Intrauterine Growth Restriction – From the OB Perspective

Kathryn E. Patrick, M.D.
Maternal Fetal Medicine Fellow, PGY5
Department of Obstetrics and Gynecology
University of Florida College of Medicine
DISCLAIMER:
I AM NOT A PEDIATRICIAN OR A NEONATOLOGIST!
I AM:
A PERINATOLOGIST in training
Terminology/Definition
Standards of Fetal Weight – It’s Complicated

• Accepted standards of normal weight for GA
  • Within 2 SD of the mean weight (2.5% – 97.5%) – Europe
  • Between 10-90% of weights – US

• Pitfalls of using 10th percentile as cutoff for lower limit of normal weight
  • Different values for the 10th percentile weight cutoff across literature – many studies do no control for fetal sex or maternal demographics)
  • Arbitrary cutoff- < 10th percentile include a large number of small fetuses that have achieved growth potential

• Many fetal growth curves published over the years
  • Beware: Biometric parameters used to calculate EFW may not be the same as growth curve EFW plotted on!

Goldenberg et al. AJOG. 1989;161:271-277
Small for Gestational Age (SGA)

Intrauterine Growth Restriction (IUGR)

- <10% of fetal weight for gestational age
- Terms used interchangeably in literature, complicating collection and interpretation of data
- Does not address
  - Constitutionally small fetus (pathologic vs nonpathologic)
  - Normally grown fetus that is not achieving growth potential
- Do not use the term “Fetal Growth Retardation”

We will be using IUGR

- <10% of fetal weight for GA
- Implying pathologic process
IUGR – Symmetric vs Asymmetric

Symmetric
- All biometric parameters are below expected values
- 20-30% of IUGR
- Traditionally represents intrinsic or early fetal insult (i.e. aneuploidy, infection)

Asymmetric
- Greater decrease in abdominal size (head sparing)
- 70-80% of IUGR
- Traditionally represents extrinsic or later fetal insult (i.e. UPI)

Timing of insult may be more important than actual pathological cause
# Normal Fetal Growth

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplasia</td>
<td>Hyperplasia/hypertrophy</td>
<td>Hypertrophy</td>
</tr>
<tr>
<td>4-20 weeks</td>
<td>20-28 weeks</td>
<td>28-40 weeks</td>
</tr>
<tr>
<td>Rapid proliferation</td>
<td>Decline in mitosis</td>
<td>Rapid hypertrophy</td>
</tr>
<tr>
<td>Increasing DNA content</td>
<td>Increasing cell size</td>
<td>Rapid increase in size</td>
</tr>
<tr>
<td>Symmetric</td>
<td>Mixed-asymmetric</td>
<td>Asymmetric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rapid accumulation of fat, muscle, and tissue</td>
</tr>
</tbody>
</table>
damns given

length of lecture
Background
Intrauterine Growth Restriction

• Incidence
  • 4-7% in developed countries
  • 6-30% in developing countries
ETIOLOGY
Differential Diagnosis & Etiology
Differential Diagnosis

- Intrauterine growth restriction
- Incorrect pregnancy dating
- Imprecise ultrasound measurements
  - Check biometric parameters and growth chart – ideally the same
- Constitutional smallness
Etiology of IUGR

Maternal

Fetal

Placenta & Cord
### Maternal

<table>
<thead>
<tr>
<th>Constitutional</th>
<th>Nutritional</th>
<th>Hypoxic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>Poor weight gain</td>
<td>Severe lung disease</td>
</tr>
<tr>
<td>Height/weight</td>
<td>Low prepregnancy weight</td>
<td>Cyanotic heart disease</td>
</tr>
<tr>
<td></td>
<td>GI – IBD, chronic pancreatitis, GI surgery</td>
<td>SCD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular</th>
<th>Renal Disease</th>
<th>Environmental</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHTN, PreE</td>
<td>Glomerulonephritis</td>
<td>High altitude</td>
</tr>
<tr>
<td>Collagen vascular dx</td>
<td>CKD</td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>IDDM</td>
<td>Renal transplant</td>
<td>Medications</td>
</tr>
<tr>
<td>APLS</td>
<td></td>
<td>Substance abuse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Past OB History</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous stillbirth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous IUGR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous PTB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fetal

Chromosome Abnormalities
- Trisomies (13, 18, 21)
- XO
- Deletions/duplications
- Uniparental disomy

Structural Malformations
- Anencephaly
- AWD
- Renal agenesis/dysplasia
- Cardiac malformations
- Multiple malformations

Multiples
- Monochorionic
- Single anomalous fetus
- Isolated IUGR
- TTTS

Infections
- Rubella
- CMV
- Varicella
- Syphilis
# Placenta and Cord

<table>
<thead>
<tr>
<th>Placental Structural Abnormalities</th>
<th>Cord Structural Abnormalities</th>
<th>Ischemic Placental Disease</th>
<th>Placental Mosaicism/Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Placenta previa</td>
<td>• SUA</td>
<td>• PreEclampsia/CHTN</td>
<td>• Confined placental mosaicism</td>
</tr>
<tr>
<td>• Circumvellate placenta</td>
<td>• Velamentous cord insertion</td>
<td>• Abruption</td>
<td>• Placental mesenchymal dysplasia</td>
</tr>
<tr>
<td>• Placental hemangioma/</td>
<td>• Marginal cord insertion</td>
<td>• Placental infarction</td>
<td>• Abnormal trophoblast invasion</td>
</tr>
<tr>
<td>• chorioangioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Placental vascular malformations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Screening & Diagnosis
Screening

- History
- Physical Exam (FH)

Ultrasound (serial)
**Diagnosing Etiology**

- **Ultrasound (serial)**
  - Growth, AFI
  - Anatomic survey
  - Dopplers (UA, MCA, ductus venosus)

- **Genetics**
  - Early, severe, symmetric
  - Ultrasound markers of aneuploidy
  - Major structural abnormalities

- **Infectious workup**
  - Maternal history/PE
  - Ultrasound markers of fetal/placental infection
  - Serologies (serum/amnio)

- **Placental pathology**
  - No antenatal diagnosis
  - Confirmation of diagnosis
Management
This is where it gets a little hairy...
Management

• Referral to a maternal-fetal-medicine physician
• Fetal surveillance and timing of delivery is *individualized* and dependent on
  • Etiology
  • GA
  • Fetal testing
    • Dopplers
    • Fluid assessment
    • NST/BPP
• Mode of delivery should be based on obstetric indications alone
  • IUGR is not an indication for cesarean delivery
  • However, IUGR fetusus have increased risk of FHT abnormalities necessitating cesarean delivery
• Placental resistance increases \( \Rightarrow \) umbilical arterial flow toward the placenta during diastole will decrease \( \Rightarrow \) increase in S/D ratio
• S/D ratio norms are dependent on gestational age \( \Rightarrow \) decrease as pregnancy increases
Venous/MCA Doppler Velocimetry

- Can be considered if there is absent or reverse end diastolic flow in the umbilical artery
- Questionable if these assessments improve neonatal outcomes in fetuses with IUGR
Timing of Delivery
**Growth Restriction Intervention Trial (GRIT)**

- RCT looking at timing of delivery of IUGR in the early preterm fetus (24-34 weeks)

- Compared neonatal outcomes between 2 groups
  - Early group: delivery within 48 hours of IUGR diagnosis (MTD: 0.4d)
  - Expectant management group: antenatal surveillance until delay in delivery was no longer deemed safe (MTD: 4.9d)

- Rates of BMS administration were the same

- Conclusions:
  - Perinatal survival was similar
  - Followup at 6–12-years showed no differences in cognitive, language, behavior, or motor abilities between the two groups

GRIT Study Group. BJOG. 2003;110:27-32
Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT)

• RCT looking at timing of delivery of IUGR in term fetus (36-41 weeks)
• Compared neonatal outcomes between 2 groups
  • Immediate delivery group
  • Expectant management group: delivery only for other indications
• There were no differences in composite neonatal outcomes between the two groups, although the study cohort was not large enough to determine differences in individual outcomes (i.e. perinatal death, maternal morbidity)

Timing of Delivery - Summary

• Plan should be individualized
• The following is recommended by the NICHD, SMFM, and ACOG
  • Isolated IUGR $\rightarrow$ 38w0d – 39w6d
  • IUGR with additional risk factors $\rightarrow$ 34w0d – 37w6d
• If delivery could occur prior to 37 weeks, administer BMS
• If delivery prior to 32 weeks, administer BMS and magnesium sulfate
Algorithm—Management of Fetal Growth Restriction

Clinical suspicion/risk factors

Sonographic assessment of fetal weight (EFW Hadlock-4)

- EFW > 10th centile
  - Routine care, consider follow-up scan in 4 wk
- EFW < 10th centile

Ensure accurate dating
Consider deriving a customised centile
Assess anatomy/placenta/amniotic fluid volume
Perform UA Doppler

Normal UA
- Repeat sonogram in 2-weekly intervals
- Assess biometry, UA and AFI
- Consider delivery at 37 wk and no later than 40 wk if good interval growth

UA Doppler (PI > 95th, + EDF)
- Repeat sonogram in weekly intervals or more frequently as necessary
- Assess UA, AFI (MCA optional)
- 2-weekly biometry assessment
- Timed corticosteroids
- Consider delivery at 37 wk or earlier if poor interval growth

UA AEDF*
- Admit, repeat sonogram in twice weekly intervals or more frequently as necessary
- Assess UA, AFI (MCA optional)
- Timed corticosteroids
- Deliver no later than 34 wk
- MgSO₄ < 32 wk

UA REDF*
- Admit, repeat sonogram in thrice weekly intervals or more frequently as necessary
- Assess UA, AFI (MCA optional)
- Timed corticosteroids
- Deliver no later than 30 wk
- MgSO₄ < 32 wk

In all the cases, delivery is also indicated by abnormal CTG, ideally based on short-term variation CTG if fetus deemed viable (i.e., GA > 24 wk and EFW > 500 g).

*In cases of AREDF, consider the opinion of a fetal medicine specialist regarding timing of delivery.

Send placenta for histopathology
Obtain arterial and venous cord pH

Offer follow-up appointment to women with IUUGR < 3rd centile and delivery < 34 wk

Review of placental histology
Consider thrombophilia screening
Modification of risk factors
Prevention with aspirin/LMWH

Complications/ Outcomes
Mortality rate 5-20x higher than AGA infants

- Asphyxia
- Meconium aspiration
- Hyperbilirubinemia
- Hypoglycemia
- Thrombocytopenia
- IVH
- Abnormal temperature regulation
- Meconium aspiration
- Altered immunity
Long-term Outcomes

• Depends on etiology and the presence of additional adverse risk factors

• Association between growth restriction/SGA and poor cognitive function and adverse neurological outcome in later childhood (no causal relationship has been established).

• In a systematic review, after stratifying for prematurity, most adverse neurological outcomes could be attributed to socioenvironmental conditions.
Prevention
Prevention

• 20% recurrence risk of IUGR
• Identify and alter modifiable risk factors (i.e. smoking cessation, limit infection/teratogen exposure)
• Optimize treatment of maternal medical conditions (i.e. HTN, APLS, DM)
  • Insufficient data to show that treatment of APLS with anticoagulation/antiplatelet therapy improves neonatal outcomes in a subsequent pregnancy
• Nutritional and dietary supplemental strategies are ineffective
• Bedrest does not decrease incidence of IUGR
• Insufficient data to support the use of aspirin to prevent IUGR
• Consider screening growth ultrasound at 32-34 weeks

There is Little We Can Do!
THE END
References


Immediate Delivery Group

- Median time to delivery = 0.9d
- Perinatal death rate = 10%
- Increase in neonatal deaths
- Increased trend toward DD at 2 years

Delayed Delivery Group

- Median time to delivery = 4.9d
- Perinatal death rate = 9%
- Increase in stillbirths

**Conclusions:**

- There is little evidence for choosing immediate delivery over delayed delivery
- We are delivering these babies at the right time based on best judgement
- GA at time of delivery is likely the most important contributor of determining neonatal and long term outcomes