Intrauterine Growth Restriction Update

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Disclosure

• No commercial interests related to topics presented

Pretest Question 1

36 year old G1P0 with history of chronic hypertension
BP well controlled with labetalol 100mg BID
Singleton pregnancy IUGR at 37 weeks
EFW at 9th percentile by Hadlock
Normal amniotic fluid. Normal NST. Normal Doppler of umbilical artery
Should delivery be offered?

1. Yes
2. No

Pretest Question 2

Patient diagnosed with IUGR (3rd percentile) at 28 weeks
Normal amniotic fluid. Normal NST. Normal Doppler of umbilical artery
Delivery should be offered

1. Yes
2. No
Pretest Question 3
G1P0 at 38 weeks
IUGR at 3\textsuperscript{rd} percentile
Induction of labor is associated with an increased risk of cesarean section compared with expectant management

1. True
2. False

Pretest Question 4
30 year old G2P1 healthy individual
Prior pregnancy was only complicated by IUGR near term
Induced labor at 39 weeks to deliver a low birth weight infant
Low dose aspirin will modify recurrence risk

1. True
2. False

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

In-utero Growth Restriction
- ACOG defined IUGR as EFW < 10\textsuperscript{th} percentile
- 4 million birth 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 (eg cHTN, DM, SLE, APLS)
  – Pregnancy related hypertension
  – Smoking and substance abuse (eg alcohol, cocaine)
  – Malnutrition
  – Teratogens (eg anticonvulsants)
• Fetal
  – Genetic disorder: chromosomal (eg T13, T18, T21), genetic syndromes
  – Structural (eg gastroschisis, CHD)
  – Infection: eg CMV, toxo, rubella (<5% of all IUGR)
  – Multiple (more common in mo/di than di/di)
• Placental
  – Chorangioma, Confined placental mosaicism
  – Abruption

Perinatal Mortality and Morbidity

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

Screening for IUGR

• Routine 3rd trimester USS
  – For low risk unselected populations does not confer benefit on mother or baby.
  – 8 trials recruiting 27024 women were included
  – Screened group has a higher C-section rate, but not statistically different
  – Not recommended

Bricker et al Cochrane Database Syst Review 2008

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)

Other studies do not find it beneficial

- Hutcheon et al
  - Cohort of 783303 births
  - Use of customized curve showed no advantage
- Grobman et al 2013
  - Secondary analysis of the BEAM study
  - Individualized growth curve does not improve the association or prediction of CP or death by age 2
Symmetric vs Asymmetric

- Symmetric
  - All parts have same degree of growth
- Asymmetric
  - Head sparing
- Doppler studies probably more helpful

Doppler

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

Fetal Circulation

Dopplers

Venous  
Umbilical Vein  
Ductus Venosus

Arterial  
Umbilical Artery  
MCA

placenta  
Uterine artery
Umbilical Artery Doppler

Doppler waveform represents downstream impedance to flow

Doppler Waveform Analysis


Umbilical Artery Doppler

- As placental insufficiency worsens, diastolic flow progressively decreases

<table>
<thead>
<tr>
<th>Decreased</th>
<th>Absent</th>
<th>Reversed</th>
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</thead>
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| Abnormal Vasculature | 30% | 70% |

Reversed End Diastolic Flow

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

- Eleven RCTs involving nearly 7000 women were included
- Reduction in perinatal deaths (OR 0.71)
- Fewer inductions of labor (OR 0.83)
- Fewer admissions to hospital
- No difference fetal distress in labor
- No difference caesarean delivery

Cochrane Database Syst Rev. 2000;(2):CD000073

Routine Doppler in Low Risk Pregnancy

- Not Recommended
  - Five trials were included which recruited 14,338 women
  - No benefit

Cochrane Database Syst Rev. 2008
**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

**MCA Doppler**

**Brain Sparing Effect**

**Cerebral Circulation**

“Brain Sparing Effect”

**Cerebral Blood Flow**
- Hypoxemia
- Hypoxemia + Acidemia

**MCA Doppler**

1. Fetus at rest
2. Circle of Willis
3. Zoom – MCA 50% of screen
4. Sample volume 1mm placed between origin of carotid and the middle of the artery
5. Angle between USS and blood flow = 0°
6. Consistent waveforms
7. Repeat 3 times
**Doppler Waveform Analysis**

![Doppler Waveform Analysis Diagram](image)

**Middle Cerebral Artery IUGR**

<table>
<thead>
<tr>
<th>MCA PI</th>
<th>PO$_2$</th>
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<tr>
<th>MCA PI</th>
<th>PO$_2$</th>
<th>2 – 4 SD</th>
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<tr>
<th>MCA PI</th>
<th>PO$_2$</th>
<th>&lt; 4 SD</th>
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**Venous Dopplers**

Reflects fetal cardiac function
Predictive of adverse perinatal outcome
Ductus Venosus

Qualitative Assessment

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

Semi-quantitative Assessment
Outcomes related to Doppler changes

<table>
<thead>
<tr>
<th>Doppler Abnormality</th>
<th>Perinatal Mortality</th>
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</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>
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</tbody>
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Venous Doppler abnormality is the strongest predictor

Survival Rate by GA

Neonatal Mortality
ACOG Opinion on Doppler Use in IUGR

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

Optimal Timing of Delivery

- Despite over 10000 publications on the topic, confusion remains
  - Definition
  - IUGR is not a homogenous group
  - Retrospective data with different threshold for delivery
- Timing of delivery for early IUGR is highly controversial

Timing of Delivery

- Limited options:
  1) Wait
  2) Deliver
- Gestational age remains a major factor for adverse perinatal outcome especially in very preterm infants

Intact Survival
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
      - No difference
    - Neurodevelopment and behavior
      - No difference


Trial of Umbilical and Fetal Flow in Europe (TRUFFLE)

- Trial performed between 2005-2010
- Participants
  - Singleton fetus 26-32 weeks
  - AC < 10th percentile with elevated UA PI
TRUFFLE

- Randomise to delivery by
  - CTG abnormality
  - Early venous abnormality
  - Late venous changes
- Primary outcome
  - Neurodevelopment age 2
- 511 patients entered randomization
  - 2005 and 2010
  - Information of intervention not disclosed yet

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

ACOG

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

Intrapartum Management

- Uteroplacental insufficiency may be exacerbated by labor
- Oligohydramnios
- Higher risk of cesarean section
- Close monitoring in labor is indicated
- Obtain cord gases
Recurrence

• Recurrence risk
  – Netherlands 1999-2007
  • 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 pregnancy


Prevention

• Avoid modifiable risk factors (e.g., smoking, poor nutrition)
• Aspirin has not been shown to be effective by larger RCT
• Dietary changes, supplements, bedrest do not prevent FGR


Thank You