Management of Fetal Growth Restriction: What Doppler Studies Should we be Doing and When

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Fetal Growth Restriction

Complex Problem:
• Various published definitions
• Poor detection rates
• Limited preventive or treatment options
• Multiple associated morbidities
• Increased likelihood of perinatal mortality

FGR

Treatment:
• Bed rest
• Aspirin
• Nutrient supplements with Calcium/Zinc
• Maternal oxygenation
• Heparin
• Plasma volume expansion
• Calcium channel blockers
• Hormonal therapy
• Smoking cessation

No Benefit

Fetal Growth Restriction

NICHD Fetal Imaging Forum 2
May 2015

• Multisociety representation

To develop a consensus on the diagnosis and optimal management of the singleton pregnancy with fetal growth restriction (FGR).

Definition

• Fetal Growth Restriction (FGR) is sonographically estimated fetal weight (SEFW) <10% for GA (PRENATAL STATUS)

• Small for gestational age (SGA) is actual birth weight (BW) < 10% for GA (POSTNATAL STATUS)

ACOG PB 2013; RCOG GG 2013; SOGC 2013; RCPI 2014

Definition

Other diagnostic criteria:
• SEFW < 5%
• SEFW < 3%
• AC < 10%
• AC < 5%
• Ac < 3%
### Risk Factors for FGR

<table>
<thead>
<tr>
<th>Material</th>
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<tbody>
<tr>
<td>Advanced maternal age</td>
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<tr>
<td>Chronic medical conditions</td>
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<tr>
<td>Chronic hypertension</td>
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<tr>
<td>Gestational hypertension</td>
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<tr>
<td>Pre-eclampsia and/or of advanced class</td>
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<tr>
<td>Renal disease</td>
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<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Hepatic disorders</td>
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<tr>
<td>Chondroma disease</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Current cardiac disease</td>
</tr>
<tr>
<td>Antibiotics and antibody screening</td>
</tr>
<tr>
<td>Infection markers, metabolites, and poor weight</td>
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<tr>
<td>Maternal exposed</td>
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<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Venereal</td>
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<tr>
<td>Rheumatology</td>
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<tr>
<td>Endocrinology</td>
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</tbody>
</table>

### Fetal

- Multiple gestation
- Hypothyroidism
- Lupus
- Toxemia
- Maternal
- Sepsis
- Chronic disease
- Chromosomal and genetic

### Placental

- Single umbilical artery
- Maternal and maternal
- Malignancies
- Retained or circumcised placenta
- Small placenta
- Combined placental measure

### Screening – ACOG Opinion

- All pregnant women should be screened for risk factors (medical and obstetric history)
- Fundal height measured at each visit > 24 weeks
  - If fundus cannot be palpated, e.g. obesity, multiple gestation, sonography is preferred
- Sonographic screening may be used in the presence of risk factors
- No evidence that routine sonography, serum analytes, or uterine artery Doppler improve outcomes

### How good are we in detecting FGR prenatally?

-Singleton births, all French maternity units in 2010, over 1 week period
- Routine US between 30 and 35 weeks
- 22% of SGA infants were suspected of FGR (but outcome was not better if FGR was suspected)
- 50% of infants suspected of FGR were not SGA (increased risk of provider-initiated early delivery in this group)

### Fetal Growth Restriction

**Prenatal detection:**

- Undetected in 30 - 50% of cases
- Incorrectly diagnosed in 50% of cases

### What is the optimal fetal surveillance in FGR?

ACOG IUGR bulletin 2000; Reaffirmed 2010


J Obstet Gynecol 1996;16:77
Fetal Assessment in FGR

Non-invasive tests:
- Fetal kick counts
- Non-stress test
- Biophysical profile
- Doppler assessment

Invasive tests:
- Amniocentesis
- Cordocentesis

No ideal test for all growth restricted fetuses.

Cardiovascular Adaptation of FGR

Early Changes / FGR

Arterial Redistribution

Brain Sparing Reflex

• ↑ impedance in UA (↑S/D)
• ↓ impedance in MCA (↓ PI)

Value of CPR

Fetal Hypoxemia

Blood Flow Redistribution

Brain Sparing Reflex

Increased
- Heart
- Brain
- Adrenal
- Spleen

Decreased
- Lungs
- GI
- Skeletal
- Other

Umbilical Arteries

Normal Waveform

Abnormal Waveform
**Umbilical Artery**

UA↑Impedance

- Obliteration of small muscular arteries in tertiary stem villi
- For A/REDF, need > 70% placental obliteration

Ultrasound Obstet Gynecol 1997;9:271
AJOG 1989;161:1055

**Fetal Hypoxemia / FGR**

UA↑Impedance

- Meta-analysis of 18 trials (> 10,000 women), concluded that use of UA Doppler in high-risk women reduced perinatal death & obstetric interventions

Syst Rev 2010;(1):CD007529

**Should Doppler be performed in low-risk women as a screening test?**

Meta-analysis of 4 trials found no difference in outcome

**Cerebral Vasculature**

**Middle Cerebral Artery**

- Most accessible cerebral vessel
- Carries 80% of cerebral flow
- Constant 3% - 7% of CO
- Excellent reproducibility

AJOG 1993;169:1393

**Circle of Willis**
Middle Cerebral Artery

Cerebral Placental Ratio (CPR)
- Ratio of MCA PI to UA PI
- Used to assess brain sparing
- Blood flow centralization present if CPR < 5% for GA or < 1.08 (similar accuracy) – associated with adverse perinatal outcome
- Can identify FGR fetuses at risk of cesarean sections for NRFHR

Bahado-Singh RO, AJOG, 1999
Cruz-Martinez R, Obstet Gynecol, 2011
Odibo A, JUM, 2005

The role of brain sparing in the prediction of adverse outcomes in intrauterine growth restriction: results of the multicenter PORTO Study

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Adverse perinatal outcome</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA (PI &gt; 90th centile)</td>
<td>85% (56/64)</td>
<td>54% (454/848)</td>
<td>6.0</td>
<td>2.9–16.5</td>
</tr>
<tr>
<td>UA (PI &gt; 90th centile, AEDF, REDF)</td>
<td>90% (37/41)</td>
<td>54% (452/831)</td>
<td>10.8</td>
<td>3.8–30.5</td>
</tr>
<tr>
<td>CPR (PI &lt; 1.0)</td>
<td>66% (27/41)</td>
<td>85% (72/84)</td>
<td>11.7</td>
<td>6.0–22.9</td>
</tr>
</tbody>
</table>

CPR = MCA PI / UA PI
Am J Obstet Gynecol 2014;211:288

Late Changes / FGR

Elevated Central Venous Pressure

Cardiac Decompensation
- ↑ EDP in RV (↑ afterload)
- ↑ Cardiac stiffness

Ultrasound Obstet Gynecol 1996;7:401
How Common is Progression of Doppler in FGR?

FGR

Early Changes
• Biometric changes
• Arterial Doppler

Late Changes
• Venous Doppler
• Heart rate tracing

Fetal Hypoxemia / FGR

Ultrasound Obstet Gynecol 2002;19:140

Research

Predictable progressive Doppler deterioration in IUGR: does it really exist?

• Multiple potential pathways of Doppler deterioration in IUGR
• UA → MCA → DV is no more common than other pathways
• Abnormal UA and MCA Doppler are strongest predictors of adverse perinatal outcome
• Only marginal added benefit to DV and cardiac indices

Importantly, the myocardial performance index is raised in small for gestational age fetuses before the arterial and venous Doppler abnormalities that characterize hypoxia are evident.

SGA: AC < 5th %
IUGR: AC < 5th % + Abnormal UA Doppler

European Journal of Obstet & Gynecol and Reproductive Biology 171 (2013) 262

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

1) CTG STV < 3.5 ms at < 29 weeks or STV < 4 ms at > 29 weeks
2) Early DV changes (PI > 95th %)
3) Late DV changes (Absent “a wave” or reverse flow)
No difference between groups for survival without neuroimpairment.

In high-risk pregnancies with suspected FGR UA Doppler assessment significantly decreases likelihood of IOL, cesarean delivery and perinatal death.

UA Doppler surveillance should be started when fetus is viable and FGR suspected.

DV, MCA and other vessels Dopplers have some prognostic value for FGR fetuses, but currently lack of RCT showing benefit and they should be reserved for research protocols.

- Low Apgar scores & cord pH < 7.0
- Increased NICU admissions & sepsis
- Increased stillbirth and neonatal mortality
- Increased learning disabilities
- Increased adult onset cardiovascular disease

ACOG IUGR bulletin 2000. Reaffirmed 2010

- Hypoglycemia
- Hyperbilirubinemia
- Hypothermia
- IVH
- NEC
- Seizures
- Sepsis
- RDS

- Cerebral Palsy
- Neonatal death
Medical Birth Registry in Norway
- Singletons, born 1996-2006
- 398 children with CP, 490,022 normally developed
- Low birth weight and HC correlates with increased risk of CP

Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE)

- Fetal outcome was better than expected
- Perinatal death was uncommon (8%)
- 70% survived without severe neonatal morbidity.

Poor Prognostic Factors:
- Presence and severity of maternal hypertensive conditions
- Gestational age at diagnosis
- Gestational age at delivery

PORTO vs. ULTRA TOT

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<thead>
<tr>
<th></th>
<th>PORTO</th>
<th>ULTRA TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive diseases/ preeclampsia</td>
<td>12% (134)</td>
<td>28% (232)</td>
</tr>
<tr>
<td>GA at enrollment</td>
<td>30.1±3.9</td>
<td>31.3±5.7</td>
</tr>
<tr>
<td>GA at delivery</td>
<td>37.8±2.0</td>
<td>35.7±3.6</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>2495±671</td>
<td>2039±675</td>
</tr>
<tr>
<td>NICU admission</td>
<td>28% (121)</td>
<td>24% (196)</td>
</tr>
<tr>
<td>Apgar&lt;7 at 5 min.</td>
<td>1% (13)</td>
<td>7.4% (62)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>4 (1:280)</td>
<td>N/A</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>4 (1:280)</td>
<td>19 (1:44)</td>
</tr>
</tbody>
</table>

When Should You Deliver Fetuses with FGR?

Timing of Delivery?
Cumulative risk of stillbirth increases for each week after 37 weeks.

The increased risk becomes significant at 39 weeks for FGR <10%.

FGR <5% there is a significant over 2-fold risk of stillbirth at 38 weeks compared to 37 weeks.

Delivery Timing with Abnormal Dopplers

Induction of Labor vs. Expectant Management in FGR?

- The Disproportionate Intrauterine Growth Intervention Trial at Term
  - Randomized trial (650 women randomized to IOL or expectant management)
  - 36+0 weeks to 41+0 weeks
    - Singleton, cephalic, suspected IUGR
    - Included normal and abnormal Dopplers

DIGITAT Trial

- No significant differences
  - Primary composite adverse neonatal outcome
  - Rate of operative delivery or cesarean
  - MAIN scores
- No fetal or neonatal deaths in either group
- No difference in developmental or behavioral outcomes at 2-year follow up
- IOL before 38 weeks associated with > NICU admit
- Either strategy acceptable

Boers KE, AIOG, 2012
Van Wyk L, AIOG, 2012
### Summary: Delivery Timing

**Uncomplicated FGR (nl UA Dopplers)**
1. EFW 5 -10% - delivery at 39 weeks
2. EFW < 5% - delivery at 37 weeks

**Complicated FGR (abnormal UA Dopplers)**
1. Elevated UA Dopplers (DEDF) - 37 weeks
2. AEDF: corticosteroids → delivery if ≥ 34 weeks
3. REDF: corticosteroids → delivery if ≥ 32 weeks

### FGR – Mode of Delivery

- **No RCTs for MOD for FGR**
- **Several small observational studies**
  - Demonstrate that FGR is a risk factor for cesarean
- **No evidence to suggest VD (or IOL) is contraindicated for FGR**
- **Even with abnormal UA Dopplers, a reasonable chance for VD**

References:
- Horowitz, KM et al. /MFNM 2014
- Chaukura, PH et al. Int J Gynecol Obstet 2005
- Maslovitz, S et al. Arch Gyn Obstet 2009

### Conclusion

- FGR is poorly detected & Incorrectly diagnosed
- FGR is associated with increased neonatal morbidity & mortality
- IOL or spontaneous labor acceptable
- Delivery at or before 37 weeks with abnormal UA Doppler
- Presence of hypertensive conditions increases adverse outcomes in FGR

### Conclusion

- Incorporating UA Doppler in clinical management is recommended
- Abnormal cardiac function is seen before conventional Doppler abnormalities in FGR
- CPR identifies fetuses at higher risk for complications but unclear how this impacts clinical management
- Currently no strong evidence supports the use of venous Doppler in clinical management

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