**Intrauterine Growth Restriction Update**

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**Disclosure**

- No commercial interests related to topics presented

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**Outline**

- Definition
- Implications of IUGR
- Etiology
- Diagnosis
  - Growth Curves
- Management
  - Fetal cardiovascular changes by Doppler
  - Umbilical artery, MCA, Venous
- Timing of delivery
  - RCTs
- Recurrence

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**In-utero Growth Restriction**

- ACOG defined IUGR as EFW < 10th percentile
- 4 million births per year -- 400,000 babies are IUGR
- Consequences
  - At birth and in infancy
  - Childhood and adult life: Barker Hypothesis
    - Risk of hypertension, hypercholesterolemia, coronary heart disease, impaired glucose tolerance and diabetes
- Enormous burden
Etiology

• Maternal
  – Chronic disease (e.g., cHTN, DM, SLE, APLS)
  – Pregnancy-related hypertension
  – Smoking and substance abuse (e.g., alcohol, cocaine)
  – Malnutrition
  – Teratogens (e.g., anticonvulsants)

• Fetal
  – Genetic disorder: chromosomal (e.g., T13, T18, T21), genetic syndromes
  – Structural (e.g., gastroschisis, CHD)
  – Infection: e.g., CMV, toxo, rubella, zika (<5% of all IUGR)
  – Multiple (more common in m/di than d/di)

• Placental
  – Chorangioma, Confined placental mosaicism
  – Abruption

Perinatal Mortality and Morbidity

PORTO Study

• Prospective cohort study in Ireland
• 1200 consecutive singleton pregnancies with EFW < 10th percentile recruited
• 24 0/7 to 36 6/7
• USS every 2 weeks with Doppler


Unterscheider J, Daly S, Geary MP et al. PORTO study
AJOG2013;208: 290. e1-6
Porto Study

- Mean GA enrolment 30.1 weeks
- Mean GA at delivery 37.8 weeks
- Only Doppler UA and EFW < 3rd percentile are associated with adverse outcome
- Oligohydramnios, EFW < 5th or < 10th are NOT associated with adverse outcome

Perinatal Morbidity

- Increased risk of spontaneous or induced preterm births
  - Preterm infants: NEC, need for respiratory support
- Neonatal Complications:
  - Neonatal asphyxia
  - Meconium aspiration
  - Hypoglycemia
  - Metabolic abnormalities
  - Polycythemia

Long Term Sequelae

- Low et al
  - 218 “high risk neonates” followed up age 11
  - 77 (35%) learning difficulties
  - IUGR independent risk factor (30/77)
- Blair et al
  - Strong association of CP and IUGR among neonates >33 weeks

Barker Hypothesis

- Barker et al found an increased risk of cardiovascular disease and low birthweight in UK
- Insulin resistance, obesity
- Others have reported association with bone density, schizophrenia, breast cancer and asthma


Screening for IUGR

- All pregnant patients should be screened for risk factors
- Fundal heights after 24 weeks
  - Sensitivity 27-86% specificity 80-90%
  - Limitations with obesity, multiple gestation, fibroid
- Consider USS if risk factors present

ACOG Technical Bulletin No. 134 May 2013

Etiology

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POP Study

- Prospective cohort study
- 4512 nulliparous women with singleton pregnancy enrolled
- They all get research ultrasounds at 28 and 36 weeks. Results were not disclosed
- Women will get USS in 3rd trimester if clinically indicated.

Bricker et al Cochrane Database Syst Review 2008

### Result

<table>
<thead>
<tr>
<th>SGA</th>
<th>Severe SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective</td>
<td>Universal</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>20%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98%</td>
</tr>
<tr>
<td>False positive</td>
<td>2%</td>
</tr>
</tbody>
</table>

Adapted from Savio et al. Lancet vol 386 2015

### Other Screening Strategies

- **Serum analytes**
  - Low PAPP-A (under 5th percentile)
  - Birth weight under 10th percentile OR 2.8
  - Positive predictive value of 16%

- **Doppler of uterine artery**
  - High impedance in flow is associated with adverse obstetric outcomes
  - Pooled likelihood ratio 3.7 / 0.8 if normal result

- **Not recommended**

### Uterine artery Doppler ultrasound scan showing normal waveform.

### Confirm EDC

<table>
<thead>
<tr>
<th>GA</th>
<th>Method</th>
<th>Discrepancy to support re-dating</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 8 6/7</td>
<td>CRL</td>
<td>&gt;5d</td>
</tr>
<tr>
<td>9 0/7 to 13 6/7</td>
<td>CRL</td>
<td>&gt;7d</td>
</tr>
<tr>
<td>14 0/7 to 15 6/7</td>
<td>BPD, HC, AC, FL</td>
<td>&gt;7d</td>
</tr>
<tr>
<td>16 0/7 to 21 6/7</td>
<td>BPD, HC, AC, FL</td>
<td>&gt;10d</td>
</tr>
<tr>
<td>22 0/7 to 27 6/7</td>
<td>BPD, HC, AC, FL</td>
<td>&gt;14d</td>
</tr>
<tr>
<td>28 0/7 +</td>
<td>BPD, HC, AC, FL</td>
<td>&gt;21d</td>
</tr>
</tbody>
</table>

McLeod L CMAJ 2008;178:727-729

ACOG Committee Opinion 611
Growth Curve

Customized or not?

Customized Growth Curve

- Gardosi et al
  - proposed standards according to individual growth potential calculated for each pregnancy
  - Standard are adjusted according to maternal characteristics (ht, wt, parity, ethnic origin) are considered
  - Pathological process are excluded (eg DM, smoking and prematurity)

Customized Growth Curve

- Other studies do not find it beneficial
  - Hutcheon et al¹
    - Cohort of 783303 births
    - Use of customized curve showed no advantage
  - Grobman et al 2013²
    - Secondary analysis of the BEAM study
    - Individualized growth curve does not improve the association or prediction of CP or death by age 2
  - POP study 2015


Not All IUGR Are the Same

- Small for gestational age (SGA)
  - “constitutionally small”
- Pathologically small
  - Maternal illness present
  - Fetal pathology present
  - No obvious reason

Doppler

Umbilical Artery (UA)
Middle Cerebral Artery (MCA)
Ductus Venosus (DV)

\[ v = \frac{fd.c}{2ft \cos \theta} \]
Fetal Circulation

Doppler waveform represents downstream impedance to flow

Dopplers

Venous
Umbilical Vein
Ductus Venosus

Arterial
Umbilical Artery
MCA

placenta

Uterine artery

Umbilical Artery Doppler

Doppler Ultrasound
Doppler Waveform Analysis

- As placental insufficiency worsens, diastolic flow progressively decreases

**Umbilical Artery Doppler**

- Decreased
- Absent
- Reversed

**Abnormal Vasculature**

- 30% Decreased
- 70% Absent

Perinatal Outcomes

- Absent or reversed flow is associated with adverse perinatal outcome
- It may be present for weeks before additional sign of fetal compromise occurs

Doppler in High Risk Pregnancy

- 18 studies with 10,000 women included for review.
- Reduction in perinatal deaths (RR 0.71)
- Fewer inductions of labor (RR 0.89)
- Fewer cesarean delivery (RR 0.9)
- No difference in operative vaginal delivery
- No difference in APGAR of < 7 at 5 min

Cochrane Database Syst Rev. 2013

Routine Doppler in Low Risk Pregnancy

- Five trials were included which recruited more than 14,000 women
- No benefit in perinatal death and neonatal morbidity
- No difference for outcomes of cesarean
- NOT Recommended

Cochrane Database Syst Rev. 2015

MCA Doppler

Brain Sparing Effect
Cerebral Circulation
“Brain Sparing Effect”

Cerebral Blood Flow

- Hypoxemia
- Hypoxemia + Acidemia

Doppler Waveform Analysis

Classic Model for Progression of Doppler Changes

Physiological Changes
- Increased placental vascular resistance
- Shunting to vital organs “Brain-sparing”
- Impaired cardiac functions

Doppler Changes
- UA S/D increases
- MCA P/I decreases
- Abnormal venous flow
PORTO Study

- "Classic Model" exists but no more frequent than any other pattern
- With UA Doppler alone, it captures 86% of all adverse outcomes


Venous Dopplers

Reflects fetal cardiac function
Predictive of adverse perinatal outcome
Late sign

Ductus Venosus

- Waste from Fetus
- Placenta
- Oxygen-rich Blood
- Oxygen-poor Blood
- Mixed Blood
- Umbilical Vein
- Umbilical Cord
Qualitative Assessment

- Blood flow should always be antegrade
- Absent or reversed flow is **always** abnormal

Semi-quantitative Assessment

Venous Doppler abnormality is the strongest predictor

<table>
<thead>
<tr>
<th>Doppler Abnormality</th>
<th>Perinatal Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD elevated</td>
<td>5.6%</td>
</tr>
<tr>
<td>AEDF/REDF</td>
<td>11.5%</td>
</tr>
<tr>
<td>Venous</td>
<td>38.8%</td>
</tr>
</tbody>
</table>


Neonatal Mortality

![Graph showing percentage of neonatal mortality vs. gestational week for DV abnormal and DV normal cases.]

ACOG Opinion on Doppler Use in IUGR

- Recommend Umbilical artery Doppler
  - In conjunction with standard fetal surveillance (NST, BPP)
  - It provides insight into underlying etiology
  - May affect timing of delivery
- Role of assessments of MCA and DV remains uncertain

ACOG Technical Bulletin no 134 May 2013

Intact Survival

![Graph showing percentage of intact survival vs. gestational week for DV abnormal and DV normal cases.]

Other Interventions

- Bedrest¹
- Plasma volume expansion²
- Maternal nutrient supplementation³
- Low dose aspirin⁴
- Maternal oxygen⁵

1. Cochrane Review 2008
2. Cochrane Review 2008
3. Cochrane Review 2003
5. Cochrane Review 2003

¹ NOT RECOMMENDED
Timing of Delivery

Optimal Timing of Delivery

Despite over 10000 publications on the topic, confusion remains.
Timing of delivery for early IUGR is highly controversial.

3 randomized trials:
- GRIT - 2003
- DIGITAT - 2010
- TRUFFLE - 2015

Growth Restriction Intervention Trial
GRIT Study

- 548 preterm IUGR (24 – 36 wks)
- Uncertainty regarding delivery
- Randomized to delivery or observation until clinical course is clear
- No difference in mortality
- No difference in long term outcome
  - Age 6 to 9 years of age

DIGITAT Study

Disproportionate Intrauterine Growth Intervention Trial at Term

- Multicenter trial done in the Netherlands
- Women with singleton pregnancy beyond 36+ weeks with suspected IUGR
  - 321 randomised to induction
  - 329 randomised to expectant monitoring
- Primary outcome – composite measure of adverse neonatal outcome (not powered to detect difference in stillbirth)

Boers et al BMJ 2010;341:c7087
**DIGITAT**

- **Result**
  - No difference
  - C-section rate similar in both groups
    - 14.0% induction vs 13.7% expectant
- **Follow-up studies**
  - Neonatal morbidity\(^1\)
    - No difference
  - Neurodevelopment and behavior\(^2\)
    - No difference


**TRUFFLE**

- **Randomize 3 arms of trigger**
  1. CTG abnormality (STV < 3.5 to 4 ms)
  2. Early venous abnormality (DV PI >95th)
  3. Late venous changes (DV no A)
- **Primary outcome**
  - Survival without neurodevelopment age 2
- **511 patients entered randomization**
  - 2005 and 2010


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**Analysis of HYPITAT and DIGITAT trials**

1172 women with unripe cervix
- Bishop score 3 to 6
- 572 IOL and 600 expectant
- No difference in C/S (15.4% vs 16.5%)
- No difference of neonatal outcome
- Fewer cases of cord pH < 7.05 in the induction group (1.7% vs 4.8%)

Benardes et al et al. *BJOG* 2016; 123: 1501-1508
Results

• Mean gestational age of delivery 30.7 week
• Mean birth weight 1019g
• 98% liveborn
• 92% survive until discharge
• 69% survived without severe morbidity
• 60% HTN at enrolment – 72% at time of delivery

<table>
<thead>
<tr>
<th>CTG STV n=166</th>
<th>DV 95 n=167</th>
<th>DV no A n=170</th>
<th>Total n=503</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivor assessed for neurodevelopment</td>
<td>131 (86%)</td>
<td>131 (84%)</td>
<td>140 (92%)</td>
</tr>
<tr>
<td>Survivor without impairment</td>
<td>111</td>
<td>119</td>
<td>133</td>
</tr>
<tr>
<td>% of survivors</td>
<td>85%</td>
<td>91%</td>
<td>95%</td>
</tr>
<tr>
<td>% of all infants</td>
<td>77%</td>
<td>84%</td>
<td>85%</td>
</tr>
<tr>
<td>Perinatal or infant death Before 2 years</td>
<td>13 (8%)</td>
<td>11 (7%)</td>
<td>17 (10%)</td>
</tr>
<tr>
<td>Impairment at 2 years</td>
<td>20 (15%)</td>
<td>12 (9%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>5 (4%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Interpretation

• No difference in survival without neuroimpairment between groups
• Neuroimpairment at 2 years is less frequent among survivors in the late DV change group

What Does ACOG Recommend?

• Isolated IUGR
  – Deliver at 38 0/7 to 39 6/7 weeks
• IUGR with additional risk factors
  – eg oligohydramnios, abnormal Doppler, maternal risk factors or co-morbidities
  – Deliver between 34 0/7 – 37 6/7 weeks

Adapted from Table 4. Lees et al Truffle trial

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- If delivery for IUGR is anticipated before 34 weeks
  - NICU
  - MFM
  - Steroid
  - If under 32 weeks, magnesium for neuroprotection

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Intrapartum Management

- Uteroplacental insufficiency may be exacerbated by labor
- Fetus may not tolerate labor as well
- Close monitoring in labor is indicated
- Obtain cord gases

Recurrence

Netherlands 1999-2007¹
- 12943 women identified with IUGR in first pregnancy
- The risk of SGA in the second pregnancy (23% vs 3.4%; adjusted odds ratio, 8.1)
- Recurrence risk is related to severity of IUGR in first pregnancy²

Prevention

- Avoid modifiable risk factors (eg smoking, poor nutrition)
- Aspirin has not been shown to be effective by larger RCT¹
- Dietary changes, supplements, bedrest do not prevent IUGR

Thank You