At the end of this presentation, participants will be able:

• To classify IUGR fetus
• To understand the cardiovascular changes that occur in IUGR fetuses
• To understand management issues of IUGR fetuses
PUBMED: FGR...IUGR

18, 920 papers
Growth Restriction Defined

- WHO classification
  - 1969: newborn less than 2500 gm (low-birth weight)

- Classification of low-birth weight
  - Preterm neonate/AGA
  - Preterm neonate/SGA
  - Term neonate/SGA
Fetal Growth Restriction

- Definitions:
  - EFW < 10th percentile\(^1\)
  - EFW < 5th percentile\(^2\)
  - EFW < 3rd percentile
  - EFW > 2 SD below mean for gestational age
  - AC <10th percentile or more than 2 week lag

The definition remains controversial because it does not make distinction among fetuses who are constitutionally small, growth restricted and small, and growth restricted but not small

\(^1\)Battaglia et al J Pediat, 1967; \(^2\)Zhang et al, Am J Epidemiol 2011
Standard for Fetal Growth

• Between 10\textsuperscript{th} – 90\textsuperscript{th} percentiles for fixed gestational age (2.5\textsuperscript{th} – 97.5\textsuperscript{th} percentile)

• Denver standards (1960-1970s)

• Regardless, the goal of prenatal detection of small fetus is to REDUCE morbidity and mortality by employing some intervention.
Rate of Normal Fetal Growth

- **First phase**
  - <16 weeks gestation
  - “Cellular hyperplasia”

- **Second phase**
  - 16-32 weeks
  - Simultaneous hyperplasia and hypertrophy

- **Third phase**
  - >32 weeks
  - “Cellular hypertrophy” (rapid increase)
Normal Fetal Growth

- 14-15 weeks gestation
  - 5 gm/day
- 20 weeks
  - 10 gm/day
- 32-34 weeks
  - 30-35 gm/day

Mean peaks 230-285 gm/week (32-34 wk)
Decreases at 41-42 weeks
Slightly less growth per week for multiples
Types of IUGR

- Asymmetrical (70-80%)
  - Normal length; weight/ abdomen is below normal

- Symmetrical (20-30%)
  - Length and weight are below normal
  - Global impairment of early fetal cellular hyperplasia

- Ponderal index
  - Birth weight (gm)/crown-heel length (cm)3 x100
  - Potential error with the length
Epidemiology

- Incidence 10% (any population)
- Developed countries: 4-8%
- Developing countries: 6-30%
Risk Factors

- Maternal medical conditions
- Smoking/substance abuse
- Severe malnutrition
- Placental disease
- Multiples
- Genetic disorders
- Exposure to teratogens
Perinatal mortality/morbidity

Fetal growth is important because →

Inverse relationship between fetal/neonatal weight percentile and adverse perinatal outcome

Modified from Manning F. Fetal Medicine 1995
Perinatal mortality/morbidity

- Early studies (1980s)
  - Infant 1500-2500 gm near term (5-30X mortality rate)
  - Infant less than 1500gm near term (50-100X)

- Overall mortality rate
  - Generally 50% higher
  - Increases with weight below 6th percentile
  - 2 times mortality at 10-15th percentile
  - Higher for preterm infants
EFW < 10\textsuperscript{th} percentile

**Normal**
- 70% ??
  - Female sex
  - Maternal ethnicity
  - Parity
  - Maternal BMI

**Pathologic**
- 30%

Manning FA, Fetal Medicine, 1995
Etiologies

- Genetic
- Congenital anomalies
- Infection
- Multiple gestation
- Placenta
- Maternal nutrition/environmental
- Maternal vascular disease
Genetic / Congenital Anomalies

• Among malformed fetus → FGR frequency = 20-60%¹
• Conversely, among FGR → Anomaly frequency = 10%²
• Aneuploidy
  • Trisomy 13, 18, 21
  • Abnormalities X/Y
• Congenital anomalies
  • Any anomaly; 22% IUGR
  • Single umbilical artery

Infection

- **Rubella**
  - Due to capillary endothelial damage during organogenesis

- **Cytomegalovirus**
  - Cytolysis and localized necrosis leading to decreased cell size

- **Protozoan infections**
  - **Toxoplasmosis**
  - Plasmodium (malaria)
Multiple Gestation

• Fetal growth rate
  • ↑ Weight LINEAR < 34-38 wk
  • Decline occurs when fetal mass near 3000-3500 gm
  • Peak weekly weight gain = 28-32 wk (160-170 gm/wk)

• IUGR, mild
  • Decreased cell size
  • Vascular anastomoses (mono/di)
Etiologies

- Genetic
- Congenital anomalies
- Infection
- Multiple gestation
  - Placenta
  - Maternal nutrition/environmental
  - Maternal vascular disease
Placental Factors

“Umbrella that covers our ignorance in terms of etiology and pathogenesis of the utero-placental chronic dysfunction”

Assali, Eur J Obstet Gynecol 1975
Placental Insufficiency

It is not the cause of IUGR but is rather the consequence of a disease process that often we do not understand.
Placental Factors

- Placenta increase in size throughout gestation

- IUGR, placental growth plateaus at 36 weeks

- Abnormalities: cord, placenta hemangiomas
Maternal Nutrition/Environmental

- Decreased protein or caloric intake
- Demonstrated in studies from WW II
  - Prolong poor nutrition lead to reduced birth weight by 400-600 gm
  - Decline in placental weight by 15%
- Oxygen
- Smoking
Maternal Disease

• Accounts for 25-30% of IUGR infants

• Hypertensive disease

• Obstructive arterionecrosis (preeclampsia)

• Thrombophilia

• Uterine anomalies
Evaluation

- History and Physical
  - Fundal height (sensitivity ranges 13-86%)
  - Abdominal palpation (sensitivity 30-50%)

- Ultrasound
  - Importance of dates
    - Abdominal circumference (sensitivity 60%)
    - Composite EFW (sensitivity 90%)
    - Umbilical artery Doppler
Management

The optimal approach to monitoring the fetus with suspected growth restriction has not been established; there is essentially no evidence from randomized trials

Grivell RM et al, Cochrane Database Syst Rev 2012
Cornerstone of Management

Serial Evaluation of:
- Growth
- Fetal behavior (BPP)
- Impedance to blood flow in fetal arterial and venous vessels

With Purpose of:
- Identify fetus at risk for intratrophic demise & neonatal morbidity
- May benefit from preterm delivery

Grivell RM et al, Cochrane Database Syst Rev 2012
Fetal Growth

- Follow estimated weight percentiles
- Follow growth velocity
- Serial sonograms q 2-4 week intervals
- Persistent growth deficiency strengthens likelihood
Umbilical Artery Doppler

Fitzgerald was the first to obtain Doppler signal in pregnancy in 1977.
Doppler in AGA and IUGR Fetuses

\[
\text{PI} = \frac{S - D}{M} \\
\text{RI} = \frac{S - D}{S} \\
\text{S/D} = \frac{S}{D}
\]
Umbilical Artery: High Placental Vascular Resistance
Umbilical Artery Doppler and Placental Vascular Histology

Giles WB et al, BJOG 1985
Umbilical Artery Doppler and Outcome

- Reduce perinatal death and unnecessary induction of labor in the preterm growth restricted fetus

- Meta-analysis use of Doppler ultrasonography reduced the odds of perinatal death by 38% (95% CI 15-55)

Doppler vs. No Doppler, Outcome = Any perinatal death (after randomization)

| Review: Fetal and umbilical Doppler ultrasound in high-risk pregnancies |
| Comparison: 1 Doppler ultrasound versus no Doppler ultrasound |
| Outcome: 1 Any perinatal death after randomisation |

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Doppler US n/N</th>
<th>No Doppler US n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
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</thead>
<tbody>
<tr>
<td>1 Singleton pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almstrom 1992</td>
<td>0/214</td>
<td>3/212</td>
<td></td>
<td>3.9 %</td>
<td>0.14 [0.01, 2.72]</td>
</tr>
<tr>
<td>Biljan 1992</td>
<td>1/338</td>
<td>4/336</td>
<td></td>
<td>4.5 %</td>
<td>0.25 [0.03, 2.21]</td>
</tr>
<tr>
<td>Haley 1997</td>
<td>1/73</td>
<td>1/77</td>
<td></td>
<td>1.1 %</td>
<td>1.05 [0.07, 16.55]</td>
</tr>
<tr>
<td>Neales 1994</td>
<td>11/236</td>
<td>14/231</td>
<td></td>
<td>15.7 %</td>
<td>0.77 [0.36, 1.66]</td>
</tr>
<tr>
<td>Nienhuis 1997</td>
<td>2/74</td>
<td>3/76</td>
<td></td>
<td>3.3 %</td>
<td>0.68 [0.12, 3.98]</td>
</tr>
<tr>
<td>Ott 1998</td>
<td>1/348</td>
<td>1/317</td>
<td></td>
<td>1.2 %</td>
<td>0.91 [0.06, 14.50]</td>
</tr>
<tr>
<td>Trudinger 1987</td>
<td>1/127</td>
<td>5/162</td>
<td></td>
<td>4.9 %</td>
<td>0.26 [0.03, 2.16]</td>
</tr>
<tr>
<td>Tyrrell 1990</td>
<td>3/250</td>
<td>3/250</td>
<td></td>
<td>3.3 %</td>
<td>1.00 [0.20, 4.91]</td>
</tr>
<tr>
<td>Williams 2003</td>
<td>0/649</td>
<td>1/691</td>
<td></td>
<td>1.6 %</td>
<td>0.35 [0.01, 8.70]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>39.4 %</td>
<td>0.59 [0.35, 1.01]</td>
</tr>
</tbody>
</table>

Total events: 20 (Doppler US), 35 (No Doppler US)  
Heterogeneity: Chi² = 3.35, df = 8 (P = 0.91); I² = 0.0%  
Test for overall effect: Z = 1.93 (P = 0.054)
Doppler vs. No Doppler, Outcome = Stillbirth

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<th>No Doppler US n/N</th>
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<td></td>
<td>4.5%</td>
<td>0.50 [0.05, 5.46]</td>
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<tr>
<td>Neales 1994</td>
<td>6/236</td>
<td>9/231</td>
<td></td>
<td>20.4%</td>
<td>0.65 [0.24, 1.80]</td>
</tr>
<tr>
<td>Nienhuis 1997</td>
<td>1/74</td>
<td>3/76</td>
<td></td>
<td>6.6%</td>
<td>0.34 [0.04, 3.22]</td>
</tr>
<tr>
<td>Trudinger 1987</td>
<td>1/127</td>
<td>2/162</td>
<td></td>
<td>3.9%</td>
<td>0.64 [0.06, 6.95]</td>
</tr>
<tr>
<td>Tyrrell 1990</td>
<td>3/250</td>
<td>1/250</td>
<td></td>
<td>2.2%</td>
<td>3.00 [0.31, 28.65]</td>
</tr>
<tr>
<td>Williams 2003</td>
<td>0/649</td>
<td>1/691</td>
<td></td>
<td>3.3%</td>
<td>0.35 [0.01, 8.70]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1961</strong></td>
<td><strong>2035</strong></td>
<td></td>
<td><strong>49.8%</strong></td>
<td><strong>0.61 [0.31, 1.19]</strong></td>
</tr>
</tbody>
</table>

Total events: 12 (Doppler US), 21 (No Doppler US)
Heterogeneity: Chi² = 2.97, df = 7 (P = 0.89); I² = 0.0%
Test for overall effect: Z = 1.44 (P = 0.15)

Zarko A et al, Cochrane Database of Systematic Reviews 2013
Brain Circulation

MCA Waveforms at 24 weeks
A = Normal

B = "Brain sparing effect"
Fetal middle cerebral artery velocimetry

MIDDLE CEREBRAL ARTERY
Cross-Sectional Study
Ductus Venosus
Is Ductus Venosus reversed flow an Indication for Delivery?
Temporal Sequence of Fetal Deterioration

- DECREASED Umbilical Venous volume
- Redistribution of fetal blood flow
- INCREASED Umbilical Artery Doppler
- DECREASED MCA Doppler

Godfrey et al. PLOS one, 2012
Biophysical Profile

- Evaluation of multiple acute and chronic fetal physiologic parameters
- Easy to perform
- Reliable test of fetal well-being

\[
\begin{align*}
\leq 5\text{cm} & \quad \text{Both FGR and Oligo = INCREASED risk of perinatal mortality} \\
> 5\text{cm} & \quad \text{NOT highly associated with either FGR or fetal demise}
\end{align*}
\]

Dayal AK et al, Am J Obstet Gynecol, 1999
FGR Delivery?

- **GRIT**\(^1\) → 24-36 wks
  - Delaying delivery of very preterm FGR fetus results in ↑ stillbirths, but immediate delivery = almost equal number of neonatal deaths; Neither approach results in better long-term neurodevelopmental outcome

- **DIGITAT**\(^2,3\) → 36 wks (IOL vs. Expectant)
  - No difference in morbidity score; development @ 2yrs same

- **TRUFFLE**\(^4\) → 26-32 wks (cohort)
  - Fetal outcome better. Death and severe morbidity significantly related to EGA (@study entry & @ delivery) and with presence of maternal hypertensive morbidity

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### Timing of Intervention

<table>
<thead>
<tr>
<th>Immediate Delivery</th>
<th>Inpatient / Betamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal Ductus Venosus</td>
<td>Women needing daily maternal or fetal assessment</td>
</tr>
<tr>
<td>≥ 32 wks with Reversed EDF</td>
<td>&lt;32 wks with Reversed EDF</td>
</tr>
<tr>
<td>≥ 34 wks with AEDF</td>
<td></td>
</tr>
<tr>
<td>≥ 37 wks with Abnormal S/D, poor interval growth, ...</td>
<td></td>
</tr>
<tr>
<td>≥ 38-39 wks with FGR, normal Doppler studies</td>
<td></td>
</tr>
</tbody>
</table>
Long-term Sequelae

- Potential intrapartum complications
  - Neonatal asphyxia
  - Meconium
- Adult disease
  - IQ / Neurodevelopment
  - Obstructive lung disease
  - Barker Hypothesis (Hypertension, Diabetes)
THANK YOU!

• Enjoy the rest of your day...

• Questions?