INTERGROWTH-21st course on maternal, fetal and newborn growth monitoring

Course overview
This Course overview will:

Discuss some of the **conceptual issues** about fetal and newborn growth monitoring.

Introduce the INTERGROWTH-21\(^{st}\) Project: **rationale, aim, design and implementation**.

Present the **key findings** from INTERGROWTH-21\(^{st}\) Project on the likeness of early human growth.

Introduce the **INTERGROWTH-21\(^{st}\) growth standards**.

Highlight challenges in standardising the measurement of fetuses and newborns around the world.
Conceptual issues

Growth monitoring (GM) is an essential aspect of evidence-based antenatal and newborn care worldwide, as it is for infants and children.

- Poor growth places babies at risk of perinatal mortality and, longer term metabolic and cardiovascular disease.
- Overgrowth increases risks of birth trauma, need for operative delivery and childhood obesity.

There is currently no agreement on the definition of ‘normal’ or ‘abnormal’ growth around the world. (Bhutta, 2013; Villar et al., 2015).

Systematic reviews demonstrate over 100 charts in use around the world to measure the size of babies in the womb; with a further 100 for measuring newborn size at birth.

This has resulted in a situation where parents may be told their baby is small on one chart, only to be then told it is normal if a different chart is used. (Villar et al., 2015).
The difference the choice of chart can make in fetal growth monitoring.

- 3rd centile
- 15th centile

Gestational age vs. Fetal Head circumference graph.
Conceptual issues

Growth is a continuum from conception, embryonic and fetal life, to early neonatal life and infancy, until childhood and adolescence.

The first 1000 days, from conception until age 2, is recognised as a crucial window for programming life long growth and development.

Integrated standards to measure growth from fetal life through to childhood would:

• Enable longitudinal assessment of skeletal growth (i.e. fetal head circumference or postnatal length) and fat-related markers (i.e. fetal abdominal circumference or postnatal weight).

• Improve our understanding of the effects of in-utero growth problems on later life outcomes.

• Integrate maternity, neonatal and paediatric clinical care delivery.
Standards for growth monitoring

In 1994 the World Health Organization (WHO) recommended the use of prescriptive standards to monitor human growth.

Standards describe growth observed under optimal conditions (nutrition, medical, environmental, social), and by definition are independent of time of place. They are prescriptive as they describe how growth should be, rather than how it actually is.

In contrast, most growth charts in use are references, derived from observing growth in a particular time of place, and are not necessarily relevant to other populations or the same population over time.

Standards have been widely accepted and adopted in child growth monitoring.
Standards in child growth monitoring


1996 The WHO Multicentre Growth Reference Study (MGRS) established to monitor growth from birth until 5 years. 8000 healthy children selected from 5 countries that were breast fed for 6 months and from non socially deprived parents.

2006 The MGRS demonstrated the growth of children to be remarkably similar around the world justifying the release of the WHO Child Growth Standards.

2016 The WHO Child growth Standards have been adopted by over 140 member states of the United Nations.
The INTERGROWTH-21st Project

The INTERGROWTH-21st Project was established to determine whether fetal and newborn growth are similar enough around the world to produce international standards for growth monitoring.

This would enable a *unified approach* to growth monitoring from conception until 5 years of age.

- This short [video](#) introduces the INTERGROWTH-21st Project.

- Watch a Webinar on the INTERGROWTH-21st Project [here](#).
INTERGROWTH-21st

WHO Child Growth Standards

Conception 1 year 2 years 3 years 4 years 5 years
The hypothesis of the INTERGROWTH-21st Project was:

The variability in skeletal growth **WITHIN** a population is larger than the variability **BETWEEN** populations when nutrition and health needs are met.

The INTERGROWTH-21st Project was done to prove this hypothesis and produce fetal and newborn growth standards that would be applicable to women everywhere.
The aim of the INTERGROWTH-21st Project was:

To produce prescriptive growth standards, which conceptually extend the World Health Organization (WHO) Multicentre Growth Reference Study (MGRS), to cover fetal and newborn life to describe:

1. Fetal growth assessed by clinical and ultrasound measures.
2. Postnatal growth of term and preterm infants up to 2 years of age.
3. The relationship between birthweight, length and head circumference, gestational age and perinatal outcomes.
The INTERGROWTH-21st Project design:

The INTERGROWTH-21st Project was a prospective, population-based, multi-ethnic study.

The study had 3 main components:

1. **The Newborn Cross-Sectional Study (NCSS)**: a study of all newborns born in the INTERGROWTH-21st study sites over 12 months.

2. **The Fetal Growth Longitudinal Study (FGLS)**: a detailed study of fetal growth from <14+0 weeks to birth, with follow-up to age 2 in women individually at low risk of fetal growth and nutritional problems.

3. **The Preterm Postnatal Follow-up Study (PPFS)**: a detailed study of the growth of all preterm infants born to women in FGLS until age 2.
Selection of study sites

Study sites were selected to represent diverse geographic, cultural and ancestral groups where environmental and socio-economic constraints on growth were low, and women received up-to-date, evidence-based, medical care and appropriate nutrition.

<table>
<thead>
<tr>
<th>Pelotas Brazil</th>
<th>Beijing China</th>
<th>Nagpur India</th>
<th>Turin Italy</th>
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<tbody>
<tr>
<td>Nairobi Kenya</td>
<td>Muscat Oman</td>
<td>Oxford United Kingdom</td>
<td>Seattle USA</td>
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INTERGROWTH-21st Project sites

INTERGROWTH-21st sites
The selection of the populations occurred on two levels—cluster and individual.

The cluster level involved selecting a geographical area (e.g. city or part of a city with clear political or geographical limits) followed by the selection, within each area, of health institutions where women at low-medium risk for impaired fetal growth attend for antenatal/delivery care and infant follow-up.

The individual level involved selecting, within these populations and hospitals, women or newborns with specific characteristics required for the project’s different components.

The institutions selected in each geographical area delivered >80% of the eligible women in the target population with >1000 deliveries per year.
Selection of populations for the INTERGROWTH-21st Project

Study Site (city/region or any other defined geographical/political area)

Within the selected geographical area, identify a target population:
- Pregnant women at low risk for health, environmental or economic conditions known to affect fetal growth (e.g. women attending antenatal care at private hospital or similar delivery institution).

Select institution that covers at least 80% of deliveries among the target population (Developed countries: general pregnant population; Developing countries: low-risk pregnant population).
- Must fulfil the criteria for selecting an institution serving the target population (see Institution selection criteria).

All these institutions will participate in NCSS

Selection of institutions that will only provide women for FGLS and preterm follow-up

Selection of women using individual criteria to be included in FGLS

Fetal Growth Longitudinal Study (FGLS)

Preterm Postnatal Follow-up Study (PPFS)
The Fetal Growth Longitudinal Study (FGLS):

The study aimed to develop new, international, fetal growth standards using 2D ultrasound to measure the most commonly acquired dimensions of fetal size, and a new, international, symphyseal-fundal height standard.

The study population were a group of apparently healthy women who could follow basic antenatal care models.

In the initial screening process, specific factors commonly used to identify women who would benefit from low-risk routine antenatal care were selected.

To accurately determine fetal growth, accurate knowledge of gestational age was essential. In the INTERGROWTH-21st Project sites, dating by first trimester ultrasound was implemented. (Papageorghiou et al., 2014; Villar et al., 2013).
Inclusion criteria in FGLS to ensure accurate determination of gestational age

<table>
<thead>
<tr>
<th>Certain last menstrual period</th>
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<tbody>
<tr>
<td>Regular 24–32-day menstrual cycles</td>
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<tr>
<td>No hormonal contraception use or breastfeeding in the preceding 2 months</td>
</tr>
<tr>
<td>Spontaneous conception</td>
</tr>
<tr>
<td>CRL measurement between 9+0 and 13+6 weeks of gestation</td>
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<tr>
<td>Discrepancy between CRL and last menstrual period estimates ≤ 7 days</td>
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</table>

“Healthy” mother criteria for Fetal Growth Longitudinal Study

a) aged ≥18 and ≤35 years;
b) BMI ≥18.5 and <30 kg/m²;
c) height ≥ 153 cm;
d) singleton pregnancy;
e) a known LMP with regular cycles (defined as a 26-30 day cycle in the previous 3 months), without hormonal contraceptive use, pregnancy or breastfeeding in the 3 months before pregnancy;
f) natural conception

g) no relevant past medical history (refer to screening form), with no need for long-term medication (including fertility treatment and over-the-counter medicines, but excluding routine iron, folic acid, calcium, iodine or multivitamin supplement);

h) no evidence of socio-economic constraints likely to impede fetal growth identified using local definitions of social risk;
i) no use of tobacco or recreational drugs such as cannabis in the 3 months before or after becoming pregnant;
j) no heavy alcohol use (defined as > 4 units (40ml pure alcohol) per week) since becoming pregnant;
k) no more than one miscarriage in the 2 previous consecutive pregnancies;
l) no previous baby delivered preterm (<37 weeks) or with a birth weight <2500g or >4500g;
m) no previous neonatal or fetal death, previous baby with any congenital malformations, and no evidence in present pregnancy of congenital disease or fetal anomaly;
n) no previous pregnancy affected by pre-eclampsia/eclampsia, HELLP syndrome or a related pregnancy-associated condition;
o) no clinically significant atypical red cell alloantibodies;
p) negative urinalysis;
q) systolic blood pressure <140 mmHg and diastolic blood pressure < 90 mmHg;
r) haemoglobin ≥11 g/dl;
s) negative syphilis test and no clinical evidence of any other sexually transmitted diseases, including clinical Trichomoniasis;
t) not in an occupation with risk of exposure to chemicals or toxic substances, or very physically demanding activity to be evaluated by local standards. Also women should not be conducting vigorous or contact sports, as well as scuba diving or similar activities

Criteria defining a low-risk study population as healthy and well-nourished (both before and during pregnancy) to ensure that fetal growth is optimal.
Fetal Growth Longitudinal Study (FGLS)

N = 4,607

- **Pregnancy**
- **Birth**
- **1 year**
- **2 years**

**Anthropometric measurements:**
- Length/height
- Weight
- Head circumference

**Ultrasound measures:**
- 9-14 weeks
- Then every 5 ± 1 weeks

**Neurodevelopment assessment:**
- Psychometric tests
- Wireless EEG
- Actigraphy

**Ultrasound measures:**
- 9-14 weeks
- Then every 5 ± 1 weeks
Fetal Growth Longitudinal Study (FGLS)

Scans every 5 ± 1 weeks

Measurements at each scan >14±0 weeks:

- Biparietal diameter
- Occipito-frontal diameter
- Head circumference
- Transverse abdominal diameter
- Anterio-posterior abdominal diameter
- Abdominal circumference
- Femur length

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

Philips HD9

The Newborn Cross-Sectional Study (NCSS):

The study aimed to produce birthweight, length and head circumference for gestational age standards describing fetal size at birth and to provide data for epidemiological studies of the different phenotypes of the impaired fetal growth and preterm delivery syndromes.

The study also examined the relationship of size at birth with neonatal morbidity and mortality.

The study population included all newborns delivered at the selected institutions occurring over a 12 month study period.

There were two subpopulations:

1. Population selected using the FGLS entry criteria to construct the prescriptive standards of size at birth.
2. Newborns from higher-risk pregnancies. (Villar et al., 2013; Villar et al., 2014)
The Preterm Postnatal Follow-up Study (PPFS):

The study aimed to develop postnatal growth charts for preterm newborns based on the INTERGROWTH-21st conceptual principles.

All preterm newborns (≥26+0 but <37+0 weeks of gestation) from the FGLS cohort were followed for 8 months after delivery to evaluate postnatal growth.

The postnatal anthropometric measurements were weight, length and head circumference.

The three measurements (plus a standard clinical evaluation and records of morbidity and food intake) were taken every 2 weeks during the first 8 weeks, and then every 4 weeks until 8 postnatal months, using essentially the same methodology employed in MGRS. (Villar et al., 2013; Villar et al., 2015)
Anthropometric measurements at birth
Standardization

All centres followed the same, standardised, clinical care protocols as described in the following manuals:

- The Correct Measurement of Fetal Crown Rump Length and Standardization of Ultrasonographers manual: to standardize CRL measurement methodology for pregnancy dating. The same CRL regression formula was used across all study sites to interpret CRL.

- The Ultrasound Operations Manual: to standardize the ultrasound technique.

- The Anthropometry Handbook: to standardize anthropometric measurements.

- The Basic Neonatal Care Manual: to standardised neonatal care protocols. Common definitions of neonatal morbidities were used across all participating institutions.

All anthropometric measurements in the INTERGROWTH-21st Project were performed on identical equipment using a highly standardised protocol. Please see the next modules for detailed instructions on measurement technique.
Data collection

All documentation and forms used were prepared by the Project Coordinating Unit, tested at the local level and introduced into the specially developed electronic data management system.

All forms were integrated and linked to reduce duplication in the data collection process and facilitate data quality control mechanisms.

Similarities among the populations of fetuses and newborns were assessed by following the same basic principles that were adopted in MGRS.

• The main fetal indicators were CRL and head circumference, complemented as a secondary parameter by femur length.

• For all newborns and preterm infants, length at birth and in the first 8 months were used as the main indicator for the comparisons.
Strategies for Statistical Analysis

In order to determine if the results of the measurements from the 8 sites were similar enough to combine in a standard, four approaches were used:

1. Comparing crude data
2. Sensitivity analysis
3. Standardised site difference
4. Variance component analysis
Results: the INTERGROWTH-21st populations

All pregnancies in 8 sites
Newborn Cross Sectional Study NCSS
n = 59,137
Results: the INTERGROWTH-21st populations

Within the total population,
Low-risk pregnancies
n = 20,486

→ From the low-risk pregnancies in NCSS International Newborn Size at birth Standards have been produced
Results: the INTERGROWTH-21st populations

Within the low-risk pregnancies, 4,607 women consented to be in the Fetal Growth Longitudinal Study (FGLS)

Low-risk pregnancies
n = 20,486
Results: the INTERGROWTH-21st populations

Low-risk pregnancies
n = 20,486

Medium-high risk pregnancies

FGLS
n = 4,607

From FGLS the International Fetal Growth Standards have been produced
Results: Preterm births in Fetal Growth Longitudinal Study

From PPFS International Preterm Postnatal Growth Standards have been produced

Preterm Postnatal Follow-up Study PPFS (n = 193)
Results: Comparability of measurements

Taking the example of fetal head circumference, how did the results of all the sites compare?
Fetal HC by gestational age for UK, USA & Italy

Each dot represents a measurement. You can see there is near perfect overlap between babies from these high-income countries. Look at the next slides to see the measurements of babies from the other countries in INTERGROWTH-21st.
Fetal HC by gestational age for UK, USA, Italy & China

Gestational age (weeks)

HC (mm)
Fetal HC by gestational age for UK, USA, Italy, China & India
Fetal HC by gestational age for UK, USA, Italy, China, India & Kenya
Fetal HC by gestational age for UK, USA, Italy, China, India, Kenya & Oman
Fetal HC by gestational age for UK, USA, Italy, China, India, Kenya, Oman & Brazil

Thus, there was near perfect overlap of the distribution of head size in all sites.
Sensitivity analysis for fetal HC measures: The effect of excluding each country one by one
### Variance component analysis for fetal CRL and HC, and newborn length

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<tbody>
<tr>
<td></td>
<td>Fetal CRL</td>
<td>Fetal HC</td>
<td>Newborn length</td>
<td>Infant length</td>
</tr>
<tr>
<td><strong>Variance among study sites</strong></td>
<td>1.9%</td>
<td>2.6%</td>
<td>3.5%</td>
<td>3.4%</td>
</tr>
<tr>
<td><strong>Unexplained variance</strong></td>
<td>98.1%</td>
<td>97.4%</td>
<td>96.5%</td>
<td>96.6%</td>
</tr>
</tbody>
</table>

Thus most of the variation (>96%) in the size of babies is due to between site differences.
Comparison between INTERGROWTH-21st data and WHO Child Growth Standards at birth in term babies

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<th>INTERGROWTH-21st</th>
<th>WHO</th>
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<tr>
<td>Birth weight</td>
<td>3.3 (0.5) kg</td>
<td>3.3 (0.5) kg</td>
</tr>
<tr>
<td>Birth length</td>
<td>49.3 (1.8) cm</td>
<td>49.5 (1.9) cm</td>
</tr>
</tbody>
</table>

You can see that the mean size of babies born in the INTERGROWTH-21st Project at term was almost identical to the mean in the WHO MGRS study over 10 years earlier!
Thus the INTERGROWTH-21st Standards directly complement the WHO Child Growth Standards

INTERGROWTH - 21st international standards

From these findings, the INTERGROWTH - 21st Project produced international standards for:

- Early pregnancy dating by Crown-Rump length
- Fetal growth from 14 weeks to 41 weeks
- Newborn weight, length, and head circumference by gestational age and sex
- Preterm postnatal growth standards
- Maternal gestational weight gain (also references for overweight women)

An application tool, the INTERGROWTH-21st Newborn Size Application Tool, was developed to facilitate the classification of birth weight, length and head circumference according to the international newborn size standards.

Watch a seminar on the Global Standards for Fetal and Newborn growth here.
INTERGROWTH-21st Project conclusions

The use of prescriptive standards is justified by the extensive biologic, genetic, and epidemiologic evidence that skeletal growth is similar from conception to childhood across geographic populations, when health, nutrition, environmental, and health care needs are met.

The INTERGROWTH-21st Project produced international standards for gestational age estimation, first-trimester fetal size, fetal growth, newborn size for gestational age, and postnatal growth of preterm infants.


These prescriptive growth standards describe how all fetuses and newborns should grow, as opposed to traditional charts that describe how some have grown at a given place and time.
Challenges in standardising the measurement of fetuses and newborns around the world

Careful planning and implementation are required to implement the new fetal and neonatal standards on a sufficiently large scale, and use the information obtained from their implementation to evaluate and revise maternal and neonatal care programmes.

Health workers, at all levels, need to be trained to obtain the information correctly and, more importantly, to use it in clinical decision-making and actions.

Practices and norms may need to be revised and modified in accordance with the INTERGROWTH-21<sup>st</sup> standards.

Adequate planning time needs to be allocated to address issues to secure success in translating the new standards into better practices.

Meeting the challenge of achieving ‘optimal’ fetal growth would include addressing embryonic and placental growth and development.

This course overview has:

• Discussed some of the **conceptual issues** about fetal and newborn growth monitoring.

• Introduced the INTERGROWTH-21\textsuperscript{st} Project: **rationale, aim, design and implementation.**

• Presented the **key findings** from INTERGROWTH-21\textsuperscript{st} Project on the likeness of early human growth.

• Introduced the **INTERGROWTH-21\textsuperscript{st} growth standards.**

• Highlighted challenges in standardising the measurement of fetuses and newborns around the world.
For more information on the INTERGROWTH-21st Project, please visit [https://intergrowth21.tghn.org/](https://intergrowth21.tghn.org/).

Click here for an interactive e-learning module “Assessing newborn size by anthropometry”.

Click here for an interactive e-learning module "Assessing Maternal Anthropometry and Weight Gain During Pregnancy"

A similar module, “Monitoring of fetal growth by ultrasound” will be available shortly.
References


References


