Standards on Fetal Growth Roundtable:

The WHO Fetal Growth Charts

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The WHO Fetal Growth Charts: 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)

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Report of WHO Expert Committee 1995:

Physical Status: The Use and Interpretation of Anthropometry, Technical Report Series

- Human growth worldwide should be evaluated using **international standards** describing how individuals *should grow*

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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

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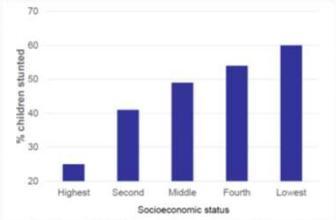
Effect on Economic Status



Source: NFHS$_2$, India 2005-2006

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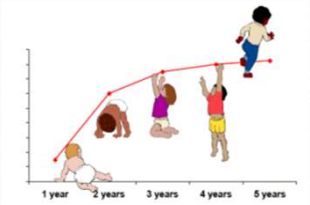
International "Prescriptive" WHO Child Growth Standards



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The WHO Fetal Growth Charts

- **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

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The WHO Fetal Growth Charts

- 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

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The WHO Fetal Growth Charts

- 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.

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The WHO Fetal Growth Charts

- 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.

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The WHO Fetal Growth Charts

- When applying the WHO fetal growth carts (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.

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READ The WHO Fetal 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.*

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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.

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The WHO Fetal Growth Charts: Results

Participants	Number
Enrolled	1,439
Withdrawn	52
Pregnancy loss/miscarriage	25
Used for statistics	1,362
Sets of U/S measurements	7,071

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The WHO Fetal Growth Charts: Results

Maternal	Median	Inter-quartile
Age (years)	28	25 – 31
Height (cm)	163	157 – 169
Weight (kg)	61	55 – 68
BMI	23.1	21.0 – 25.4
Nutrition (cal/d)	1,848	1,487 – 2,222
Para 0 (%)	58	

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The WHO Growth Charts: Results

	Median	P value
Birthweight (g)	3,300	p = 0.0018 – p <0.0001 for diff.
Gestational Age (d)	276	p <0.0001 for diff.
Mode of delivery	Cesarean Section 32% (range 5.5 – 70%)	

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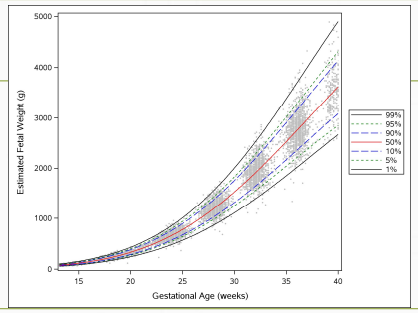

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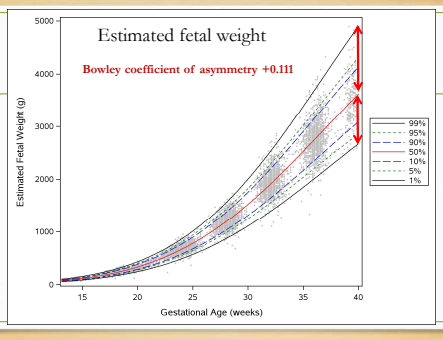

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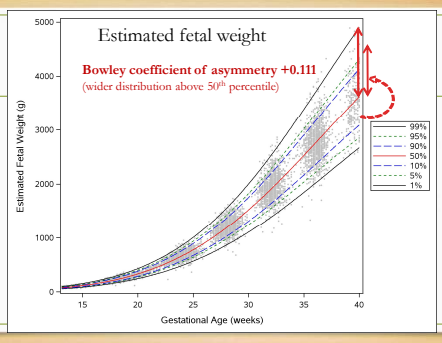

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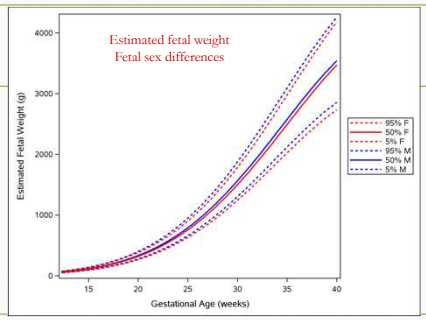

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The WHO Fetal Growth Charts: Results

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

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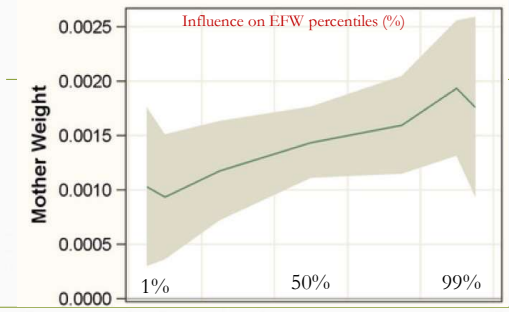

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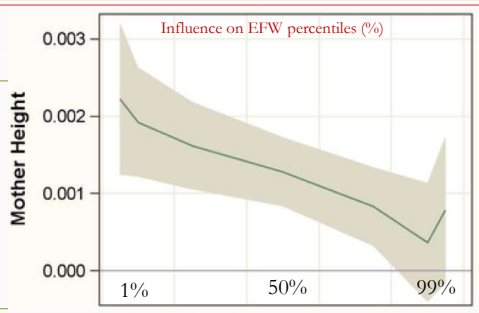

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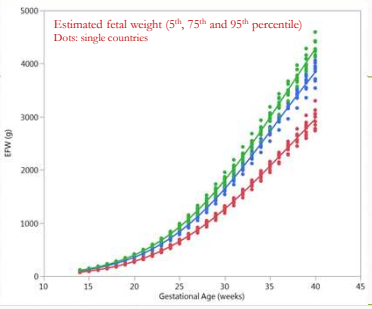

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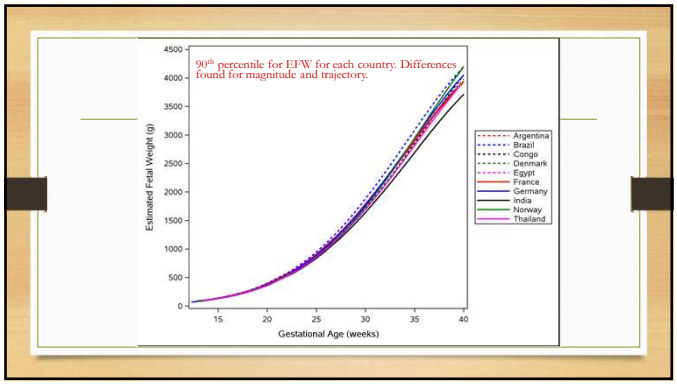

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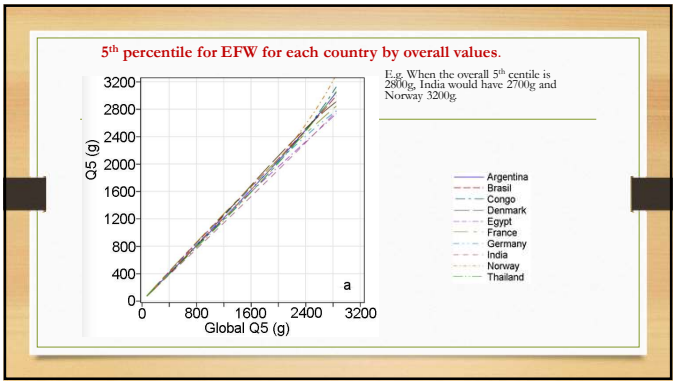

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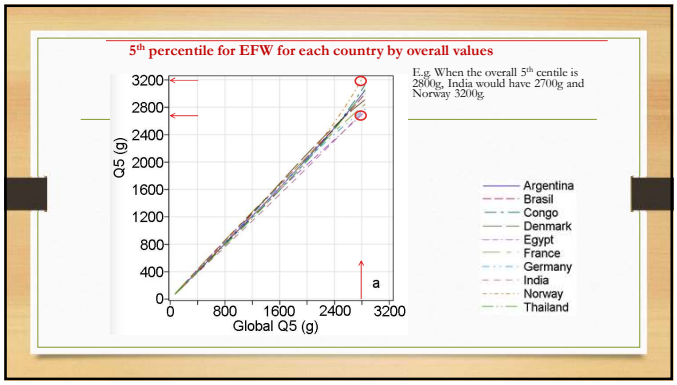

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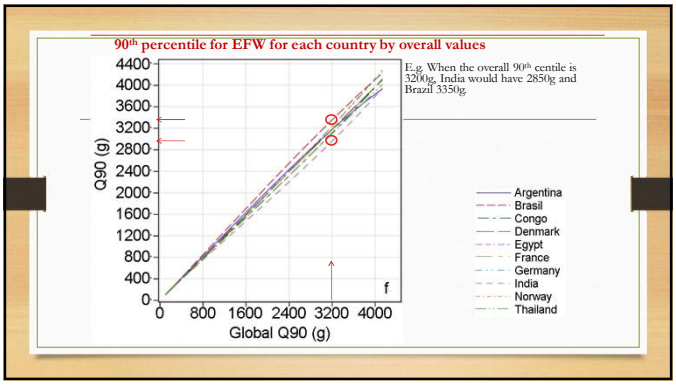

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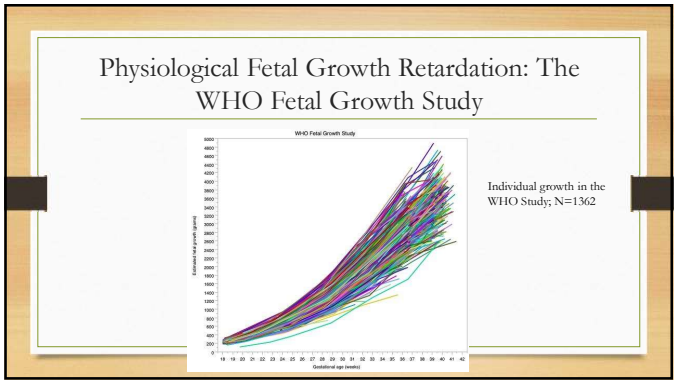

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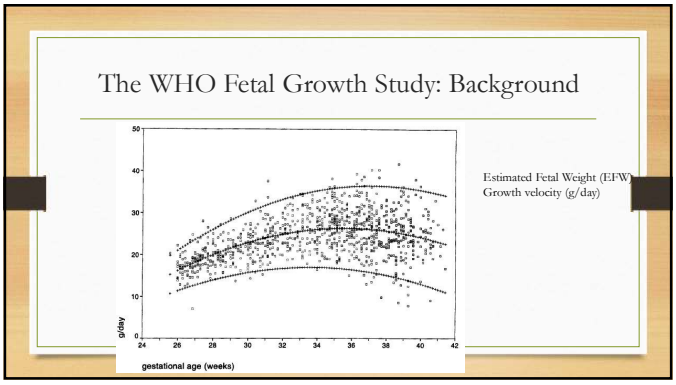

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The WHO Fetal Growth Study: Motivation & Aim

- Recently, growing interest in growth velocity as a predictor of perinatal outcome. [Sovia U, et al. Lancet 2015; 386: 2089-97; Sovia U, et al. Diabes Care 2016; 39: 982-7]
- Do we know sufficient about normal growth dynamics in the latter part of pregnancy?
- Thus, the aim of this study was to determine normal variation of growth velocity during the second half of pregnancy with a particular focus on growth retardation.

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The WHO Fetal Growth Study: Material & Methods

- 1,439 low-risk participants
- 1,298 has ≥2 serial assessments of estimated fetal weight
- Growth velocity: Δg/week and acceleration as Δg/week^2
- Quantile regression

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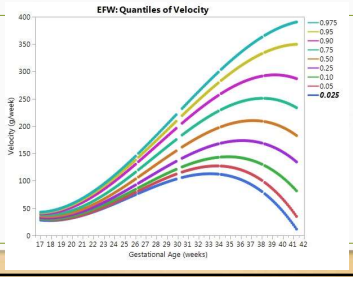
The WHO Fetal Growth Study: Results

g/week



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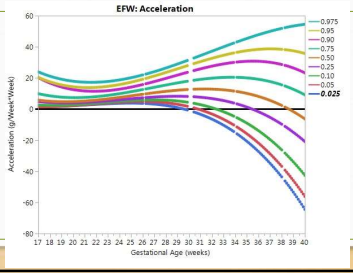
The WHO Fetal Growth Study: Results

g/week



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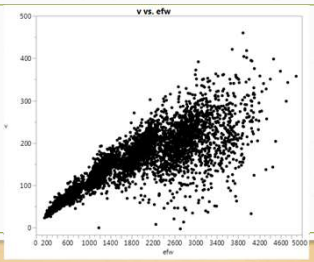
The WHO Fetal Growth Study: Results

g/week



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The WHO Fetal Growth Study: Conclusion

- Growth retardation is part of normal growth physiology
- Starting point graded across the centiles during 3rd trimester
- The lowest centiles start early and the high centiles late

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Optimal Fetal Growth: A Misconception?

Hanson M, Kiserud T, et al. Am J Obstet Gynecol 2015; 213 (3): 332.e1-332.e4

- 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.

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Optimal Fetal Growth: A Misconception?

Hanson M, Kiserud T, et al. Am J Obstet Gynecol 2015; 213 (3): 332.e1-332.e4

- 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.

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Optimal Fetal Growth: A Misconception?

Hanson M, Kiserud T, et al. Am J Obstet Gynecol 2015; 213 (3): 332.e1-332.e4

- 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

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Optimal Fetal Growth: A Misconception?

Hanson M, Kiserud T, et al. Am J Obstet Gynecol 2015; 213 (3): 332.e1-332.e4

- 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 a maternal height, fetal growth and BW merits further consideration.

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Optimal Fetal Growth: A Misconception?

Hanson M, Kiserud T, et al. Am J Obstet Gynecol 2015; 213 (3): 332.e1-332.e4

- 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?**

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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.

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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?

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INTERGROWTH-21st Sites

BILL & MELINDA GATES foundation

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INTERGROWTH-21st Populations

- ALL pregnancies in 8 sites
- N=59,137

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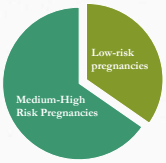
INTERGROWTH-21st Populations

- Low-risk pregnancies
- N=20,486



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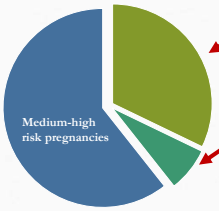
INTERGROWTH-21st Populations



- Low-risk pregnancies
- N=20,486

- Fetal Growth Longitudinal Study
- N=4,607

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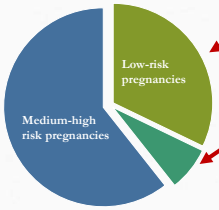
INTERGROWTH-21st Populations



- Low-risk pregnancies
- N=20,486

- Fetal Growth Longitudinal Study
- N=4,607

International Fetal Growth Standards

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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

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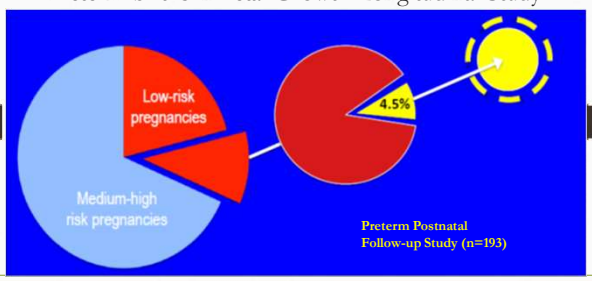
Preterm births in Fetal Growth Longitudinal Study



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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

Fernandes, et al. PLoS One 2014; 9 (11): e113360

52

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, Ihunnaya 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-21*)

Lancet Diabetes Endocrinol 2014; 2: 781-792

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Fetal size <14+0 weeks by CRL

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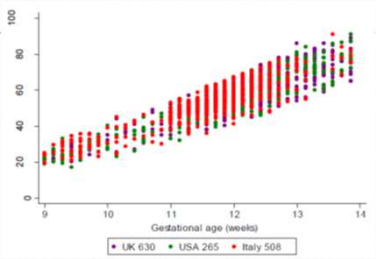
Early fetal size: CRL by GA for UK, USA & Italy



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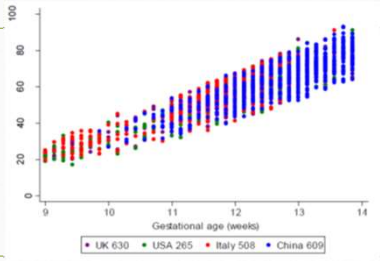
Early fetal size: CRL by GA for UK USA, Italy & China



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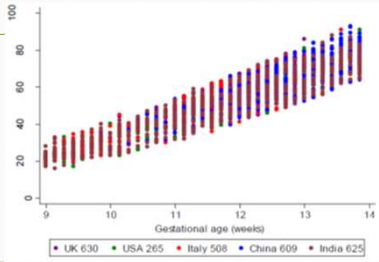
Early fetal size: CRL by GA for UK USA, Italy, China & India



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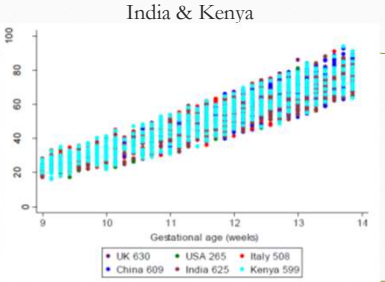
Early fetal size: CRL by GA for UK USA, Italy, China, India & Kenya



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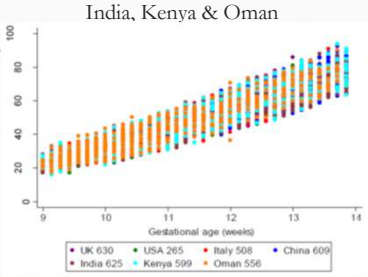
Early fetal size: CRL by GA for UK USA, Italy, China, India, Kenya & Oman



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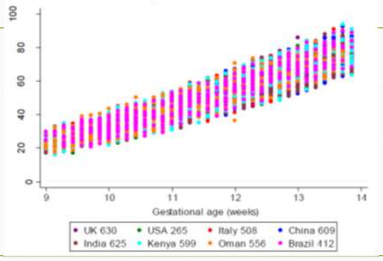
Early fetal size: CRL by GA for UK USA, Italy, China, India, Kenya, Oman & Brazil



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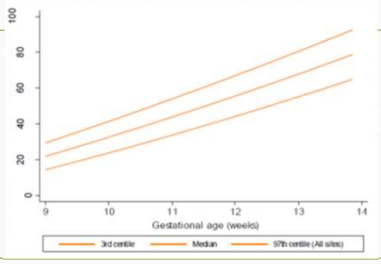
CRL centiles by GA: All 8 sites



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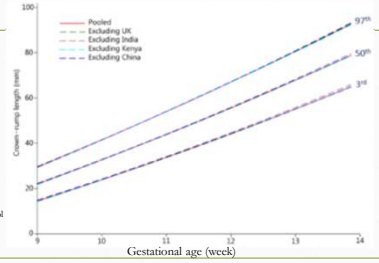
Sensitivity analysis for CRL measures: All 8 sites, excluding UK, India, Kenya & China separately



Lancet Diabetes Endrocrinol 2014; :781-792

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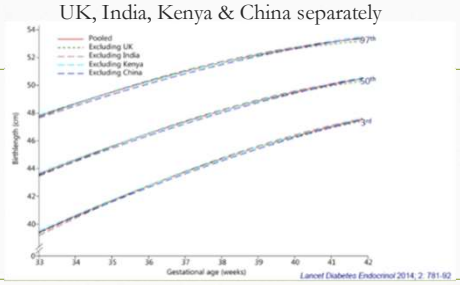
Sensitivity analysis for birth length: All 8 sites, excluding UK, India, Kenya & China separately



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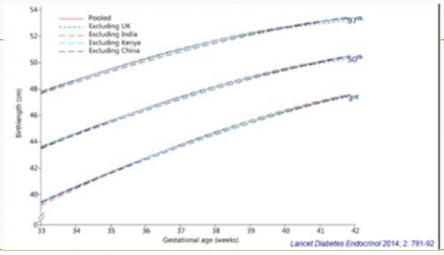
Sensitivity analysis for fetal head circumference (HC) measures: All 8 sites, excluding UK, India, China & Kenya separately



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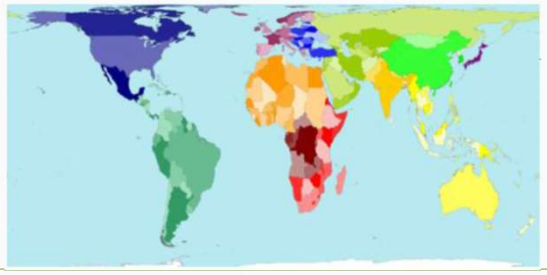
Skeletal growth variance between study sites and among individuals within a site

	Fetal CRL	Fetal HC	Newborn length	Preterm infant length
Variance between study sites	1.9%	2.6%	3.5%	0.2%
Variance among individuals within a site + unexplained variance	98.1%	97.4%	96.5%	99.8%

Villar et al. Am J Obstet Gynecol 2015; 213: 494-499

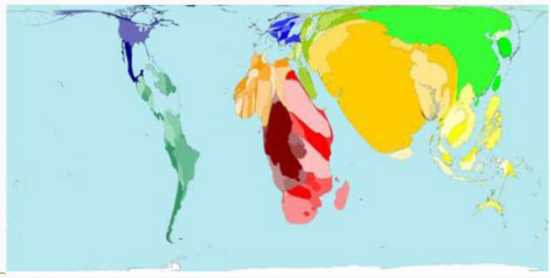
66

The trouble with customization … by country



67

Malnutrition

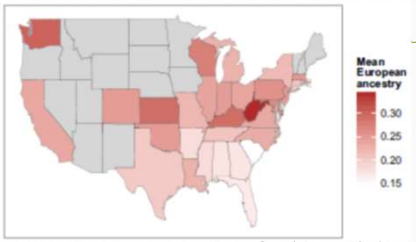


68

By race/ethnicity, a social construct?

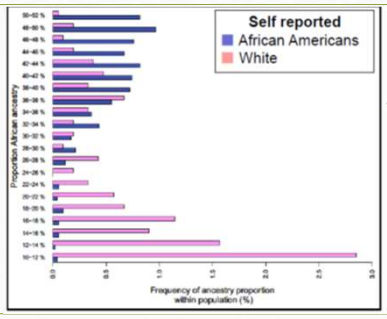
69

The distribution of ancestry of self-reported African Americans across the US



Bryc et al. Am J Human Genetics 2015; 96: 37-5

70



Bryc et al. Am J Human Genetics 2015; 96: 37-5

71

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

72

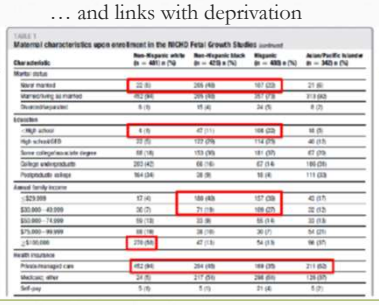
Race/ethnicity is a social construct …

- The U. S. Census Bureau defines the ethononym 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

73

… and links with deprivation

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



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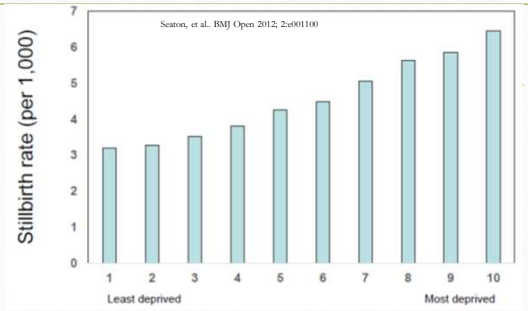
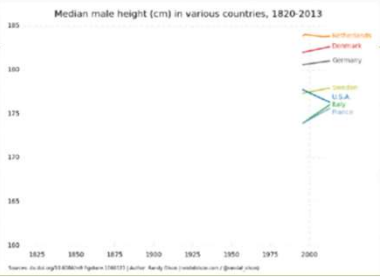


Seaton, et al.. BMJ Open 2012; 2:e001100

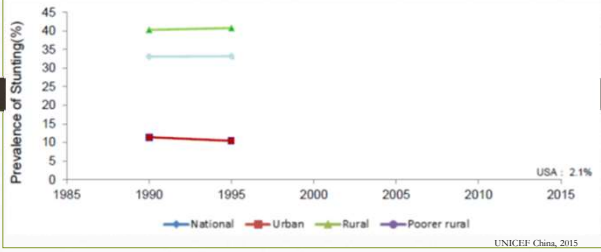
75

What about height?



76

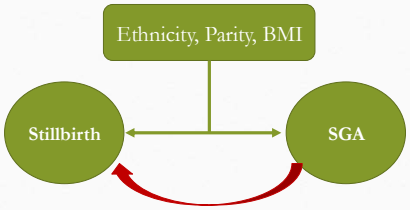
Time trends in prevalence of stunting among children under 5 years in China (1990-2013)



UNICEF China, 2015

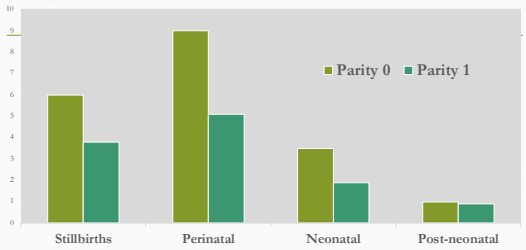
77

The rationale for customization?



78

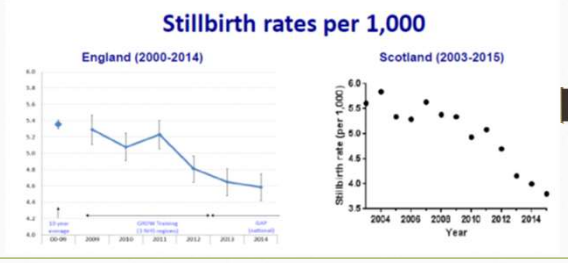
Stillbirth rate per 1,000



ONS Bulletin 2012

79

Be skeptical of observational data



http://www.perinatal.org.uk (ONS data) http://www.nrscotland.gov.uk/statistics-and-data/statistics/

80

International Growth Standards

- The future … integrating growth monitoring from 1st trimester to 5 years of age

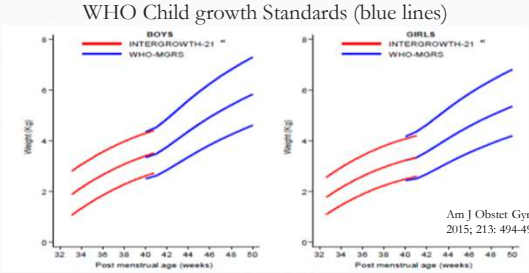
81

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)

82

INTERGROWTH-21st Newborn Standards (red lines) WHO Child growth Standards (blue lines)



Am J Obstet Gynecol 2015; 213: 494-499

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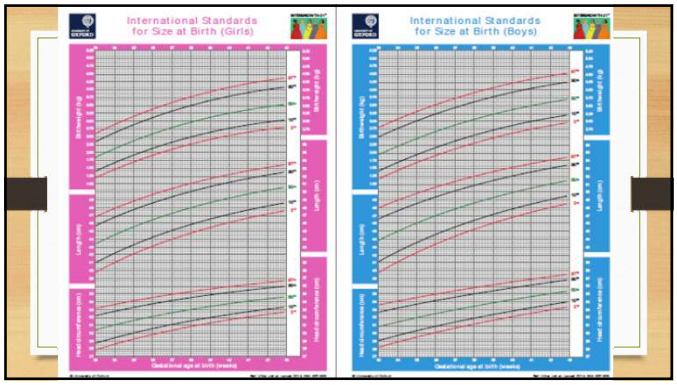

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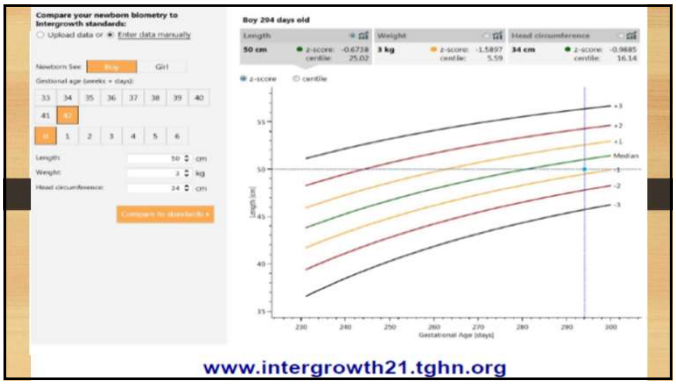

86

87

Management of fetal growth restriction

Alberry M, Soothill P. Arch Dis Child Fetal Neonatal 2007; 92: F62-F67

- Focus of study was on the pathophysiology and management of FGR caused by placental diseases
- FGR is complex and difficult to achieve a definitive diagnosis of the etiology and planning management
- Fetal biometry, AF volume, heart rate patterns, arterial and venous Doppler, BPP variable allow for a comprehensive fetal evaluation
- **No evidence supports the use of CTG or the BPP as improving perinatal outcome**

88

Biophysical profile in the treatment of IUGR fetuses who weigh <1000 g

Kaur S, et al. Am J Obstet Gynecol 2008; 199 93): 264.e1-264.e4

- Aim: determine the usefulness of BPP in predicting cord pH, base access, and timing of delivery
  - 48 IUGR fetuses
  - Abnormal: 2/10 in 1 single occasion; 4/10 on 2 consecutive occasions 2 hours apart
- Conclusion: BPP alone – not reliable test in treatment of preterm IUGR fetuses – high FP and negative results
- Good BPP providing reassurance for ~24 hrs – not applicable in severely preterm IUGR fetuses weighing <1000 g

89

Compare BPP with conventional monitoring (CTG only or MBPP) on pregnancy outcome in HR pregnancies

Lalor JG, Alfirevic Z, et al. Cochrane Database of Systematic Reviews 2008: 1: CD000038

- 5 trials included in this review; 2,974 women
- Overall incidence of adverse outcomes was low
- Evidence of RCTs did not support use of BPP as test for fetal well-being in HR pregnancies
  - Combined data from 2 trials suggested an increase in C/S in BPP group (n=280, small group)
- **In 2008: add'l evidence is required in order to be definitive regarding the efficacy for use in HR pregnancies**
  - **Insufficient evidence from RCTs to support use of PP as a test for fetal-well-being in HR pregnancies**
  - **Same conclusion as 1996 review**

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Slide 87

J1 Jane, 2/5/2017

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

WHO Multicentre Growth Reference Study Group. Acta Paediatr 2006; 450 (Suppl): 76-85

91

International standards for fetal growth based on serial ultrasound measures: The Fetal Growth Longitudinal Study (FGLS) of the INTERGROWTH-21st Project
Papageorghiou AT, et al. Lancet 2014; 384: 869-879

- 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

92

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

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Standards are needed for growth monitoring

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INERGROWTH-21st Project: FGLS Study

US Parameter	3rd Percentile	50th Percentile	97th Percentile
HC	2.25 mm (SD 3.0)	0.02 mm (SD 3.0)	-2.69 mm (SD 3.2)
BPD	0.83 mm (SD 0.9)	-0.05 mm (SD) 0.8)	-0.84 (SD 1.0)
OFD	0.63 mm (SD 1.2)	0.04 mm (SD 1.1)	-1.05 mm (SD 1.3)
AC	2.99 mm (SD 3.1)	0.25 (SD 3.2)	-4.22 mm (SD 3.7)
FL	0.62 mm (SD 0.8)	0.03 mm (SD 0.8)	-0.65 mm (SD 0.8)

95

International standards for early fetal size and pregnancy dating on US measurement of CRL in the 1st trimester of pregnancy
Papageorghiou AT, et al; for INTERGROWTH-21st. Ultrasound Obstet Gynecol 2014; 44: 641-648

- 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

96

Standardisation and QC of US measurements taken in the INTERGROWTH-21st Project

Sarris I, et al; for INTERGROWTH-21st. BJOG 2013; 120 (Suppl 2): 33-37

- Standardization of protocols and ongoing quality assurance monitoring is essential to ensuring consistency in data collection and for minimizing systematic errors in research studies, especially in multicenter studies
- INTERGROWTH-21st Project established a central US Quality Unit to oversee the process for this study

97

Ethical issues arising from the INTERGROWTH-21st Fetal Growth Longitudinal Study

Burton F; for INTERGROWTH-21st. BJOG 2013; 120 (Suppl 2) 77-80

- Adopted in 1964 and last amended in 2013, the WMA developed the Declaration of Helsinki a statement of ethical principles for medical research involving human subjects.
- This was the underlying ethical framework for members of the INTERGROWTH-21st Project.
- However, these guidelines presented a challenge for cultural sensitivity among the participating members.
- Each study site would also have to work within the guidelines of their own local ethics committee and adhere to all stringent requirements set nationally.

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Ethical issues arising from the INTERGROWTH-21st Fetal Growth Longitudinal Study

Burton F; for INTERGROWTH-21st. BJOG 2013; 120 (Suppl 2) 77-80

- Gender ID during U/S presented a unique challenge.
  - Illegal in India
  - Openly communicated in Brazil
- "Inducements" also presented a challenge (better antenatal care for participating in the study vs not participating)
  - Emphasis was placed on providing benefit to future generations rather than any specific or immediate benefits to an individual
- Set-up of the FGLS presented a significant concern … how to address the issue of any clinical problems identified during the extra U/S scans
- Lastly, issue of the storage and retrieval of information from the FGLS study was addressed.
  - Participants had the right to withdraw at any time, to request destruction of their personal data, to now that all data would be stored in an anonymous/protected manner, and good records would be kept

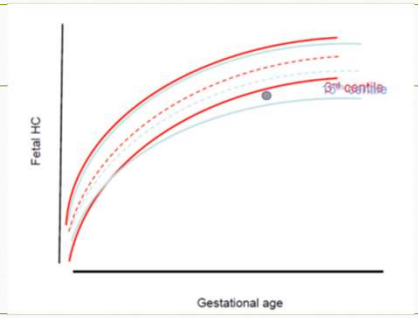
99

Translating research into clinical practice: INTERGROWTH-21st

Chatfield A, et al; INTERGROWTH-21st. BJOG 2013; 120 (Suppl 2): 139-142

- INTERGROWTH-21st developed a package of int'l clinical standards, tools and guidelines
- What's next? Translating the findings into clinical practice through global dissemination
- Goal: pre-empt barriers to implementation by drawing from published literature; gathering input from policymakers and practitioners; incorporating input from local experts; and collecting/analyzing data generated by a monitoring/evaluation system
- Understanding of the effectiveness of varying approaches will be enhanced towards translating the outcomes into clinical practice

100



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Defining Fetal Growth Standards: The NICHD Fetal Growth Study Approach

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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)

103

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

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Clarifying Point: Two Types of References

1. Formula used to calculate the estimate fetal weight (EFW)
2. Once you determine the EFW, you need a reference to determine what percentile the EFW is for a given gestational age

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Clarifying Point: Two Types of References

- EFW formula reference, i.e. Hadlock et al. AJOG 1985

Fetal Parameters	Regression Equations
HC, AC FL	Log_{10} weight = 1.326 – 0.00326 AC x FL + 0.0107 HC + 0.08438 + 0.158 FL

- EFW %tile reference, i.e. Hadlock et al. Radiology 1991
  - EFW 1465g at 32 weeks = 5th percentile

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References vs. Standards – *The Basics*

References	Standards
Population-specific, non generalizable	Non population-specific, more generalizable
Including abnormals	Excluding abnormals
Representative	Optimal conditions
Descriptive, reference intervals	Proscriptive, variance restricted

Percentiles and their interpretation not the same

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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

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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/m^2)
- 171 women with dichorionic twin gestations

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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/m^2
  - 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

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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

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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 $\leq$ 1.0)
  - Accurate reporting of energy outputs
- Non-passing scans (score <80%) required submission of a supplemental scan in the same trimester

Adapted from Karin Fuchs and Mary D'Alton

112

Firm Dating Criteria

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

Gestational Age	Number of Days Difference
8w 0 d go 10 w 6 d	5 days
11 w 0 d – 12 w 6 d	6 days
13 w 0 d – 13 w 6 d	7 days

113

Ultrasonography Randomization

- Following enrollment sonogram 10 – 13 weeks:

Group	Gestational week for ultrasound exam				
A	16	24	30	34	38
B	18	26	31	35	39
C	20	28	32	36	40
D	22	29	33	37	41

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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

115

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

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Results

Characteristics	White (n=481)	Black (n=426)	Hispanic (n=488)	Asian (n=342)
Age, mean (SD)	30.3 (4.3)	25.5 (5.4)	26.9 (5.4)	30.5 (4.4)
BMI (kg/m^2), mean (SD)	23.1 (2.8)	24.0 (3.1)	24.2 (2.8)	22.1 (2.5)
Marital status, %				
Never married	5	48	22	6
Married/living as married	94	44	73	92
Divorced/separated	1	4	5	1
Health insurance, %				
Private/managed care	94	48	35	62
Medicaid	5	51	61	37
Self-pay	1	1	4	2

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Characteristics	White (n=481)	Black (n=426)	Hispanic (n=488)	Asian (n=342)
Education, %				
< High school	1	11	22	5
High school/GED	5	29	23	12
Some college	18	36	27	20
College undergraduate	42	16	14	31
Postgraduate college	34	9	4	33
Family income, %				
<$29,999	4	49	39	17
$30,000 - $49,999	7	19	27	12
$50,000 - $74,999	13	9	14	13
$75,000 - $99,999	19	10	7	21
≥ $100,000	58	13	13	37
Current paid jobs, %				
0	19	33	45	39
1	72	61	53	59
≥ 2	10	6	2	2

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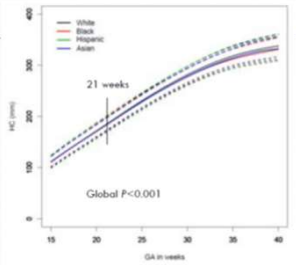
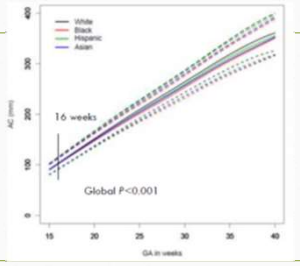
Results: Head Circumference



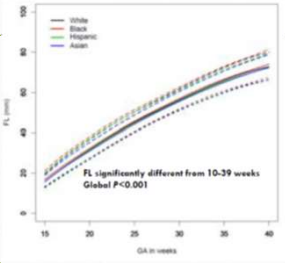
119

Results: Abdominal Circumference (AC)



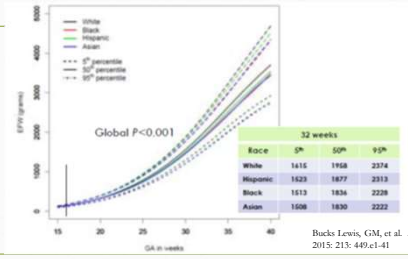
120

Results: Femur Length (FL)



121

Singleton Standard difference significantly by race/ethnicity starting at 16 weeks gestation extending to delivery

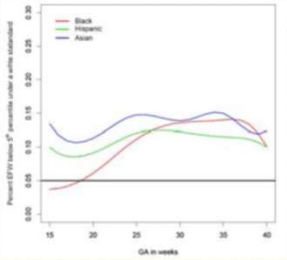


32 weeks			
Race	5th	50th	95th
White	1615	1958	2374
Hispanic	1623	1877	2313
Black	1513	1836	2228
Asian	1508	1830	2222

Bucks Lewis, GM, et al. Am J Obstet Gynecol 2015: 213: 449.e1-41

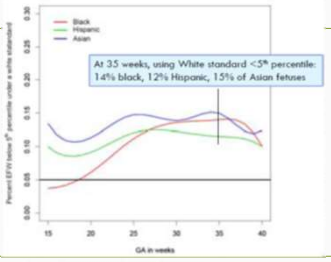
122

Results: Misclassification under White Standard



123

Results: Misclassification under White Standard



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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)

Bucks Lewis GM, et al. Am J Obstet Gynecol 2015; 213: 449.e1-41

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NICHD Standard Conclusions

- 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

Bucks Lewis GM, et al. Am J Obstet Gynecol 2015; 213: 449.e1-41

126

To pool or not to pool?

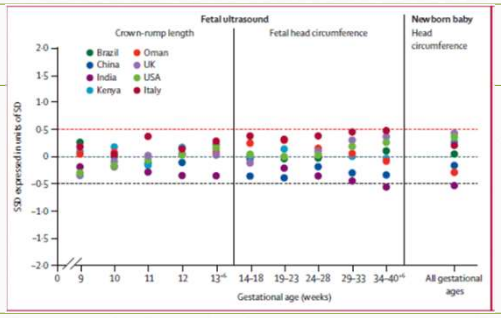
- How similar do groups have to be to pool them together into one fetal growth standard?
- Or, … how different is too different?

127

INTERGROWTH-21 Assessment of "Likeness" of Fetal Growth Across 8 Countries

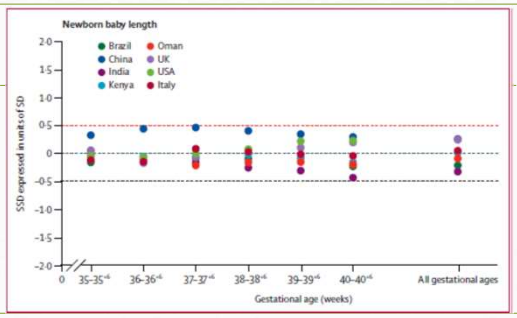
- Analysis of variance to calculate percentage of variance within site and between sites
- Calculated difference between the mean from that site ad mean of all sites together
  - Standardized site difference:
    - SDD = (individual site man – overall mean) / overall standard deviation
  - SDD from -0.5 to 0.5: Criteria to pool all sites together
- Sensitivity analysis: Repeated analyses excluding 1 site at a time (may not be sensitive enough)

128



Villar K. et al. Lancet 2014; Oct 2: 781-792

129



Villar K. et al. Lancet 2014; Oct 2: 781-792

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Table 3: Variance component analysis for CFL, fetal HC, and newborn length

	Crown-rump length (N=4265)		Fetal head circumference (N=4237)		NCSS FGLS-like subpopulation birthlength† (N=20 166)	
	Estimate (SE)	Proportion	Estimate (SE)	Proportion	Estimate (SE)	Proportion
Variance between sites	0·65 (0·38)	1·9%	5·15 (2·82)	2·6%	0·12 (0·06)	3·5%
Variance between individuals within a site	‡	–	36·64 (1·54)	18·6%	‡	–
Residual variance	33·64 (0·73)	98·1%	155·70 (3·73)	78·8%	3·34 (0·02)	96·5%

FGLS=Fetal Growth Longitudinal Study. *Adjusted by gestational age as a fixed effect. †FGLS-like subpopulation represents the low-risk proportion of the total Newborn Cross-Sectional Study (NCSS) population selected with the same eligibility criteria as FGLS. Therefore, the subpopulation also included the newborn measures obtained from those enrolled in the FGLS cohort. (Variance between individuals within sites cannot be estimated because measures were collected only once per patient (cross-sectional).

Table 3: Variance component analysis for crown-rump length, fetal head circumference, and newborn length*

Villar K. et al. Lancet 2014; Oct 2: 781-792

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What are the implications of pooling?

- A key determinant of their decision to pool across sites was whether the standardized site difference (SSD(at different gestational ages was <0.5
- Criterion could be too liberal, resulting in inappropriate pooling of sites
- To show this potential, we calculated the possibility of being below the lower limit of the standard for a particular site when the standard was constructed using data pooled across different sites for values of SDD from -0.5 to 0.5

Albert PS and Grantz KL. Lancet Diabetes Endocrinol 2014

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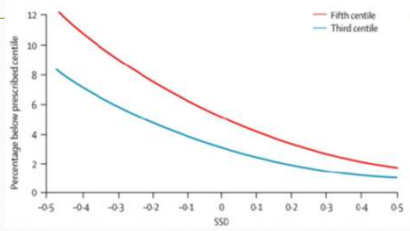
Percent below prescribed 5th and 3rd centile when using a pooled standard



Albert PS and Grantz KL. Lancet Diabetes Endocrinol 2014

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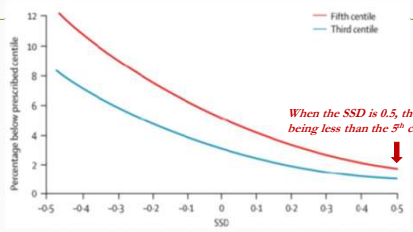
Percent below prescribed 5th and 3rd centile when using a pooled standard

When the SSD is -0.5, the probability of being less than the 5th centile is 12.6%.

Albert PS and Grantz KL. Lancet Diabetes Endocrinol 2014

134

Percent below prescribed 5th and 3rd centile when using a pooled standard

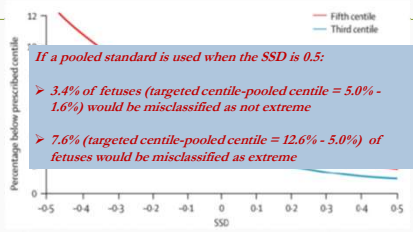


When the SSD is 0.5, the probability of being less than the 5th centile is 1.6%.

Albert PS and Grantz KL. Lancet Diabetes Endocrinol 2014

135

Percent below prescribed 5th and 3rd centile when using a pooled standard



If a pooled standard is used when the SSD is 0.5:

- *3.4% of fetuses (targeted centile-pooled centile = 5.0% - 1.6%) would be misclassified as not extreme*
- *7.6% (targeted centile-pooled centile = 12.6% - 5.0%) of fetuses would be misclassified as extreme*

Albert PS and Grantz KL. Lancet Diabetes Endocrinol 2014

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INTERGROWTH-21 Assessment of "Likeness" of Fetal Growth Across 8 Countries: Summary

- Evaluated CRL and HC only
  - CRL is known to not vary as much
  - HC also has less variation, especially early o (differences emerged at 21 weeks in the NICHD Study)
- Variations in other parameters ot evaluated
  - NICHD Study – had significant differences in AC emerged at 16 weeks, and FL starting at 10 weeks

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INTERGROWTH-21 Assessment of "Likeness" of Fetal Growth Across 8 Countries: Summary

- Only reported magnitude of within and between site variation, but never formally tested a site effect
- Some of the variances reported might be highly significant
  - Ex. Longitudinal HC, the variance of subject-level random effect was 36.64 and site-leel 5.15
- SSD is descriptive, with no formal statistical testing
  - 0.5 threshold to claim "no site effect" is somewhat arbitrary

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  - 0.5 threshold to claim "no site effect" is somewhat arbitrary
- **Conclusion: pooling ha potential for misclassification**

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Differences in Neonatal Anthropometrics for Healthy, Low-risk, Term Deliveries (IG-21)

	Brazil	China	India	Italy	Kenya	Oman	UK	USA	Total
BW, kg	3.3	3.4	2.9	3.3	3.3	4.1	3.5	3.4	3.3
Length, cm	49.0	49.7	48.6	49.4	49.1	49.0	49.9	49.9	49.3
HC, cm	34.2	33.6	33.1	34.0	34.2	33.6	34.5	34.5	33.9

Healthy women, no history of pregnancy complications, low risk for SGA or LGA
N=4,321 in FGLS analysis + N=20,486 in FGLS-like subpopulations

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NICHD vs. IG-21 Fetal Growth

NICHD

Buck Louis GM, Grewal J, Albert PS, Sciscione A, Wing DA, Grobman W, Newman R, Wapner RJ, D'Alton ME, Skupski D, Nageotte MP, Ranzini A, Owen J, Chien EK, Craigo S, Hediger ML, Kim S, Zhang C, Grantz KL. Racial/Ethnic Differences in Fetal Growth, the NICHD Fetal Growth Studies. *American Journal of Obstetrics & Gynecology*. 2015 Oct;213(4):449.e1-449.e41.

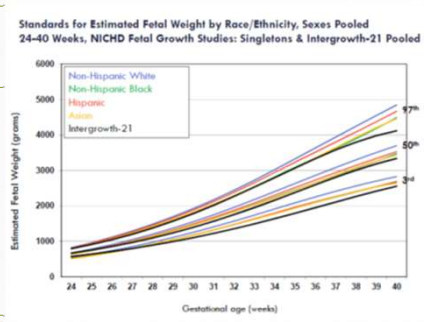
INTERGROWTH-21st

Papageorghiou AT et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. *Lancet*. 2014 Sept; 384: 869-879.

Villar J et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet*. 2014 Sept; 384: 857-868.

Stirnemann J et al. International Estimated Fetal Weight Standards of the INTERGROWTH-21st Project. *Ultrasound Obstet Gynecol*. 2016 Nov 2. doi: 10.1002/uog.17347. [Epub ahead of print]

141



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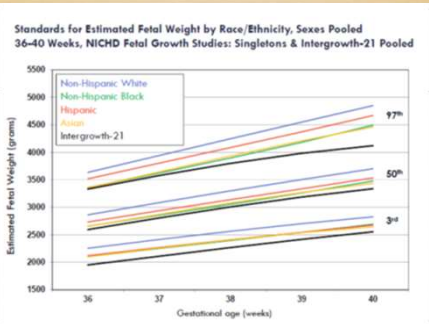

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NICHD vs. IG-21 EFW Formulas

- IG-21: created a new formula (based on HC and AC)

  $\text{Log(EFW)} = 5.084820 - 54.06633\text{x}(\text{AC}/100)^3 - 95.80076\text{x}\text{AC}/100)^3 \text{ x } \log(\text{AC}/100) + 3.136370\text{x}(\text{HC}/100)$

- NICHD: Hadlock (based on HC, AC and FL)

  $\text{Log}_{10}\text{ weight} = 1.326 - 0.00326\text{ AC x FL} + 0.0107\text{ HC} + 0.0438\text{ AC} + 0.158\text{ FL}$

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NICHD vs. IG-21 EFW: Difference due to different EFW formulas?

- Compare the percentiles of HC, AC and FL
- Use the NICHD data to compare the EFW calculated using the Hadlock formula from HC, AC, and FL and IG-21 formula
- Comparison of birthweights

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NICHD vs. IF-21 EFW: Differences are not fully explained by difference EFW formulas

- Compare the percentiles of FL, HC and AC
  - HC for NICHD whites larger than IG-21, IG-21 similar to other race/ethnic groups
  - AC for NICHD whites, Hispanic, Asian larger than IG-21, IG-21 similar for NICHD blacks
- Use the NICHD data to compare the EFW calculated using the Hadlock formula from HC, AC and FL and IG-21
  - IG-21 EFW formula performs very close to NICHD Asian race/ethnic group, but not as close for the other race/ethnic groups
- Comparison of birthweights
  - U. S. birthweights (Duryea ref) are higher than IG-21

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IG-21st EFW Formula Comments

- Formula excludes FL, reason EFW are smaller than Hadlock?
- Methods are more advanced than Hadlock, questions remain
  - Formula developed in their own cohort – applicable to other populations?
  - Which formula is more accurate?
- IG-21 makes big point that we should not rely on EFW, but use individual parameters
  - Good point
  - Big differences in the parameter %tiles between NICHD and IG-21 especially in A and FL which IG-21 did not assess for variation across sites
  - Pooling across sites still has significant potential for misclassification for the individual parameters

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Standards Summary

- Race/ethnic differences in birth weights for fetuses that are "optimally grown"
- Race/ethnic differences in fetal growth, and differences vary by the various parameters (HC, BPD, AC, FL) and EFW
- Using a pooled standard may be more convenient, but has potential for misclassification

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Distinguishing Constitutional from Pathologic Fetal Growth

- A one-time measurement (i.e., EFW <10th percentile at a given gestational age) remains standard clinical practice, in spite of recognition that a single measurement can only indicate size
- At least two measurements separated in time are needed to estimate fetal growth

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Scotland Cohort Study: Customized/Non-customized Birth Weight Centiles and Prediction of Stillbirth and Infant Mortality and Morbidity

- 979,912 term singleton pregnancies between 1992-2010
- Aim to determine birth weight thresholds at which mortality and morbidity increased and the predictive ability of non-customized and partially customized centiles to identify fetuses at risk
- Primary outcomes: infant death stillbirth, overall mortality (infant and stillbirth), Apgar score <7 at 5 min, NICU admission
- Birth weights ≤ 25th centile were associated with higher risk for all mortality and morbidity outcomes
- Stillbirth, low Apgar score, and NICU admission risk increased from the 85th centile
- Conclusion:
  - Birth weight remain strongly associated with the risk of stillbirth and infant death and neonatal morbidity.
  - **Partial customization does not improve performance**
  - Early term delivery or closer surveillance for those with a predicted birth weight ≤25th or ≥85th centile may reduce adverse outcomes

Iliodromiti S, et al. PLoS Med 1027; 14 (1): e1002228

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Defining abnormal fetal growth and perinatal risk: population or customized standards?

- Appropriate unified standards are needed
  - Two different approaches to fetal/neonatal growth assessment have been advocated
  - 1 – based on the premise that genetic factors strongly influence fetal growth (customized charts)
  - 2 – define optimal fetal growth standards at a population level (theory that growth potential is similar across populations
- WHO study created international population standard fetal growth charts. However, found significant variable in growth between countries with a difference in median birth weight of ~300 g in countries with comparable maternal complication rates (significantly greater than the difference between male and female infants. Study also concludes that charts may need to be adjusted for local use.

Kiserud T, PLoS Med 2017; 14 (1): e1002220

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Defining abnormal fetal growth and perinatal risk: population or customized standards?

- Appropriate unified standards are needed
  - Two different approaches to fetal/neonatal growth assessment have been advocated
  - 1 – based on the premise that genetic factors strongly influence fetal growth (customized charts)
  - 2 – define optimal fetal growth standards at a population level (theory that growth potential is similar across populations
- INTERGROWTH-21 aimed to create population standards for serial measurements of normal pregnancies. Study excluded women with OB conditions that may influence fetal growth and saw less variability in fetal growth between the 8 included countries.
- In contrast, significant differences in EFW between racial groups in the US was recently identified

Papageorghiou AT, et al. Lancet 2014; 384: 869-879

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Defining abnormal fetal growth and perinatal risk: population or customized standards?

- Both studies support the concept that robustly developed population growth standards are appropriate for the diagnosis of fetal growth disorders **but that thresholds of risk at relevant to local populations should be considered.**
- Whatever method is used, the benefits of detecting growth disorders can only be realized if we can effectively reduce risk of sequelae
- Using optimized charts and threshold will not prevent over-intervening in many normal cases to prevent complications in the few
- US assessment of fetal growth has its limitations
- Better methods of risk prediction are needed to prevent death and disability in babies

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Hadlock v. INTERGROWTH-21st Standards: Predicting Adverse Perinatal Outcomes in the Third Trimester

Zhu C, et al. BioMed Res International 2019; doi.org/10.1155/2019/7698038

- Study Purpose: To study the association between low EFW percentile in the 3rd trimester and the risk of APOs and compare predictions of APOs between Hadlock and INTEGROWTH 21st standard
  - Cohort, 690 singleton pregnancies, 3rd trimester U/S, between March 2015 and March 2016 in China
  - Cox proportional hazard models were used to assess the relationship between low EFW percentile (i.e., <5th %tile) and the risk of APOs
  - Compared to fetuses with ≥ 5th %tile, fetuses with <5th %tile of the EFW were much more likely to have an APO, adj hazard ratio of 35.0 (95% CI, 13.9-88.5) and 17.5 (7.7-39.6) for the Hadlock and INTERGROWTH 21st standards, respectively
- **Hadlock EFW had a higher predictive accuracy for APOs than the INTERGROWTH EFW**
- Hadlock: sensi/speci 93.9% and 81.2%, cutoff value of percentile 8.65
- INTERGROWTH: sensi/speci 87.9% and 80.5%, cutoff value of percentile 11.61
- Fetuses with low EFWs (<5th tile) were associated with an increased risk of APOs
- **APOs were more accurately predicted when EFWs were measured by the Hadlock standard**

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Comparison of the accuracy of INTERGROWTH-21 formula with other U/S formula in fetal weight estimation

Kong CW, To WWK. Taiwanese J Obstet Gynecol 2019; 58: 273-277

- Aim to compare the accuracy of determining EFW using INTERGROWTH-21 standards vs Hadlock-1 and Shepard
- All pregnant patients who delivered at United Christian Hospital (Hong Kong) between January – December 2016, U/S performed within 7 days of delivery, 403 patients recruited
- Hadlock-1, Shepard and INTERGROWTH-21 formulas were used to determine EFW and their accuracies were compared to actual birthweight of neonates
- **Lowest mean absolute percentage error:**
  - **Hadlock 7.34 Shepared 9.00 (p <0.001) INTERGROWTH-21 9.07 (p <0.001)**
  - INTERGROWTH-21 had the lowest proportion of patients having EFW within 10% discrepancy from the actual BW (57.6^
  - Hadlock-1 (71.2%, p <0.0001) and Shepard 66.3%, p = 0005
- IUGR or fetal macrosomia were both associated with significantly higher MAPE in Hadlock-1 and INTERGROWTH-21. IUGR (p – 0.005) and macrosomia (p = 0.004 remained significant in the final equation of LR model that affect the precision of EFW in Hadlock-1, while only IUGR was significant in INTERGROWTH-21 (p ,0.001)
- **Hadlock-1 and Shepard formulas continue to be more precise in determining EFW than INTERGROWTH-21**
- **Future prospective studies would be required to evaluate the accuracy of INTERGROWTH-21 formula, especially at the extremes of BW**

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Comparison of BW, Length, and HC between BRISA-RP and INTERGROWTH-21 Cohorts

Pimenta JRR, et al. J Pediatr (Rio J) 2019; pii: S0021-7557(18)31079-9 doi: 10.1016/j.jped.2019.03.003

- Objective: (A) to determine the 3rd, 50th, and 97th %tiles of BW, length and HC of newborns from Riberião Preto BRISA cohort by GA and gender versus INTERGROWTH-21 standard. (B) to estimate SGA (<3rd %tile) LGA (>97th %tile), stunting (length <3rd %tile), and wasting (BMI <3rd %tile)
- Observational study, cohort, 7,702 newborns between January-December 2010. The 3rd, 50th, and 97th %tiles were determined for the anthropometric measurements using fractional polynomial regression
- BW difference between BRISA-RP and INTERGROWTH-21 was small – more pronounced in preterm infants (mean difference between the two populations was +266 g); for full-term newborns (+66g); for post-term infants (-113g)
- Mean variation for length was always <1 cm; for HC, preterm newborns varied >1 cm and full-term and post-term showed a variation of <1 cm. SGA and LGA DR were 2.9% and 4.3%, respectively
- Stunting affected 6.5% of all newborns and wasting 1.5% with predominance in girls and in full-term pregnancies; both conditions were present in 0.4% of the sample
- **When compared to the INTERGROWTH-21 standing, newborns from Riberião Preto are heavier, longer have a larger HC until they reach full-term**

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Developing BW for GA Charts and Comparison with Current Charts in a Polish Population

Kajdy A, et al. J Matern Fetal Neonatal Med 2019; 1-8

- Aim to obtain reference curved of BW by GA %tiles for the Polish population and compare to published charts for SGA and LGA newborns
- 39,092 singleton deliveries, 24 to 42 wks gestation used for reference curves , nomograms included 3rd to 97th %tiles and SD
- **Theoretical and true proportions of %tiles were based on six growth charts [Fenton, INTERGROWTH, Global Reference Chart, Yudkin, Dubiel, and WHO chart)**
- 50th %tile male and female newborns at 40 wks weighed 3645.8 and 3486.7 g, respectively. Difference was 159.1 g
- Ranges between 3rd and 97th %tile at 40 wks were 1481.5g for males, 1423.5 g for females. Total of 9.8% SGA and 10.27% LGA were defined – higher than that identified using the Fenton charge and even higher than identified using the INTERGROWTH charts
- **Feasibility of a Polish population growth chart needs to be validated for predicting APO**

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Fenton 2013 Growth Curves vs INTERGROWTH-21 Standards to Assess IUGR and EUGR in Preterm Neonates ≤32 Wks

Reddy KV, et al. J Matern Fetal Neonatal Med 2019; 1-8

- Compare the incidence of IUGR and EUGR in preterm neonates ≤32 wks GA based on Fenton and INTERGROWTH-21 growth curves
- Retrospective cohort, tertiary care neonatal unit, all newborns with GA ≤32 wks (230 6/7 days) admitted to NICU within 24 h of birth over a 3-yr period
- 603/821 neonates included, mean BW, length and HC were 1356.683 ± 335.91 g, 39.244 + 3.124 cm and 27.819 ± 1.906 cm, respectively
- Proportion of IUGR infants with regards to BW, length, and HC were 15.1, 14.4, and 9% on both charts
- Proportion of EUGR at discharge with regards to BW, length, and HC were 45.7, 29.8, and 32.3%, respectively
- **Conclusion: proportion of IUGR infants at birth and EUGR at discharge differed on the usage of INTERGROWTH charts in comparison to Fenton growth charts. IUGR infants identified by INTERGROWTH charts alone had higher incidence of morbidities.**

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Excessive Gestational Weight Gain and the Risk of GDM: Comparison of INTERGROWTH-21, IOM Recommendations and a Local Reference

Chuvao J, et al. Diabetes Res Clin Pract 2019; 158: 107912

- To compare the abilities of INTERGROWTH-21 standards, IOM recommendations and a Chinese reference on gestational weight gain to identify women at-risk of GDM and GDM-related APO
- 13,366 women, singleton infants between 2013-2017 in Tongzhou district of Beijing, China, Poisson regression with robust error estimates used to estimate risk ratios of GDM in different GWG groups
- 39.97%, 46.31% and 39.93% of women gaining weight above the three standard. Women with GWG above INTERGROWTH and Chinese reference had 27% (aRR 1.27, 95% CI 1.16-1.37) and 30% (aRR 1.30, 95% CI, 1.21-1.40) **increased** risks of GDM respectively versus 225 (aRR, 122, 95% CI, 1.13-1.32) for IOM recommendations
- **Compared with IOM recommendations, GWG above INTERGROWTH standards or the Chinese reference was associated with higher risks of GDM and GDM-related APO. These two prospective standards could additionally assess the severity of abnormal GWG and are feasible for dynamic monitoring**.

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