Learning Objectives

After completing this presentation, the participant should be able to:

1. Describe the use and potential limitations of population-based weight reference ranges/standards for fetal size assessment
2. Discuss other approaches for fetal size assessment including customized growth curves and individualized growth assessment
3. List indications for maternal and fetal Doppler ultrasound in detecting and monitoring fetuses with growth abnormalities
4. Explain how fetal soft tissue assessment can improve the precision of fetal weight estimation

Outline

1. Fetal Growth Overview
2. Sonographic Criteria for Dating Pregnancies
3. Fetal Macrosomia
4. Fetal Growth Restriction
5. Doppler Ultrasonography for Fetal Growth
6. Fetal Soft Tissue Evaluation
7. Conclusions

I. Fetal Growth
   General Overview

“Fetal growth is a function of both seed and soil. It is dependent upon the growth potential of the fetus and the availability of intrauterine nutrition, in its broadest sense, to fulfill this potential. The result of these two factors is a wide distribution of birth size at any one gestational age, and a wide variation in the state of nutrition at birth.”

Am J Obstet Gynecol 1966;94:951-963
Growth Abnormalities

Depends on how pathological growth processes are defined

Fetal Size Assessment  Neonatal Growth Outcome

A standard of fetal growth for the United States of America

WILLIAM E. BRENNER, M.D.
DAVID A. EDELMAN, Ph.D.
CHARLES J. HENDRICKS, M.D.
Chapel Hill and Research Triangle Park, North Carolina

The appropriate interpretation of monitored fetal growth throughout pregnancy in individual patients and populations is dependent upon the availability of adequate standards. There is no adequate standard of fetal weight throughout pregnancy that is suitable for patients in the U.S.A. To determine such a standard for infants delivered at about sea level the 10th, 25th, 50th, 75th, and 90th percentiles of fetal weight for each menstrual week of gestation were calculated from 430 fetuses at 8 to 20 menstrual weeks' gestation aborted with pentaganésectomy and from 30,772 liveborn infants delivered of patients at 21 to 44 menstrual weeks' gestation. Median fetal crown-heel lengths and crown-rump lengths were derived from measurements of 696 aborted fetuses of 8 to 21 weeks' gestation. Fetal weight correlation factors for parity, race (socioeconomic status), and fetal sex were calculated. The derived fetal growth norms are useful for clinical, public health, and investigational purposes. (Am. J. Obstet. Gynecol. 126: 555, 1976.)

Birth Weight vs EFW

Birth weight (BW) is directly measured as an indicator of neonatal growth outcome.

Estimated fetal weight (EFW) is calculated to indirectly evaluate fetal nutritional status

Sonographic Fetal Weight Estimation

Which Model Should Be Used?

26 different birth weight prediction models

3,705 sonographic EFW < 3 days delivery

For most models, estimates were within 15% of actual BW in more than 80% of cases.
Considerable variation among different models, although most showed good overall accuracy.

Models with 3-4 fetal biometric indices were better than models with only 1 or 2 indices (BW range 1000 - 4500 g)

Accuracy decreased at BW extremes, with overestimation in low-BW categories vs underestimation for BW > 4000 g

Model precision was lowest in the low-BW groups.

Once EFW is calculated, this result is compared to a population-based standard

Radiology 1991;181:129-133

Weight for gestational age percentiles are individualized for maternal influences on fetal growth

Stepwise Multiple Regression

- maternal height
- pre-pregnancy BMI
- ethnicity
- parity
- fetal gender

optimal 280 day BW predicted for each infant


Since not all babies are born at 280 days, the target BW is extrapolated to the exact GA at birth using a Hadlock proportionality formula (1991)

Infant’s BW is compared to target BW

Any newborn with actual BW < 10th pct of assumed distribution around target weight is considered SGA

“Customised birthweight standards are widely recognised to improve the prediction of adverse perinatal outcomes compared with conventional birthweight-for-gestational-age charts.”

“However, their apparent benefits are more likely to have been derived from their incorporation of intrauterine-based (EFW) reference values at preterm ages than their adjustment for maternal characteristics.”

“Although maternal characteristics are able to explain population-level differences in birthweight, they are not strong enough predictors for individual-level prediction of birthweight.”

“With maternal characteristics accounting for only a small percent of total factors influencing BW, the best estimate of an infant’s BW remains close to the population average, explaining the ineffectiveness of adjusting for maternal characteristics.”

**International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project**

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aris T. Papaioannou</td>
<td>University of Athens</td>
<td>Principal investigator, INTERGROWTH-21st Project.</td>
</tr>
<tr>
<td>Evi D. Oikonomou</td>
<td>University of Athens</td>
<td>Investigator.</td>
</tr>
<tr>
<td>Douglas A. Colvin</td>
<td>University of Auckland</td>
<td>Investigator.</td>
</tr>
<tr>
<td>Thanos T. Karavelas</td>
<td>University of Athens</td>
<td>Investigator.</td>
</tr>
<tr>
<td>Anna Zampeli</td>
<td>University of Athens</td>
<td>Investigator.</td>
</tr>
<tr>
<td>Vasilis A. Matsas</td>
<td>University of Athens</td>
<td>Investigator.</td>
</tr>
<tr>
<td>Stephen W. Harrow</td>
<td>University of Toronto</td>
<td>Investigator.</td>
</tr>
</tbody>
</table>

Summary

Background In 2006, W01D produced international growth standards for infants and children up to age 5 years on the basis of recommendations from a W01D expert committee. Using the same methods and conceptual approach, the Fetal Growth Longitudinal Study (FGLS), part of the INTERGROWTH-21st Project, aimed to develop international growth and size standards for fetuses.

4,321 women - prospective longitudinal study
8 countries
Fetal biometry obtained q 5 weeks (14-42 weeks)

1,387 women - prospective longitudinal US study (7 scans)
Low risk singleton pregnancies
Fetal growth variation observed among 10 countries


Individualized Growth Assessment

2nd TM growth velocities provide estimates of growth potential and predict 3rd TM size trajectories/birth characteristics

• Each fetus serves as it's own control
• Biological variability is substantially reduced
• Fetal growth characterized by individual/composite anatomical parameters


2. Sonographic Criteria for Dating Pregnancies

ACOG/SFM/AIUM
Guidelines for Dating Based on Ultrasonography

Accurate Dating is Crucial for Fetal Growth Assessment

• US measurement of embryo or fetus ≤ 13 6/7 weeks most accurate way to establish or confirm age
• Prioritize use of assisted reproductive technology (ART), if available, based on age of embryo and date of transfer
As soon as data from the last menstrual period (LMP), the first accurate ultrasound examination, or both are obtained, the gestational age and the EDD should be determined, discussed with the patient, and documented clearly in the medical record.

Subsequent changes to the EDD should be reserved for rare circumstances, discussed with the patient, and documented clearly in the medical record.

3. Fetal Macrosomia

Fetal Macrosomia - Increased Risks

- cesarean delivery
- shoulder dystocia
- clavicular fracture
- brachial plexus injury

Fetal Macrosomia Incidence

<table>
<thead>
<tr>
<th>Menstrual Age</th>
<th>50th Percentile</th>
<th>90th Percentile</th>
<th>95th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 weeks</td>
<td>3,117</td>
<td>3,755</td>
<td>3,956</td>
</tr>
<tr>
<td>38 weeks</td>
<td>3,263</td>
<td>3,867</td>
<td>4,027</td>
</tr>
<tr>
<td>39 weeks</td>
<td>3,400</td>
<td>3,980</td>
<td>4,107</td>
</tr>
<tr>
<td>40 weeks</td>
<td>3,495</td>
<td>4,060</td>
<td>4,185</td>
</tr>
<tr>
<td>41 weeks</td>
<td>3,527</td>
<td>4,094</td>
<td>4,217</td>
</tr>
<tr>
<td>42 weeks</td>
<td>3,522</td>
<td>4,098</td>
<td>4,213</td>
</tr>
</tbody>
</table>


Fetal Macrosomia Prediction

- 1717 women with singleton pregnancies
- EFW performed during preceding week
- clinical EFW before ruptured membranes

<table>
<thead>
<tr>
<th>EFW (grams)</th>
<th>Clinical EFW</th>
<th>US EFW</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infants</td>
<td>-0.01 ± 10.4%</td>
<td>-1.4 ± 10.7%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>&lt; 2500</td>
<td>10.0 ± 15.4%</td>
<td>6.8 ± 12.6%</td>
<td>&lt; 0.015</td>
</tr>
<tr>
<td>2500 - 4000</td>
<td>0.2 ± 9.2%</td>
<td>-1.2 ± 10.3%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 4000</td>
<td>-8.2 ± 6.9%</td>
<td>-8.3 ± 7.9%</td>
<td>NS</td>
</tr>
</tbody>
</table>

• Reviewed 63 accuracy studies (51 EFW, 12 AC)
• ROC curves for predicting EFW > 4,000 grams
• No differences between EFW or AC > 36 cm seen

“No difference in accuracy between ultrasonographically EFW and AC in the prediction of a macrosomic baby at birth. A positive test result is more accurate for ruling in macrosomia than a negative test result for ruling it out.”


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suspected fetal macrosomia is not an indication for labor induction because induction does not improve maternal - fetal outcomes. (Level B)

• labor and vaginal delivery are not contraindicated for women with EFW up to 5,000 g in the absence of maternal diabetes (Level B)

• with EFW > 4,500 grams, a prolonged 2nd stage of labor or arrest of descent in the second stage is an indication for delivery (Level B)

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• consider cesarean delivery for suspected fetal macrosomia with EFW > 5,000 g in women without diabetes and > 4,500 g in women with diabetes

• suspected fetal macrosomia is not a contraindication to attempted vaginal birth after a previous cesarean delivery

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4. Fetal Growth Restriction

1 in every 12 newborns in the United States are delivered with low birth weight (< 2,500 grams)

• perinatal death
• developmental delay
• learning disabilities
• cerebral palsy
• hearing loss

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Fetal Growth Restriction

Fetal growth restriction, also known as intrauterine growth restriction, is a common complication of pregnancy that has been associated with a variety of adverse perinatal outcomes. There is a lack of consensus regarding terminology, diagnostic criteria for fetal growth restriction, with uncertainties surrounding the optimal management and timing of delivery for the growth-restricted fetus. An additional challenge is the difficulty in differentiating between the fetus that is constitutionally small and fulfilling its growth potential and the small fetus that is not fulfilling its growth potential because of an underlying pathologic condition. The purpose of this discussion is to review the topic of fetal growth restriction with a focus on terminology, etiology, diagnosis, and surveillance tools, and guidance for management and timing of delivery.

Lee

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Birth Weight (g) for Gestational Age

Adapted from Alexander GR, et al. Obstet Gynecol 1996;87:163-8

Birth Weight (g) for Gestational Age

Which Population Cut-Off is Used?

Fetal Growth Restriction - Dx
Requires Accurate Gestational Dating Criteria
- certain LMP with regular menstrual cycles
- early pregnancy scan (e.g. 1st trimester)

Suspect FGR in the presence of US findings
- EFW < 10th percentile
- decreased amniotic fluid volume
- abnormal fetal Doppler study (UA, MCA, CPR)

Early Fetal Growth Restriction < 32 weeks
Findings:
Maternal-fetal placental vascular abnormality
High-resistance uterine artery flow velocity
40-70% risk of associated pre-eclampsia
Elevated fetal UA pulsatility index common

Management:
Revolves around prematurity and hypertensive disease

Late Fetal Growth Restriction > 31-34 weeks
Findings:
Placental villous diffusion and perfusion defects
Variable cerebral or UA Doppler abnormalities

Management:
Emphasizes timing of diagnosis and stillbirth prevention

Fetal Growth Restriction - Dx
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Management:
Emphasizes timing of diagnosis and stillbirth prevention

12,317 singleton infants (1988-1996) ≥ 37 weeks gestation

<table>
<thead>
<tr>
<th>Birth Weight %</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th-5th</th>
<th>6th-10th</th>
<th>11-15th</th>
<th>16-25th</th>
<th>26th-75th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Infants</td>
<td>3184</td>
<td>2085</td>
<td>5264</td>
<td>5400</td>
<td>10,867</td>
<td>55,601</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apgar ≤ 3, 5 min</td>
<td>7 (0.3)*</td>
<td>1 (&lt;0.1)</td>
<td>6 (0.1)</td>
<td>5 (0.1)</td>
<td>9 (0.1)</td>
<td>36 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA Cord pH ≤ 7.0</td>
<td>26 (0.9)*</td>
<td>12 (0.6)</td>
<td>28 (0.5)</td>
<td>27 (0.5)</td>
<td>37 (0.3)</td>
<td>212 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intubation Del Rm</td>
<td>70 (2.2)*</td>
<td>11 (0.5)</td>
<td>39 (0.7)</td>
<td>39 (0.7)</td>
<td>70 (0.6)</td>
<td>317 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures (1st 24 hrs)</td>
<td>14 (0.4)*</td>
<td>4 (0.2)</td>
<td>14 (0.3)*</td>
<td>9 (0.2)</td>
<td>16 (0.1)</td>
<td>68 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis (+ blood cult)</td>
<td>16 (0.5)*</td>
<td>6 (0.3)</td>
<td>12 (0.2)</td>
<td>15 (0.3)</td>
<td>28 (0.3)</td>
<td>125 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (1st 28 days)</td>
<td>9 (0.3)*</td>
<td>2 (0.1)</td>
<td>2 (&lt;0.1)</td>
<td>3 (0.1)</td>
<td>3 (&lt;0.1)</td>
<td>18 (&lt;0.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05 refers to data compared to 26th-75th percentile

Adapted from Engl J Med 1999;340:1234-8

Fetal Growth Restriction - Dx
Requires Accurate Gestational Dating Criteria
- certain LMP with regular menstrual cycles
- early pregnancy scan (e.g. 1st trimester)

Suspect FGR in the presence of US findings
- EFW < 10th percentile
- decreased amniotic fluid volume
- abnormal fetal Doppler study (UA, MCA, CPR)
**SGA Infant - Risk Factors**

**Maternal Risk Factors**
- short maternal stature
- low maternal weight
- Indian or Asian ethnicity
- nulliparity
- mother was SGA
- cigarette smoking
- cocaine use

**Maternal Disease**
- chronic hypertension
- renal disease
- anti-phospholipid syndrome
- malaria

**SGA Infant - Postnatal Sequelae**

- intraterine demise
- neonatal morbidity
  - hypoglycemia
  - hyperbilirubinemia
  - hypothermia
  - intraventricular hemorrhage
  - necrotizing enterocolitis
  - seizures
  - sepsis
  - respiratory distress syndrome
- neonatal death
- cognitive delays in childhood
- adult diseases

**Long Term Outcomes - SGA Children at Age 10**

- More Learning Problems
- Smaller Head Circumference
- More Inattentive
- Less Educated Parents
- More Deficiencies in Neurological Performance
- Lower Socioeconomic Status
- More Timid
- Poorer Perceptual Organization Ability
- More Restless
- Lower IQ Scores

**Fetal Origins of Adult Disease - Barker Hypothesis**

- Abnormal growth of various organs from fetal undernutrition
- Reduced birth size
- Risk factors for vascular disease
- Type 2 diabetes

Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study

Lee, Go, Lee 4th MBBS, Allan O'Shea, Dorothy Reaney, Gordon C S Smith

Prospective Cohort Study (2008-2012)
- 4,512 nulliparous Women
- fetal biometry at 20, 28, 36 weeks gestation

Universal 3rd trimester fetal biometry roughly tripled detection of SGA infants


5. Doppler Ultrasonography for Fetal Growth

Doppler Equation

\[ \text{blood velocity} = \frac{(\text{frequency shift}) \cdot \text{sound velocity}}{2 \cdot (\text{transducer frequency}) \cdot \cos \theta} \]

Fetal Cardiovascular and Behavioral Variables With Decline in Metabolic Status in Fetal Growth Restriction


“Don’t screen for intrauterine growth restriction with Doppler flow studies”

The Society for Maternal-Fetal Medicine


**Umbilical Artery Doppler Flow - Normal**

<table>
<thead>
<tr>
<th>Doppler Parameters</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD Ratio (Stuart, 1980)</td>
<td>s/d</td>
</tr>
<tr>
<td>Resistive Index (Pourcelot, 1974)</td>
<td>(s-d)/s</td>
</tr>
<tr>
<td>Pulsatility Index (Gosling, 1976)</td>
<td>(s-d)/mean</td>
</tr>
</tbody>
</table>

**Umbilical Artery - Absent End Diastolic Flow (AEDF)**

**Normal Ductus Venosus Doppler**

**Normal Umbilical Venous Doppler**

**Doppler US Findings with Poor Perinatal Outcomes**

**Normal Middle Cerebral Artery Doppler**
Cerebroplacental Ratio (CPR)
Predictor of Adverse Outcome

MCA PI
UA PI

Moore KL. The Developing Human. 1988

Cerebroplacental Ratio (CPR)
Evaluation of Well-Being in SGA and AGA Fetuses

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study type</th>
<th>Doppler indices</th>
<th>Computation of ratio</th>
<th>Abnormal criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abellé et al.</td>
<td>1989</td>
<td>Cross-sectional</td>
<td>S-DOS, MCA</td>
<td>MCA</td>
<td>Ratio &lt; 1</td>
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<tr>
<td>Abellé et al.</td>
<td>1994</td>
<td>Cross-sectional</td>
<td>PI</td>
<td>MCA</td>
<td>Ratio &lt; 2</td>
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<tr>
<td>Comeau et al.</td>
<td>1992</td>
<td>Cross-sectional</td>
<td>PI</td>
<td>MCA</td>
<td>Ratio &lt; 1.00</td>
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<tr>
<td>Banaste-Grigni et al.</td>
<td>1999</td>
<td>Cross-sectional</td>
<td>PI</td>
<td>MCA, MHI</td>
<td>Ratio &lt; 0.60 MHI</td>
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<tr>
<td>Ranchat and Grieder</td>
<td>2003</td>
<td>Cross-sectional</td>
<td>PI</td>
<td>MCA</td>
<td>Ratio &gt; 5th percentile</td>
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<tr>
<td>Delisle et al.</td>
<td>2005</td>
<td>Cross-sectional</td>
<td>PI</td>
<td>MCA</td>
<td>Ratio &lt; 1.00</td>
</tr>
<tr>
<td>Ettinger et al.</td>
<td>2007</td>
<td>Longitudinal</td>
<td>PI</td>
<td>MCA</td>
<td>&lt; 2.00 centiles</td>
</tr>
<tr>
<td>Mari et al.</td>
<td>2014</td>
<td>Cross-sectional</td>
<td>PI</td>
<td>MCA</td>
<td>Ratio &gt; 5th percentile or MHI &lt; 0.5766</td>
</tr>
</tbody>
</table>

SGA, small for gestational age; MCA, middle cerebral artery; MHI, middle cerebral artery index; PI, pulsatility index; S-DOS, spectral Doppler analysis; SGA, small for gestational age; AGA, appropriate for gestational age.

DeVore GR. Am J Obstet Gynecol 2015;213:5-15

DeVore GR. Am J Obstet Gynecol 2015;213:5-15

“Low CPR in AGA fetuses is an equally important marker of low neonatal pH secondary to placental underperfusion as is being SGA”

Cruz-Martinez et al. Obstet Gynecol 2011;117:618-26

retrospective study of 2927 term fetuses

6. Fetal Soft Tissue Assessment

Lee

Obstetrics

Is fetal cerebroplacental ratio an independent predictor of intrapartum fetal compromise and neonatal unit admission?

Ahsan A. Khali, MD, MRCOG; Jose Morales-Rosello, MD; Madalena Morlando, MD; Hasna Hameed, MD; Hadi Bhude, MD, MRCOG; Atef Papageorgiou, MD, MRCOG; Radu Thilaganathan, FDS, MRCOG

retrospective cohort study - 9772 singleton pregnancies

“Third-trimester CPR is an independent predictor of stillbirth and perinatal mortality”

Am J Obstet Gynecol 2015;213:54.e1-10

Lee

Lee

Lee

Lee
Why is Fetal Soft Tissue Important?

- Fetal growth is a complex process and should be characterized using a combination of skeletal and soft tissue parameters.
- Soft tissue assessment improves precision of EFW and now adds another key nutritional component to the weight estimation process.

Neonatal Thighs

- Growth Restriction - 2845 grams, 39.7 weeks, menstrual age
- Macrosomia - 4368 grams, 38.4 weeks, menstrual age

Fractional Limb Volume

Limb Sub-Volume Based on 50% of Long Bone Diaphysis Length


Fractional Thigh Volume - 20 weeks


Fractional limb volume – a soft tissue parameter of fetal body composition: validation, technical considerations and normal ranges during pregnancy

Conclusions

Fetal growth assessment requires accurate gestational dating criteria
- sure LMP with regular menstrual cycles
- early pregnancy scan (e.g. 1st trimester)

Suspect fetal macrosomia if EFW > 4,000 grams or > 90th percentile for gestational age

Key References


DeVore GR. The importance of the cerebroplacental ratio in the evaluation of fetal well being and SGA and AGA fetuses. Am J Obstet Gynecol 2016;213: 5-15


Conclusions

Suspect fetal growth restriction for US findings
- EFW < 10th percentile
- decreased amniotic fluid volume
- abnormal fetal Doppler study (UA, MCA, CPR)

Fractional limb volume can be used to assess fetal soft tissue development - this 3D parameter adds a nutritional component to the weight estimation process and improves the precision of EFW