Fetal Growth Restriction: diagnosis, use of dopplers and management

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Diagnosis

- EFW < 10th percentile
  - Ensure accurate dating
  - 1st trimester CRL best method of dating
  - Can’t account for fetus who is not small but isn’t achieving growth potential
- AC < 5th percentile

Constitutionally small fetus vs pathologic growth restriction?

- Constitutionally small:
  - Modest smallness (EFW 5th – 10th %ile)
  - Normal growth velocity
  - Normal dopplers and AVF
  - AC above lowest decile
  - Appropriate size in terms of maternal characteristics (ht/wt/ethnicity)

Use lower threshold?

- PORTO: 1100 pregnancies < 10th %ile
  - 2% of fetuses at 3rd – 10th %ile had adverse perinatal outcome
  - 6.2% of fetuses < 3rd %ile had adverse outcomes
  - All mortalities in this group
  - Combination of EFW < 3rd percentile + abnormal umbilical artery dopplers (PI > 95th % and AEDV/REDV) strong predictor of adverse outcome
  - 17% had IVH, PVL, HIE, NEC, BPD, sepsis or death

Etiology

<table>
<thead>
<tr>
<th>Etiology</th>
<th>5-20%: esp symmetric FGR &lt; 20 weeks, esp Trisomy 13 and 18</th>
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</thead>
<tbody>
<tr>
<td>Fetal genetic abn</td>
<td>Especially CHD, spina bifida</td>
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<td>Fetal infection</td>
<td>1-10%. CMV and toxemia most common in developed countries,</td>
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<td>Others: rhabdomyosarcoma, diabetes, etiology, HIV</td>
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<tr>
<td>Fetal structural anomaly</td>
<td>Especially CHD, spina bifida</td>
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<td>Multiple gestation</td>
<td>Proportioned to % fetuses, type of placememt, increased in</td>
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<tr>
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<td>pre eclampsia, maternal condition</td>
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<tr>
<td>Placental</td>
<td>SGA, IUGR, abnormally shaped placenta, confined placental</td>
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<tr>
<td></td>
<td>insertion</td>
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<tr>
<td>Cross cord/placental abn</td>
<td>Single umbilical artery, umbilical cord insertion, marginal</td>
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<tr>
<td></td>
<td>cord insertion, bilateral circumscription placentas, placental</td>
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<tr>
<td></td>
<td>hemangioma</td>
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<td>Maternal genetic factors</td>
<td>Women who themselves had IUGR or had FGR fetus</td>
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<tr>
<td>Maternal medical/ob conditions</td>
<td>ECL, abruption, Chl, HTN, renal disease, DM, SLE, ANA,</td>
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<tr>
<td></td>
<td>cystic fibrosis, diabetes, chronic disease, scarring,</td>
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<td></td>
<td>cyanotic heart disease, pulmonary disease, chronic</td>
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<td></td>
<td>disease, vitamin, Omega-3 fatty acids, PAPP-A, HLA</td>
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<td>Teratogens/environmental agents</td>
<td>Vitamins, valproic acid, folate acid antagonists, cigarettes,</td>
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<td></td>
<td>alcohol</td>
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<td>Assisted reproductive technology</td>
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<tr>
<td>Live pre-preg weight, poor nutrition</td>
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<td>High altitude</td>
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<td>Extreme of age</td>
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Work-up: anatomic survey

- 10% FGR have congenital anomalies
- 20–60% fetuses with anomalies will have FGR
  - Especially: omphalocele, CDH, skeletal dysplasias, CHD
Work up: Fetal genetic testing

- Early FGR, < 5th percentile, symmetrical
- Fetal structural anomalies
- Multiple soft markers
  - Increased nuchal fold, short femurs, echogenic bowel

Work up: Infectious causes

- Maternal history
- Fetal ultrasound findings
  - Echogenic bowel
  - Calcifications in brain, liver
  - Hydrops
- Maternal blood: CMV, toxo, rubella, varicella, malaria (in endemic areas/travel)
- Amniotic fluid for PCR

Work up: Thrombophilies

- Weak association for inherited thrombophilias
  - FVL, PGM, MTHFR C677T, Protein S deficiency?
- Consider w/u for acquired thrombophilia
  - Anticardiolipin antibodies, anti-beta2-glycoprotein, Lupus anticoagulant

FGR and uteroplacental insufficiency

- No structural defects
- Chromosomally normal
- Cornerstone of management
  - Serial US for growth
  - BPP
  - Impedance to blood flow in fetal arterial/venous vessels (Doppler velocimetry)

Sequence of fetal response to stress may vary by cause/progression

- Primary adaptive response
  - Decreased fetal growth rate
  - Circulatory redistribution
  - Fetal energy conservation
  - Decreased fetal movement
  - Decreased FHR variability
  - Falling cerebral flow impedance
  - Risking umbilical and aortic impedance
  - Increased efficiency placental exchange
  - Polycythemia – greater O2 carrying capacity

- Secondary adaptive response
  - Hypoxia > respiratory acidosis > metabolic acidosis
  - High impedance – AEDV in umbilical arteries
  - Decreasing AFV
  - Loss of fetal movement
  - Loss of FHR variability
  - Persistent late decelerations > agonal decelerations
  - Fetal death
Monitoring

- Serial US for growth every 2–4 weeks, depending on severity FGR and dopplers
- BPPs at least weekly depending on severity, Dopplers, afv, maternal status
- Dopplers

Few words about dopplers

- Reflect blood velocity
  - Presence and direction of flow
  - Volume of flow
  - Impedance to flow
- Doppler waveform analysis

Uterine Artery
Spiral Artery Remodeling

Summary: Uterine artery dopplers

- Abnormal 1st and 2nd trimester ut A dopplers: increased adverse outcomes (preeclampsia, FGR, perinatal mortality)
- Low risk women:
  - low predictive value
  - No available interventions
  - Routine screening not recommended
- High risk women: (h/o chronic HTN or preeclampsia, prior FGR or stillbirth) with singleton:
  - Abnormal testing – increased surveillance
  - Normal testing – less surveillance

UMBILICAL ARTERY
Factors affecting waveform

- Gestational age: EDV increases with advancing GA
- Fetal heart range: no affect at normal FHR
- Fetal breathing: causes dynamic variability: only measure during fetal apnea
- Cord sampling:
  - Indices higher at placental end
  - Use loop or fetal end of cord
  - Keep angle of insonation close to 0

Umbilical Artery

- Assesses resistance to blood perfusion of the fetoplacental unit
- Maternal/placental conditions that obliterate the small muscular arteries in the placental stem villi result in progressive decrease in end-diastolic flow
  - 30% are obliterated when Dopplers elevated
  - 70% are obliterated when reversed

UAD: How to perform

- Waveforms obtained near placental end reflect downstream resistance and show higher end-diastolic flow
  - Use free loop or at abdominal cord insertion
- Obtain measurement in the absence of breathing

AEDV and REDV

- Increase in perinatal mortality (17–28%)
- Increase NICU, IVH, prematurity
- REDV, GA, and BW independently associated with neurodevelopmental delay
- Clinical effectiveness
  - Cochrane review 18 trials, 10,225 women
  - 29% decline in perinatal mortality (RR 0.77, 95% CI 0.52–0.98) – NNT 203 high risk pregnancies to reduce 1 perinatal death
  - Low risk women – no benefit routine UA dopplers between 28–34 weeks

** Bricker et al 2000 *BJOG 1997**
Normally continuous forward flow throughout cardiac cycle

- Decreased, absent, or reversed flow in the a wave represents increased ventricular end-diastolic pressure from increase in RV afterload

**DV: how to perform**
- Identify the DV as it branches from the umbilical vein in transverse or sagittal section
- Waveform is biphasic with first peak ventricular systole, second peak during passive filling in ventricular diastole, followed by a nadir in late diastole (atrial contraction)

- Scan in the upper abdomen in a mid-sagittal longitudinal plane
- Scan to the left first, identifying the fetal stomach bubble
- In the same plane, activate color Doppler over the fetal liver
- Identify the umbilical vein and the ductus venosus
- Velocities in the DV may be higher than the umbilical vein, and gain may need to be adjusted
- Aliasing is a cue that the DV is being imaged.
- Sample volume size may be in the 2 mm range

**Pathologic changes in venous flow in fetal growth restriction**
- Increased umbilical artery resistance
- Impaired cardiac performance
- Right ventricle decompensation, TR
- Increase central venous pressure
- Reduced diastolic flow in DV and other large veins
- Vasodilation of DV decreases O2 to heart
- Increases retrograde transmission of atrial pressure
- DV resistance increases
- Loss/reversal a wave
- Impending acidemia/death

**Middle Cerebral Artery**
In the presence of fetal hypoxemia, central redistribution of blood flow causes increased blood flow to brain, heart and adrenals:
- “brain-sparing reflex”
- See increased end-diastolic velocity in MCA

MCA Doppler

MCA Doppler: normal waveform
Elevated End-diastolic flow

Cerebroplacental ratio (CPR):
- MCA pulsatility (or resistance) index / umbilical artery pulsatility (or resistance) index
- Low CPR – brain sparing, predicts adverse outcome
  - CPR < 1: serious adverse outcome 18% vs 2% if higher*
  - Most useful if umbilical artery PI > 95th %ile
  - Unclear what threshold to use

Which Dopplers should be done when IUGR suspected?
- Umbilical artery
  - Significantly reduces IOL, c-section and perinatal death without increasing the rate of unnecessary interventions
  - DV
  - Identifies fetuses at advanced stage of compromise
  - TRUFFLE trial: no immediate neonatal benefit from delaying delivery until DV showed absent or reversed flow but a possible small benefit in neurodevelopment outcomes at 2 years of age

Use in IUGR, continued
- MCA
  - Has been shown to identify a subset of IUGR fetuses at risk for c-section due to abnormal fetal FHR patterns and for neonatal acidosis.
  - No RCT
  - No specific interventions have been shown to improve outcomes based on abnormal findings

*Umbilical artery is the preferred vessel to interrogate by Doppler to guide management in pregnancies complicated by suspected IUGR*

Neonatal Mortality Rates
- Elevated UAD = 5.6%
- Absent or Reversed = 11.5%
- Venous abnormality = 38.8%

- DV
  - Identifies fetuses at advanced stage of compromise
  - TRUFFLE trial: no immediate neonatal benefit from delaying delivery until DV showed absent or reversed flow but a possible small benefit in neurodevelopment outcomes at 2 years of age


*Umbilical artery significantly reduces IOL, c-section and perinatal death without increasing the rate of unnecessary interventions

*TRUFFLE trial: no immediate neonatal benefit from delaying delivery until DV showed absent or reversed flow but a possible small benefit in neurodevelopment outcomes at 2 years of age

*Umbilical artery is the preferred vessel to interrogate by Doppler to guide management in pregnancies complicated by suspected IUGR*


Singletons with IUGR 36–41 weeks
- Randomized to IOL vs. expectant management
- N=650
- Primary outcome: composite adverse event
  - Death before discharge, 5min Apgar <7, pH<7.05, NICU admission
  - No difference between the groups
  - Similar adverse outcomes, C/D rates
  - More hyperbilirubinemia in IOL group
  - Similar outcomes at 2 years of age

Women with IUGR 24–36wks and clinical uncertainty regarding delivery
- N=1095
- Groups: immediate delivery or deferred delivery until was no longer unclear (ie testing worsened)
- Immediate group: Fewer stillbirths but more neonatal and infant deaths
- F/u at 13 years: no differences in cognition, language, motor or parent-assessed behavior scores
- Conclusion: similar deaths (whether stillbirth or neonatal/infant death) and similar long term outcomes

Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial
- Trend toward increased neurologic morbidity with immediate delivery
  - Most of the difference was in babies born <30wks
- Concluded doctors should be discouraged to deliver until cannot delay any longer
  - Especially <30 weeks

General management of FGR
- Determine if constitutionally small
  - Maternal history
- Aneuploidy screening/invasive testing
- US to look for signs of infection
  - If suspect: maternal serum ab titer or amnio for PCR
- Fetal growth US
- Dopplers as indicated
- Twice-weekly NSTs with AFV assessment OR once-weekly BPPs and umbilical artery dopplers
  - MCA and DV if AEDF/REDF
- Consider admission if AEDF/REDF and steroids

Management: algorithm for use of Doppler US in suspected FGR

Conel et al Obstet and Gynecol May 2014
Delivery

- Preterm
  - Abnormal antenatal surveillance
  - No growth over 2 weeks
  - If < 32 weeks consider Magnesium for neuroprotection
- Deliver at 37 weeks or more
  - EFW < 5th percentile
  - EFW < 10th percentile with oligo or worsening antenatal testing
- Elective at 39 weeks with no other findings
  - c/s for obstetric indications

Gestational age key factor

- > 28 weeks
  - abnormal umbilical artery dopplers not associated with lower developmental scores at 3 and 6 years of age*
- < 29 weeks
  - AEDF/REDF had increased risk of cognitive impairment at age 5–8 (restricted to males)**

Postnatal outcomes

- Gestational age key factor
  - > 28 weeks
    - abnormal umbilical artery dopplers not associated with lower developmental scores at 3 and 6 years of age*
  - < 29 weeks
    - AEDF/REDF had increased risk of cognitive impairment at age 5–8 (restricted to males)**

THANK YOU!