment Battery for Children, the Developmental Intelligence Scale for Young Children and the Wechsler Preschool and Primary Scale:

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Conclusion – Cerebral Doppler

- In early onset FGR – studies stratifying appropriately by MCA Doppler are lacking

Conclusions – Cerebral Doppler

- In early onset FGR – studies stratifying appropriately by MCA Doppler are lacking
Aorta, Isthmus & neurodevelopment

Ley, 1996, Tideman 2006

Abnormal antenatal Doppler velocimetry and cognitive outcome in very-low-birth-weight infants at 2 years of age

M. Lipponen1, E. Hänninen1, K. Palosuo1, J. Manninen1, P. Mursula1, B. Parkkonen1, J. Laitinen1, H. Lappalainen1, L. Hietala2, P. Raitava2*†; and the Finnish Study Group

• 85 FGR delivered at 32 weeks gestation - 2 year Bayley
  - AREDV, abnl CPR & abnormal aorta associated with cognitive delay
  - Isthmus blood flow non-contributory

Main determinant of cognitive outcome was cerebral volume

Suboptimal neurodevelopment in very preterm infants is related to fetal cardiovascular compromise in placental insufficiency

Tuula Kaakinen, MD,*† Juha Räikkönen, MD, PhD,*† Brittta Hervo, MD, PhD,*† Dhonulkumar D. Patel, MD, PhD,*† Mikko Hallman, MD, PhD,*†

• Declining cardiac output & abnormal venous Doppler main factors.
• Isthmus non-contributory

Infant neurodevelopment following fetal growth restriction: relationship with antepartum surveillance parameters

A. A. Baschat, B. M. Yovich, S. Hysy-Gardner, N. Harvis, and C. Harmel

Cerebral palsy (8.3%)
• Gestational age \( r^2 = 0.52, p=0.0001 \)
• Birthweight
• Neonatal morbidity
• UA REDV

Global delay (23.6%)
• UA REDV \( r^2 = 0.31, p=0.006 \)
• Birthweight
• Gestational age

Neurosensorial delay (52%)
• Birthweight \( r^2 = 0.54, p=0.0001 \)
Conclusion - Central hemodynamics

- Even when central hemodynamics are considered
  Head size, overall growth delay
  Gestational age at delivery
  Placental Doppler parameters
  Are primary determinants of neurodevelopment

- Fetal deterioration and abnormal venous Doppler parameters play a small contributory role

Summary

Management & neurodevelopment


<table>
<thead>
<tr>
<th>Immediate delivery</th>
<th>Delivered when no longer in doubt</th>
</tr>
</thead>
<tbody>
<tr>
<td>BJOG 2003</td>
<td></td>
</tr>
<tr>
<td>C-section</td>
<td>91%</td>
</tr>
<tr>
<td>FOSU</td>
<td>2</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>27</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>29</td>
</tr>
<tr>
<td>Prematurity-related</td>
<td>17</td>
</tr>
<tr>
<td>Dev. delay</td>
<td>14</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>4</td>
</tr>
<tr>
<td>A/IOFS 2010</td>
<td>9-13 year Follow-up: Griffith IQ, CP, Mortality</td>
</tr>
<tr>
<td>Identical Long-term outcomes</td>
<td></td>
</tr>
</tbody>
</table>

2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial

<table>
<thead>
<tr>
<th>AC ≤95% &amp; abnormal UA Doppler</th>
</tr>
</thead>
<tbody>
<tr>
<td>cCTG STV only</td>
</tr>
<tr>
<td>DV &gt;95% or abnl. STV</td>
</tr>
<tr>
<td>DV RAV or abnl. STV</td>
</tr>
<tr>
<td>Survival without impairment</td>
</tr>
<tr>
<td>85%</td>
</tr>
<tr>
<td>90%</td>
</tr>
<tr>
<td>Impairment at age 2</td>
</tr>
<tr>
<td>15%</td>
</tr>
<tr>
<td>9%</td>
</tr>
<tr>
<td>Global impact of growth delay</td>
</tr>
<tr>
<td>Cognition</td>
</tr>
<tr>
<td>speech / communication</td>
</tr>
<tr>
<td>Apparent in childhood</td>
</tr>
</tbody>
</table>

Germinal matrix / IVH
Primary effects are motor
Apparent to prematurity
Apparent by 2 years
Conclusions

- Fetal neurodevelopment is abnormal when FGR is clinically apparent.
- Lagging head growth is the physical characteristic with the greatest impact on neurodevelopment.
- Gestational age overrides effects of UA Doppler until early third trimester.
- Abnormalities in central hemodynamics appear to play a small contributory role.
- Motor delay is related to prematurity. Cognitive delay becomes apparent later and is more related to fetal status.