Standards on Fetal Growth

What’s with all these new Fetal Growth Charts

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Standards are needed for growth monitoring
INTERGROWTH-21ST Systematic Reviews

- Crown-rump length / gestational age estimate (Napolitano et al 2014, BJOG)
  - 29 published charts
  - Only 4 charts satisfied minimum quality criteria

- Fetal growth monitoring by ultrasound (Ioannou et al 2012, BJOG)
  - 83 published charts
  - Only 12 charts used reliable dating method

- Birth weight charts (Giuliani et al 2015, Acta Paediatrica)
  - 102 published charts
  - Only 8 charts satisfied minimum quality criteria

- Preterm postnatal growth charts (Giuliani et al 2016 AJCN)
  - 61 published longitudinal charts
  - Limitations in GA estimation, anthropometric measures, feeding
Human growth worldwide should be evaluated using international standards describing how individuals should grow.
References vs. Standards

- **References** describe how fetuses, newborns and infants *have* grown at a particular time and/or place.
- **Standards** describe how fetuses, newborns and infants *should* grown when nutritional, environmental and constraints on growth are minimal.
- The distribution of biometry within a population does **not** constitute a standard.
Effect on Economic Status

Source: NFHS, India 2005-2006
International “Prescriptive” WHO Child Growth Standards
Optimal Fetal Growth: A Misconception?

• Birthweight is a problematic measure of fetal development because of different environmental exposures, patterns of fetal growth and durations of pregnancy can lead to similar BW.

• Socio-economic factors are associated with relatively less variation in BW than in other parameters, i.e., height, adiposity

• Birthweights can vary substantially in the same community, the same family, and even in the same woman as socio-economic changes can lead to unhealthy behaviors, obesity, increased stress, excessive gestational weight gain, and a higher prevalence of type 2 diabetes and GDM.
Optimal Fetal Growth: A Misconception?

• What controls fetal growth?
• Genetics and environmental factors interact to influence the development of phenotypic attributes, including BW
• Epidemiological studies have confirmed that BW is relatively unaffected, even during periods of famine
• Are the mother and child in competition with each other so the mother can survive to reproduce again?
• Intrauterine fetal growth is more important than size at birth. It cannot be considered in isolation from the conditions in utero which provide the stimulus for the growth or lack of.
What is optimal fetal growth? The INTERGROWTH-21 study proposed adopting a universal standard for fetal growth, assuming that optimal conditions for the mother (i.e., education, nutrition, and socio-economic status in disparate cultural settings) will lead to similar fetal growth patterns. This is deemed to be optimal fetal growth.

INTEGROWTH-21 proposes that there is a universal, optimal pattern of human fetal growth.

- It does not take into consideration the developmental plasticity that allows each fetus to regulate its own development
Optimal Fetal Growth: A Misconception?

• What are the consequence of a universal fetal growth standard? The INTERGROWTH-21 assumptions for “optimal fetal growth” do not take into considerations that many populations around the world do not conform to such prescribed optimal conditions.

• Ethnic or cultural differences between the mother’s habitus and fetal growth emphasize that one pattern of fetal growth does not fill all. The world’s communities are not cookie cutters.

• Adopting a universal fetal growth standard may not be scientifically valid or clinically beneficial.

• Issues of equity and ethical standard that are important in women’s and children’s health may be exacerbated. Other factors such as maternal height, fetal growth, and BW merits further consideration.
Optimal Fetal Growth: A Misconception?

- The physiological function of the prenatal environment warrants further study as well as fetuses adapt their responses to their environment.

- Finally, … should the mother’s, the fetus’, the healthcare provider’s, or society’s interests dictate what is an optimal fetal growth?
The WHO Fetal Growth Study

• **Motivation**
  - Combat global perinatal mortality and morbidity
  - Prevent non-communicable diseases in adulthood

• **Aim**
  - Establish fetal growth charts for international use

• **Methods**
  - Prospective, longitudinal, observational, multi-center study: 10 centers 1,400 inclusions, 7 scheduled U/S examinations
  - Statistics: Quantile Regression
The WHO Fetal Growth Study: a multinational, longitudinal study of U/S biometric measurements and estimated fetal weight

- **Members:**
  - Torvid Kiserud, Gilda Piaggio, Guillermo Carroli, Mariana Widmer, José Carvalho, Lisa Neerup Jensen, Daniel Giordano, José Guilherme Cecatti, Hany Abdel Aleem, Sameera A. Talegawkar, Alexandra Benachi, Anke Diemert, Antoinette Tshefu Kiloto, Jadsada Thinkhamrop, Pisake Lumbiganon, Ann Tabor, Alka Kriplani, Rogelio Gonzalez, Kurt Hecher, Mark A. Hanson, A. Metin Gulmezoglu, Lawrence D. Platt

- **Participating Countries:**
  - Argentina (Rosario), Brazil (Campinas), Democratic Republic of Congo (Kinshasa), Denmark (Copenhagen), Egypt (Assiut), France (Paris), Germany (Hamburg), India (New Delhi), Norway (Bergen), Thailand (Kohn Kaen), United States (California)
The WHO Fetal Growth Charts: Results

<table>
<thead>
<tr>
<th>Participants</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>1,439</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>52</td>
</tr>
<tr>
<td>Pregnancy loss/miscarriage</td>
<td>25</td>
</tr>
<tr>
<td>Used for statistics</td>
<td>1,362</td>
</tr>
<tr>
<td>Sets of U/S measurements</td>
<td>7,071</td>
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</table>
## The WHO Fetal Growth Charts: Results

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Median</th>
<th>Inter-quartile</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>28</td>
<td>25 – 31</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163</td>
<td>157 – 169</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61</td>
<td>55 – 68</td>
</tr>
<tr>
<td>BMI</td>
<td>23.1</td>
<td>21.0 – 25.4</td>
</tr>
<tr>
<td>Nutrition (cal/d)</td>
<td>1,848</td>
<td>1,487 – 2,222</td>
</tr>
<tr>
<td>Para 0 (%)</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>
## The WHO Growth Charts: Results

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>3,300</td>
<td>p = 0.0018 – p &lt;0.0001 for diff.</td>
</tr>
<tr>
<td>Gestational Age (d)</td>
<td>276</td>
<td>p &lt;0.0001 for diff.</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>Cesarean Section 32% (range 5.5 – 70%)</td>
<td></td>
</tr>
</tbody>
</table>
Estimated fetal weight

Bowley coefficient of asymmetry +0.111
Estimated fetal weight

Bowley coefficient of asymmetry +0.111
(wider distribution above 50th percentile)
Estimated fetal weight
Fetal sex differences

Estimated Fetal Weight (g)

Gestational Age (weeks)
The WHO Fetal Growth Charts: Results

• **Influencing Factors:**
  • Maternal Height
  • Maternal Weight
  • Maternal Age
  • Parity
  • Fetal Sex
  • Country
Influencing factors

Maternal height
Maternal weight
Maternal age
Parity
Country

Influence on EFW percentiles (%)
Influencing factors

Maternal height
Maternal weight
Maternal age
Parity
Country

Influence on EFW percentiles (%)
Estimated fetal weight (5th, 75th and 95th percentile)
Dots: single countries
90th percentile for EFW for each country. Differences found for magnitude and trajectory.
5th percentile for EFW for each country by overall values.

E.g. When the overall 5th centile is 2800g, India would have 2700g and Norway 3200g.
E.g. When the overall 5\textsuperscript{th} centile is 2800g, India would have 2700g and Norway 3200g.
90th percentile for EFW for each country by overall values

E.g. When the overall 90th centile is 3200g, India would have 2850g and Brazil 3350g.
The WHO Fetal Growth Study

• The WHO study is based on 10 different sites/populations and therefore, is more suitable for international use than previous reference ranges based on single populations.

• However, the study showed significant differences in fetal growth and birthweight between countries.

• Fetal population growth turned out to be asymmetric, i.e., there was a slightly wider distribution below the 50th percentile in early second trimester that shifted to a notable widened distribution above the 50th percentile in the third trimester.

• There was an effect of fetal sex EFW.
The WHO Fetal Growth Study

- Maternal characteristics influenced EFW, but did not explain all the differences between countries. These effects, however, comprised only a few percentages of the total variation.
- Interestingly, maternal characteristics commonly had a differential effect on fetal growth, e.g., maternal height had a stronger influence on fetuses at the lowest percentiles compared with those growing at the highest percentiles.
The WHO Fetal Growth Study

• Self-reported ethnicity is a crude and ill-defined classification. Secondly, ethnicity is closely associated with cultural and social traditions that might contribute to differences, and difficult to discern from ethnicity. In our study, ethnicity was largely following country classification. We, therefore, kept country as a classification, and interpret the differences with caution.

• Limitations: Taking into account the substantial anthropometric variation in the various areas of the world, we acknowledge that the sample of 10 centers restricts the extrapolation of our results to be of general validity.
The WHO Fetal Growth Charts

• When applying the WHO fetal growth charts (or any reference chart) in a population, it is commendable to check that it performed accordingly to the needs it is meant to cover. If not, it is prudent to adjust its use, e.g., if the 10th percentile includes a larger proportion of the population than 10%, one should consider to adjust the cut-off.

• Improved test performance for the individual fetuses may also be achieved by customizing for fetal sex (separate charts for female and male fetuses have been provided) and for maternal characteristics (e.g., maternal height, parity, etc.). Another method of more individualized assessment and monitoring would be conditioning, i.e., assessing fetal size, but conditioned on a previous measurement.

• If such techniques do not prove efficient, it should be considered establishing high-quality population-specific growth charts.
Are we so sure that the prescriptive recruitment strategy used in the WHO and INTERGROWTH-21 studies constitutes the optimal conditions for developing healthy individuals? Although restricting the participants to those with “normal” BMI, the affluent life these families may conduct may not be the best for a healthy life course.
The WHO Fetal Growth Charts

- In short, an overall fetal growth chart is now available for general use. The users should be aware of the significant variation in fetal growth that exists determined by site, maternal and fetal factors. To achieve an individualized assessment, the use of customization according to fetal sex, maternal characteristics and population, and conditioning in serial measurements should be considered, also when population-specific charts are in use.
INTERGROWTH-21

- Large international collaboration. All exams were performed by expert sonographers adhering to very strict standards. Longitudinal study design.
- Only ~30% of presenting women were eligible. Exclusion criteria included short stature, obesity, socio-demographic parameters.
- Study showed that women of similar baseline parameters of body composition and SES produce similar fetuses.
- No information regarding the proportion of fetuses affected by FGR or other problems.
INTERGROWTH-21

• Does the over-idealized population exclude the natural variation among human populations?
• How are we to account for observable differences between women of varying ethnicity?
• Ethnic variation might be observed among the excluded – both in growth trajectory of healthy fetuses, and in observed prevalence of growth restriction.
• What is the approach to women and their fetuses, who would have been excluded from the population?
INTERGROWTH-21st Populations

- ALL pregnancies in 8 sites
- N=59,137
INTERGROWTH-21st Populations

- Low-risk pregnancies
  - N=20,486
- Medium-high risk pregnancies
- Fetal Growth Longitudinal Study
  - N=4,607
- International Fetal Growth Standards
INTERGROWTH-21st

• Measurements at each scan >14+0 weeks, every 5 ± 1 week
  • Biparietal diameter
  • Occipito-frontal diameter
  • Head circumference
  • Tranverse abdominal diameter
  • Anterio-posterior abdominal diameter
  • Abdominal circumference
  • Femur length

• Measurements obtained 3 times from 2 separately obtained images of each structure in blinded fashion (no measurement visible) and submitted electronically

Burton F, International Fetal and Newborn Growth Consortium for the 21st Century. BJOG 2013; 120 Suppl 2: 77-80
Preterm births in Fetal Growth Longitudinal Study

Preterm Postnatal Follow-up Study (n=193)
Assessing neurodevelopmental outcomes at 2 yrs in FGLS cohort

- Cohort sites: Brazil, India, Italy, Kenya & United Kingdom
- Assessed
  - Vision
  - Cognition, language development, behavior and fine/gross motor skills
  - Attention
  - Auditory processing
  - Sleep

The likeness of fetal growth and newborn size across non-isolated populations in the INTERGROWTH-21st Project: the Fetal Growth Longitudinal Study and Newborn Cross-Sectional Study

José Villar, Aris T Papageorghiou, Ruyan Pang, Eric O Ohuma, Leila Cheikh Ismail, Fernando C Barros, Ann Lambert, Maria Carvalho, Yasmin A Jaffer, Enrico Bertino, Michael G Gravett, Doug G Altman, Manorama Purwar, Thunnaya O Frederick, Julia A Noble, Cesar G Victora, Zulfiqar A Bhutta*, Stephen H Kennedy*, for the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st)
Early fetal size: CRL by GA for UK, USA & Italy
Early fetal size: CRL by GA for UK USA, Italy & China
Early fetal size: CRL by GA for UK USA, Italy, China & India
Early fetal size: CRL by GA for UK USA, Italy, China, India & Kenya
Early fetal size: CRL by GA for UK USA, Italy, China, India, Kenya & Oman
Early fetal size: CRL by GA for UK USA, Italy, China, India, Kenya, Oman & Brazil
CRL centiles by GA: All 8 sites
Sensitivity analysis for CRL measures: All 8 sites, excluding UK, India, Kenya & China separately

Lancet Diabetes Endocrinol
2014; 781-792
Sensitivity analysis for birth length: All 8 sites, excluding UK, India, Kenya & China separately
Sensitivity analysis for fetal head circumference (HC) measures: All 8 sites, excluding UK, India, China & Kenya separately
Skeletal growth variance between study sites and among individuals within a site

<table>
<thead>
<tr>
<th></th>
<th>Fetal CRL</th>
<th>Fetal HC</th>
<th>Newborn length</th>
<th>Preterm infant length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variance between study sites</td>
<td>1.9%</td>
<td>2.6%</td>
<td>3.5%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Variance among individuals within a site + unexplained variance</td>
<td>98.1%</td>
<td>97.4%</td>
<td>96.5%</td>
<td>99.8%</td>
</tr>
</tbody>
</table>

The trouble with customization … by country
Malnutrition
By race/ethnicity, a social construct?
The distribution of ancestry of self-reported African Americans across the US

Race/ethnicity is a social construct …

• Most populations have large genetic admixture due to global migration, invasions, refugees, etc.
• At least 116 definitions of self-reported race or ethnicity appear in the biomedical literature
• Nearly 700 genetic variants are implicated in human stature, but only a few are associated with skin pigmentation
Race/ethnicity is a social construct …

- The U. S. Census Bureau defines the ethnonym Hispanic or Latino to refer to

- … “a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin regardless of race” and states that Hispanics or Latinos can be of any race, any ancestry, any ethnicity
... and links with deprivation

Buck Louis, et al.  
Am J Obstet Gynecol 2015; 449.e10449.e41

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-Hispanic white n (%)</th>
<th>Non-Hispanic black n (%)</th>
<th>Hispanic n (%)</th>
<th>Asian/Pacific Islander n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>22 (5)</td>
<td>205 (49)</td>
<td>167 (23)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>Married/living as married</td>
<td>452 (94)</td>
<td>205 (49)</td>
<td>357 (73)</td>
<td>313 (92)</td>
</tr>
<tr>
<td>Divorced/Separated</td>
<td>8 (1)</td>
<td>15 (4)</td>
<td>24 (5)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; High school</td>
<td>4 (1)</td>
<td>47 (11)</td>
<td>108 (22)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>High school/GED</td>
<td>22 (5)</td>
<td>122 (29)</td>
<td>114 (23)</td>
<td>40 (12)</td>
</tr>
<tr>
<td>Some college/associate degree</td>
<td>83 (18)</td>
<td>153 (33)</td>
<td>181 (37)</td>
<td>67 (20)</td>
</tr>
<tr>
<td>College undergraduates</td>
<td>203 (42)</td>
<td>66 (16)</td>
<td>67 (14)</td>
<td>105 (31)</td>
</tr>
<tr>
<td>Postgraduate college</td>
<td>164 (34)</td>
<td>38 (9)</td>
<td>18 (4)</td>
<td>111 (33)</td>
</tr>
<tr>
<td>Annual family income</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤ $29,999</td>
<td>17 (4)</td>
<td>169 (43)</td>
<td>157 (39)</td>
<td>43 (17)</td>
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<tr>
<td>$30,000–49,999</td>
<td>30 (7)</td>
<td>71 (19)</td>
<td>109 (27)</td>
<td>32 (12)</td>
</tr>
<tr>
<td>$50,000–74,999</td>
<td>50 (13)</td>
<td>33 (9)</td>
<td>65 (14)</td>
<td>33 (13)</td>
</tr>
<tr>
<td>$75,000–99,999</td>
<td>83 (19)</td>
<td>38 (19)</td>
<td>30 (7)</td>
<td>54 (21)</td>
</tr>
<tr>
<td>≥ $100,000</td>
<td>270 (53)</td>
<td>47 (11)</td>
<td>54 (13)</td>
<td>96 (37)</td>
</tr>
<tr>
<td>Health Insurance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private/managed care</td>
<td>452 (94)</td>
<td>204 (49)</td>
<td>169 (33)</td>
<td>211 (62)</td>
</tr>
<tr>
<td>Medicare, other</td>
<td>21 (5)</td>
<td>217 (51)</td>
<td>298 (61)</td>
<td>129 (37)</td>
</tr>
<tr>
<td>Self-pay</td>
<td>5 (1)</td>
<td>5 (1)</td>
<td>21 (4)</td>
<td>5 (2)</td>
</tr>
</tbody>
</table>
The rationale for customization?
Be skeptical of observational data

International Growth Standards

- The future … integrating growth monitoring from 1\textsuperscript{st} trimester to 5 years of age
INTERROWTH-21st Project: International Standards

- Fetal growth by ultrasound (Lancet 2014)
- Newborn size for gestational age and sex (Lancet 2014)
- Symphyseal-fundal height (BMJ 2016)
- Maternal weight gain in pregnancy (BMJ 2016)
- Postnatal growth of preterms (Lancet Glob Health 2015)
- Preterm phenotypes (JAMA Ped 2015)
- SGA phenotypes (JAMA Ped 2015)
- Late pregnancy dating (Ultrasound Obstet Gynecol 2014)
- Estimated fetal weight (Ultrasound Obstet Gynecol 2016)
INTERGROWTH-21st Newborn Standards (red lines)
WHO Child growth Standards (blue lines)

Am J Obstet Gynecol
2015; 213: 494-499
Compare your newborn biometry to Intergrowth standards:

- Upload data or Enter data manually

Newborn Sex: **Boy**  **Girl**

Gestational age (weeks + days):

- 33 34 35 36 37 38 39 40
- 41 42

40

- 1 2 3 4 5 6

Length: 50 cm

Weight: 3 kg

Head circumference: 34 cm

**www.intergrowth21.tghn.org**
Multicentre Growth Reference Study

- Initiated by the WHO
- Study published in 2006 – new infant and child growth standards
- Allows for evaluation of growth from birth to age 5 years
- “Standardize” methods of across worldwide populations

International standards for fetal growth based on serial ultrasound measures: The Fetal Growth Longitudinal Study (FGLS) of the INTERGROWTH-21st Project

• Using the same methods and conceptual approach recommended from the WHO expert committee, the FGLS arm of the INTERGROWTH-21 Project aimed to develop international growth and size standards for fetuses

• 13,108 women screened, antenatal care <14 wks 0 days – 4,607 (35%) eligible, 4,321 (94%) eligible had pregnancies without major complications and delivered live singletons without congenital malformations
# INERGROWTH-21st Project: FGLS Study

<table>
<thead>
<tr>
<th>US Parameter</th>
<th>3rd Percentile</th>
<th>50th Percentile</th>
<th>97th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>2.25 mm (SD 3.0)</td>
<td>0.02 mm (SD 3.0)</td>
<td>-2.69 mm (SD 3.2)</td>
</tr>
<tr>
<td>BPD</td>
<td>0.83 mm (SD 0.9)</td>
<td>-0.05 mm (SD 0.8)</td>
<td>-0.84 (SD 1.0)</td>
</tr>
<tr>
<td>OFD</td>
<td>0.63 mm (SD 1.2)</td>
<td>0.04 mm (SD 1.1)</td>
<td>-1.05 mm (SD 1.3)</td>
</tr>
<tr>
<td>AC</td>
<td>2.99 mm (SD 3.1)</td>
<td>0.25 (SD 3.2)</td>
<td>-4.22 mm (SD 3.7)</td>
</tr>
<tr>
<td>FL</td>
<td>0.62 mm (SD 0.8)</td>
<td>0.03 mm (SD 0.8)</td>
<td>-0.65 mm (SD 0.8)</td>
</tr>
</tbody>
</table>
International standards for early fetal size and pregnancy dating on US measurement of CRL in the 1st trimester of pregnancy


- INTERGROWTH-21st developed prescriptive standards for 1st trimester CL measurements and pregnancy dating for global use
- 13,108 women screened
  - 4,607 enrolled
  - 4,265 CRL measured between 9+0 and 13+6 wks gestation according to LMP
Defining Fetal Growth Standards: The NICHD Fetal Growth Study Approach
Importance of Optimal Fetal Growth

• Foundation for long-term health
• Fetal growth as risk factor for chronic disease
  • In utero programming

• Developmental origins of health and disease (Gluckerman PD. J Intern Med 2007)
Assessing Fetal Growth

• Identifying normal fetal growth remains a pressing challenge
• Birth weight references
  • Limitations: includes neonates with growth restriction – particularly an issue preterm
• Ultrasound-based references (prior to 2009)
  • Small numbers
  • Generally not longitudinal
# References vs. Standards – *The Basics*

<table>
<thead>
<tr>
<th><strong>References</strong></th>
<th><strong>Standards</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Population-specific, non generalizable</td>
<td>• Non population-specific, more generalizable</td>
</tr>
<tr>
<td>• Including abnormals</td>
<td>• Excluding abnormals</td>
</tr>
<tr>
<td>• Representative</td>
<td>• Optimal conditions</td>
</tr>
<tr>
<td>• Descriptive, reference intervals</td>
<td>• Proscriptive, variance restricted</td>
</tr>
</tbody>
</table>

__Percentiles and their interpretation not the same__
NICHD Fetal Growth Study Aims

• To established *standards* for normal (or optimal) fetal growth and size-for-gestational age in the U.S.
  • Separately for racial/ethnic groups where prevailing differences in maternal size and/or body proportions may result in altered (but still normal) trajectories
• To create an individualized standard for fetal growth potential
• To improve accuracy of fetal weight estimation
NICHD Fetal Growth Studies

- Comprised of 12 U.S. clinical sites between 2009-2013
- 2,334 healthy women, low risk for fetal growth restriction or overgrowth
  - 4 race/ethnicity groups:
    - Non-Hispanic white
    - Non-Hispanic black
    - Hispanic
    - Asian & Pacific Islander
- 468 obese women (BMI 30-45 kg/m²)
- 171 women with dichorionic twin gestations
**Study Design: Singletons**

**Eligibility criteria**
- Viable singleton pregnancy
- 8⁺⁰ – 13⁺⁶ weeks gestation
- Maternal age: 18-40 years
- Pre-gravid BMI: 19.0-29.9 kg/m²
- Delivery at participating hospital

**High quality images**
- Standardized ultrasound protocol
- *Ante hoc* credentialing of sonographers
- 5% random sample (n=740) of scans re-measured for quality assurance
Sonographer Education and Credentialing

- Demonstrated that intensive training and image review can be used to credential sonographers to perform standardized 2D ultrasound of fetal biometry
- Multi-day education session with didactic and hands-on training of standardized ultrasound procedures
- Submission of 15 passing credentialing scans, 5 in each trimester
  - Parameters of credentialing scans identical to components of study scan in same trimester
Review of 2D Credentialing Materials

- Materials independently reviewed by two experienced reviewers
- Review criteria:
  - Imaging quality and image plane
  - Caliper placement
  - Qualitative or quantitative interpretation (if needed)
  - Compliance with safety thresholds (mechanical and thermal index ≤ 1.0)
  - Accurate reporting of energy outputs
- Non-passing scans (score <80%) required submission of a supplemental scan in the same trimester

Fuchs et al
Firm Dating Criteria

- Singleton, viable pregnancy
- $8^{+0} - 13^{+6}$ weeks of gestation
- LMP – date and ultrasound date match within

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Number of Days Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>8w 0 d go 10 w 6 d</td>
<td>5 days</td>
</tr>
<tr>
<td>11 w 0 d – 12 w 6 d</td>
<td>6 days</td>
</tr>
<tr>
<td>13 w 0 d – 13 w 6 d</td>
<td>7 days</td>
</tr>
</tbody>
</table>
Ultrasonography Randomization

- Following enrollment sonogram 10 – 13 weeks:

<table>
<thead>
<tr>
<th>Group</th>
<th>Gestational week for ultrasound exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>16, 24, 30, 34, 38</td>
</tr>
<tr>
<td>B</td>
<td>18, 26, 31, 35, 39</td>
</tr>
<tr>
<td>C</td>
<td>20, 28, 32, 36, 40</td>
</tr>
<tr>
<td>D</td>
<td>22, 29, 33, 37, 41</td>
</tr>
</tbody>
</table>
Statistical Methods – Modeling Fetal Growth

- Linear mixed models with cubic splines for estimating racial/ethnic-specific fetal growth curves
- 5th, 50th and 95th percentiles were estimated
- EFW & individual parameters tested for overall differences in the racial/ethnic-specific curves (LRT test)
  - If global test significant, tested for week-specific differences by race/ethnicity (Wald tests at each week)
- Significance testing with and without adjustment for maternal age, height, weight, parity, employment and marital status, health insurance, income & education
NICHD Fetal Growth Studies

• 2,334 healthy women, low risk for fetal growth restriction or overgrowth
• Excluded pregnancy complications, neonatal conditions (aneuploidy, death), n=1,737 (74%)
  • 4 race/ethnicity groups:
    • Non-Hispanic white n=481
    • Non-Hispanic black n=426
    • Hispanic n=488
    • Asian & Pacific Islander n=342
## Results

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>White (n=481)</th>
<th>Black (n=426)</th>
<th>Hispanic (n=488)</th>
<th>Asian (n=342)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong>, mean (SD)</td>
<td>30.3 (4.3)</td>
<td>25.5 (5.4)</td>
<td>26.9 (5.4)</td>
<td>30.5 (4.4)</td>
</tr>
<tr>
<td><strong>BMI</strong> (kg/m²), mean (SD)</td>
<td>23.1 (2.8)</td>
<td>24.0 (3.1)</td>
<td>24.2 (2.8)</td>
<td>22.1 (2.5)</td>
</tr>
<tr>
<td><strong>Marital status, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>5</td>
<td>48</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Married/living as married</td>
<td>94</td>
<td>44</td>
<td>73</td>
<td>92</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Health insurance, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private/managed care</td>
<td>94</td>
<td>48</td>
<td>35</td>
<td>62</td>
</tr>
<tr>
<td>Medicaid</td>
<td>5</td>
<td>51</td>
<td>61</td>
<td>37</td>
</tr>
<tr>
<td>Self-pay</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Characteristics</td>
<td>White (n=481)</td>
<td>Black (n=426)</td>
<td>Hispanic (n=488)</td>
<td>Asian (n=342)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>------------------</td>
<td>--------------</td>
</tr>
<tr>
<td><strong>Education, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; High school</td>
<td>1</td>
<td>11</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>High school/GED</td>
<td>5</td>
<td>29</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Some college</td>
<td>18</td>
<td>36</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>College undergraduate</td>
<td>42</td>
<td>16</td>
<td>14</td>
<td>31</td>
</tr>
<tr>
<td>Postgraduate college</td>
<td>34</td>
<td>9</td>
<td>4</td>
<td>33</td>
</tr>
<tr>
<td><strong>Family income, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$29,999</td>
<td>4</td>
<td>49</td>
<td>39</td>
<td>17</td>
</tr>
<tr>
<td>$30,000 - $49,999</td>
<td>7</td>
<td>19</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>$50,000 - $74,999</td>
<td>13</td>
<td>9</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>$75,000 - $99,999</td>
<td>19</td>
<td>10</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>≥ $100,000</td>
<td>58</td>
<td>13</td>
<td>13</td>
<td>37</td>
</tr>
<tr>
<td><strong>Current paid jobs, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19</td>
<td>33</td>
<td>45</td>
<td>39</td>
</tr>
<tr>
<td>1</td>
<td>72</td>
<td>61</td>
<td>53</td>
<td>59</td>
</tr>
<tr>
<td>≥ 2</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Results: Head Circumference

21 weeks

Global $P<0.001$
Results: Abdominal Circumference (AC)

Global $P<0.001$
Results: Femur Length (FL)

FL significantly different from 10-39 weeks
Global $P<0.001$
Singleton Standard difference significantly by race/ethnicity starting at 16 weeks gestation extending to delivery

Results: Misclassification under White Standard
Results: Misclassification under White Standard

At 35 weeks, using White standard <5th percentile:
14% black, 12% Hispanic, 15% of Asian fetuses
Summary of Findings

• By 2nd trimester in uncomplicated pregnancies …
  • Significant differences in EFW, HC, AC & FL (also BPD & HL) by self-identified race/ethnicity
    • Earliest differences for FL & HL 10 weeks
    • AC 16 weeks
    • HC 21 weeks
    • BPD 27 weeks
    • EFW 16 weeks
  • The White derived standard erroneously classified up to 15% of non-white fetuses on SGA (EFW <5th percentile)

• Assessment of fetal growth by ultrasound needs to be evaluated clinically using racial/ethnic-specific standards
  • *One size does not fit all in our cohort*
• Findings help inform clinical management consistent with precision medicine initiative
• Future research should also address heterogeneity within the broad racial/ethnic groups

To pool or not to pool?

• How similar do groups have to be to pool them together into one fetal growth standard?
• Or, … how different is too different?
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