Neurodevelopment & placental dysfunction

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Important outcomes in FGR

- Hypoxemia
- Acidemia
- Stillbirth
- Prematurity
- Morbidity
- Neonatal death

for the obstetrician

for the neonatologist

for parents

A normal child

Nutrient partitioning in the fetus

Active placental nutrient transport

- GLUCOSE
- AMINO ACIDS
- FATTY ACIDS

Umbilical vein
Fetal circulation

Fetal circulation - nutrient streaming

60-70%

Fatty acids

O2

O2

O2

O2

O2

O2

Insulin / IGF
Glycogen
Ductus arteriosus
Ductus venosus
Foramen ovale

Natural disease progression:
The 3 phases of FGR

Preclinical: Venous redistribution & evolving growth delay
Clinical: Growth delay and arterial redistribution
Deterioration: Fetal decompensation
Maternal compartment

ET-1

Fetal compartment

ET-1

TX A2

VENOUS REDISTRIBUTION

Insulin / IGF axis

Liver size

maternal Compartment

Insulin / IGF axis

Liver size

fetal Compartment

Umbilical artery

Middle cerebral artery

Branch of the circle of Willis

Use parietal bone window

Parallel to wings of sphenoid

Insonate at 0 degrees

Two parameters of importance

Increased peak systolic velocity (0º)

Decreased pulsatility index

Fetal anemia

Increased paCO₂

Fetal hypoxemia

Fetal hypertension

indistinguishable by waveform.

Cerebroplacental Doppler ratio (CPR)

“centralization” =

middle cerebral artery Pulsatility index

umbilical artery Pulsatility index

* A cerebral-umbilical Doppler ratio below 1.08 can be considered as evidence of centralization of cardiac output towards the fetal brain.

**Arterial Redistribution**

- Increased venous pressure
- Ductus venous dilatation
- High placental afterload
- Fetal Acidemia
- Cardiac dysfunction

Vascular Doppler in the fetus with absent end-diastolic flow in the umbilical artery.

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**Two Types of FGR (n=1024)**

- Pre-clinical phase
  - Growth
  - Circulation
  - Metabolism

- Clinical phase
  - Alteration of nutrient partitioning & endocrine axis
  - Cerebral switching of nutrient utilization

- Deterioration
  - Metabolic deterioration
  - Arterial redistribution
  - Venous redistribution

**Examinations prior to stillbirth**

- Reactive CTG
- Tone / Movement
- Oligohydramnios
- Brain sparing

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**Two Types of FGR**

- Early onset FGR: Evolution over 4-6 weeks
  - Normal umbilical artery
  - Normal ductus venosus
  - Normal middle cerebral artery

- Late onset FGR: Evolution over 6-9 weeks
  - Declining AFI
  - Nonreactive FHR
  - Loss of breathing
  - Declining amniotic fluid volume
  - Loss of movement

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- Baschat 2010
- Baschat et al., Am J Obstet Gynecol 2009
- Baschat et al., Am J Obstet Gynecol 2009
- Hecher et al., UOG 2001

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- A. umbilikalis
- D. venosus
- MCA
- DV
- cCTG
- BPP
- AFI
- UA

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- Early changes
- Late changes

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- <34 SSW
- >34 SSW

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- Brain sparing
Proposed origins of damage

Hypoxemia
Acidemia
Neurologic Damage
Stillbirth
Delivery!

If this were true...

- FGR fetuses should be normal before deterioration
- Deterioration should be associated with worse neurodevelopmental outcome
- Early intervention should make a difference

The Growth Restriction Intervention Trial: long-term outcomes in a randomized trial of timing of delivery in 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

Basic control
High baseline
Little variability

Reactive control
Lower baseline
Higher variability
Accelerations with activity

Behavioral control
Lower baseline
Higher variability
Changes with behavioral state

CARDIAC OUTPUT IS ADJUSTED TO BODY NEEDS
### 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>2F</td>
<td>3F</td>
<td>4F</td>
</tr>
<tr>
<td>Rem</td>
<td>Par</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>25 min</td>
<td>3 min</td>
<td>14 min</td>
<td>2 min</td>
</tr>
</tbody>
</table>

**Descriptors**
- Absent
- Present
- Periodic

**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

- **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
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    - Increased baseline
    - Decreased variability and variation

- **Abnormal fetal neurodevelopment**
  - Lower perceptual performance
  - Motor disability
  - Poor cognition
  - Poor concentration
  - Deficient short-term memory
  - Poorer school achievement

### Conclusions

- Fetal neurodevelopment is abnormal when FGR is diagnosed

### Fetal growth and neurodevelopment

- **Conclusions**
  - Fetal neurodevelopment is abnormal when FGR is diagnosed
  - Lagging head growth is the physical characteristic with the greatest impact on neurodevelopment with gestational age as 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**

**UA Doppler & early onset FGR**

**Bredezki 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 & 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

**Shah et al., Aust 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 & early onset FGR**

**Vassbæk et al., Eur J Pediatr 2000**
- 40 AREDV & 40 gestational age matched controls delivered at 37 weeks
- 16 completed Bayley or Kaufman ABC

<table>
<thead>
<tr>
<th>AREDV</th>
<th>Control</th>
<th>P</th>
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<tbody>
<tr>
<td>MDI Bayley</td>
<td>76</td>
<td>98</td>
</tr>
<tr>
<td>Delay/Rehabilitation</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>MPC Kaufman</td>
<td>57</td>
<td>89</td>
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<tr>
<td>Severe motor impairment</td>
<td>6</td>
<td>3</td>
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</table>

**Morsing et al., Pediatrics 2011**
- AREDV had lower verbal and global IQ compared to controls
- Boys at greater risk for developmental delay

**UA Doppler & Childhood development**

**Wienerreither et al., Obstet Gynaecol 2001**
- 35 AREDV vs gestational age matched controls delivered 33 weeks
- 6 year Kaufman ABC - no single determinant identified

**UA Doppler & Adolescent development**

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

- Poor performance with REDV persisted after correction for BA
**UA Doppler & late onset FGR**

McCowan et al., Am J Obstet Gynecol 2002
- 220 SGA infants with 2 year Bayley, stratified by UA Doppler
  - Average gestational age at delivery 36 weeks
  - MDI of 96 lower than reference population, 20% abnormal MDI, 14% abnormal PDI
  - Delivery for maternal hypertension protected motor development
  - PDI related to HC, NICU stay and breastfeeding

Figueiras et al., EJOG 2008, Pediatrics 2009
- Term SGA with normal UA Doppler
  - Abnormal NBAS for attention, habituation, social and state regulation.
- Term SGA with normal UA Doppler matched with AGA
  - 2 year ASQ – lower scores for problem solving and social domains.
  - Abnormalities relate to frontal lobe function

**Conclusion – UA Doppler**
- In early onset FGR
  - Gestational age overrides effects of UA doppler until early third trimester
  - Compared to PEDV – AREDV have worse motor development at age 2
  - Childhood intelligence, psychomotor, speech development worse with AREDV
- In late onset FGR
  - Even with normal UA Doppler neonatal state organization is abnormal
  - Among SGA psychomotor development primarily related to HC
  - Compared to AGA controls worse frontal lobe function with abnormal UA

**Cerebral Doppler & neurodevelopment**

Kutchera et al., EJOBG 2002
- 16 ARED matched with abnormal CPR & Controls delivered at 32 weeks
  - 3-6 year Kaufman ABC
  - ARED & abnormal CPR are associated with similar degree of impaired neurodevelopment

**Early onset FGR**

**Scherjon et al., 1996, 1998, 2000, 2010**

**Late onset FGR**

Oros et al., UOG 2010, Cruz-Martinez et al., AJOG 2009
- 935 term FGR with ACA & MCA Doppler and NBAS (28 days of life)
  - MCA brain sparing : abnormal motor function & state organization
  - ACA brain sparing : poor state organization
  - Decreased frontal lobe flow : abnormal social interactive, state organization and attention scores

Roza et al., Am J Epidemiol 2008
- 128 term FGR & AGA controls stratified by MCA Doppler – ASQ at 2 years
  - Brain sparing : 51-57% communication delay
  - 39-41% abnormal problem asking
**Conclusions – Cerebral Doppler**

- **In early onset FGR**
  - Studies stratifying appropriately by MCA Doppler are lacking

- **In late onset FGR**
  - Abnormal MCA Doppler is associated with worse neurodevelopment
  - Regional alterations in brain blood flow impedance have differential effects

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**Ley, 1996, Tideman 2006**

<table>
<thead>
<tr>
<th>Age</th>
<th>FGR &amp; GA matched controls</th>
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<tbody>
<tr>
<td></td>
<td>Normal DAO - BFC</td>
</tr>
<tr>
<td>7 years</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
</tr>
<tr>
<td></td>
<td>Verbal IQ</td>
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<tr>
<td></td>
<td>Verbal SQ</td>
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<tr>
<td></td>
<td>Global IQ</td>
</tr>
<tr>
<td></td>
<td>Global SQ</td>
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<tr>
<td>18 years</td>
<td>Normal</td>
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<tr>
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<td>MND -1</td>
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<td></td>
<td>MND -2</td>
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**Abnormal antenatal Doppler velocimetry and cognitive outcome in very-low-birth-weight infants at 2 years of age**

- 85 FGR delivered at 32 weeks gestation – 2 year Bayley
- AREDV, ant 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**

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**Aorta, Isthmus & neurodevelopment**

**Correlation between prenatal velocity waveforms in the aortic isthmus and neurodevelopmental outcome between the ages of 2 and 4 years**

- Net antegrade flow: 49% suboptimal development
- Net retrograde: 100% suboptimal development

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**Venous Doppler, BPS & development**

- Isthmic flow index <0.7 predicts suboptimal development with 85% sensitivity & 95% specificity
- Prediction independent of UA Doppler

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**Declining cardiac output & abnormal venous Doppler main factors.**
- Isthmus non-contributory
Infant neurodevelopment following fetal growth restriction: relationship with antepartum surveillance parameters

A. A. Barchat*, B. M. Vescy, E. H. USEY-GARNER, N. DAPPI, and C. HURSTON

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

- Regional perfusion
  - State organization
  - Mental processing
  - Apparent at 2 years

- Germinal matrix / IVH
  - Primary effects are motor
  - Primarily related to prematurity
  - Apparent by 2 years

- Global impact of growth delay
  - Cognition
  - Speech / communication
  - Apparent in childhood
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.
- Independent contribution of MCA Doppler is more apparent in the vulnerable term brain.
- 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.