

# International standards for early fetal size and pregnancy dating based on ultrasound measurement of crown-rump length in the first trimester

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**Key words:** crown-rump length; gestational age; dating; growth; pregnancy; global health;

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.13448

## Abstract

**Objectives:** There are no international standards for relating fetal crown-rump length (CRL) to gestational age (GA), and most existing charts have considerable methodological limitations. The INTERGROWTH-21<sup>st</sup> Project aimed to produce the first, international standards for early fetal size and ultrasound dating of pregnancy based on CRL measurement.

**Methods:** Urban areas in eight geographically diverse countries that met strict eligibility criteria were selected for the prospective, population-based recruitment, between 9<sup>+0</sup> to 13<sup>+6</sup> weeks of gestation, of healthy well-nourished women with singleton pregnancies at low risk of fetal growth impairment. GA was calculated on the basis of a certain LMP, regular menstrual cycle and lack of hormonal medication or breastfeeding in the preceding two months. CRL was measured using strict protocols and quality control measures. All women were followed up throughout pregnancy until delivery and hospital discharge. Neonatal and fetal deaths, severe pregnancy complications and congenital abnormalities were excluded.

**Results:** A total of 4,607 women were enrolled in the Fetal Growth Longitudinal Study (FGLS), one of the three main components of the INTERGROWTH-21<sup>st</sup> Project, of whom 4,321 women had a live singleton birth in the absence of severe maternal conditions or congenital abnormalities detected by ultrasound or at birth. The CRL was measured in 56 women at <9<sup>+0</sup> weeks of gestation, resulting in 4,265 women who contributed data to the final analysis. The mean CRL and standard deviation (SD) increased with GA almost linearly. Their relationship to GA is defined by the two equations: Mean CRL (mm) = -50.6562 + 0.815118\*GA + 0.00535302\*GA<sup>2</sup>, and SD of CRL (mm) = -2.21626 + 0.0984894\*GA, where GA is expressed in days. The formula for GA estimation is defined by the two equations: GA (days) = 40.9041 + 3.21585\*CRL<sup>0.5</sup> + 0.348956\*CRL, and SD of GA (days) = 2.39102 + 0.0193474\*CRL, where CRL is expressed in mm.

**Conclusions:** We have produced international prescriptive standards for early fetal linear size and ultrasound dating of pregnancy in the first trimester that can be used throughout the world.

## Introduction

During pregnancy, accurate estimation of gestational age (GA), at the level of the individual, is essential to interpret fetal anatomy and growth patterns <sup>1</sup>, predict the date of delivery <sup>2</sup> and gauge the maturity of the newborn.<sup>3</sup> At a population level, GA estimation is required to determine rates of small-for-GA <sup>4</sup> and preterm birth <sup>5</sup> accurately so as to allocate resources appropriately.

GA has traditionally been calculated from the first day of the last menstrual period (LMP). However, in a proportion of pregnancies, depending on the locality, the LMP is unknown or the information is unreliable.<sup>6</sup> In such cases, GA can be estimated by ultrasound measurement of fetal crown-rump length (CRL) or head circumference (HC) at <14 weeks and ≥14 weeks of gestation, respectively.<sup>7,8</sup> Between 9-13 weeks of gestation, linear growth evaluated by CRL is rapid and the standard deviation (SD) rather small, which means that GA can be estimated accurately. In later pregnancy, HC is typically used for dating as CRL can no longer be measured due to curling of the growing fetus; however, variation is greater meaning less accurate GA estimation.<sup>9</sup> For this reason, ultrasound estimation of GA during the first trimester is recommended in clinical practice.<sup>8</sup>

Various studies have been conducted to derive CRL reference charts to estimate GA, mostly in single institutions or geographical locations. A review of their methodological quality has shown several limitations including highly heterogeneous study designs and approaches to statistical analysis and reporting.<sup>10</sup> All the studies have been “descriptive”, whereas we have consistently argued that “prescriptive” standards should be used in clinical practice, reflecting how fetuses *should* grow rather than how they have grown in a given place and time. This is achieved by first selecting pregnant populations at low risk of fetal growth impairment, living in environments with minimal exposure to factors that have an adverse effect on growth. From such populations, women at low risk of adverse pregnancy outcomes who deliver healthy newborns without congenital malformations are then identified.<sup>11-13</sup>

Our aim, therefore, was to generate CRL data according to GA using an optimal study design and prescriptive approach so as to develop international, population-based, standards for early fetal linear size and ultrasound dating of pregnancy in the first trimester that can be used throughout the world.

## Methods

INTERGROWTH-21<sup>st</sup> is a multicentre, multiethnic, population-based project, conducted between 2008 and 2013 in eight countries: the cities of Pelotas, Brazil; Turin, Italy; Muscat, Oman; Oxford, UK; Seattle, USA; Shunyi County, Beijing, China; the central area of the city of Nagpur (Central Nagpur), Maharashtra, India; and the Parklands suburb of Nairobi, Kenya.<sup>13</sup> Its primary aim was to study growth, health, nutrition and neurodevelopment from <14<sup>+0</sup> weeks of gestation to 2 years of age, using the same conceptual framework as the WHO Multicentre Growth Reference Study (MGRS)<sup>12</sup>, so as to produce prescriptive growth standards to complement the existing WHO Child Growth Standards.<sup>14</sup>

These urban areas had to be located at low altitude (<1,600m); women receiving antenatal care had to plan to deliver in these institutions or in a similar hospital located in the same geographical area and there had to be an absence or low levels of major, known, non-microbiological contamination such as pollution, domestic smoke, radiation or any other toxic substances, evaluated during the study period at the cluster level using a data collection form specifically developed for the project. In the eight urban areas, we selected all institutions providing pregnancy and intrapartum care where >80% of deliveries occurred.<sup>15</sup>

To generate the CRL data for our stated aims, women with a singleton pregnancy that was conceived naturally were asked to participate in the Fetal Growth Longitudinal Study (FGLS), one of the three main components of the INTERGROWTH-21<sup>st</sup> Project. The study methods have been described in detail elsewhere.<sup>13</sup> Briefly, we recruited women from the selected populations with no clinically relevant obstetric or gynaecological history, who met the entry criteria of optimal health, nutrition, education and socio-economical status so as to create a group of educated, affluent, clinically healthy women who were at low risk of intrauterine growth restriction and preterm birth. Recruitment occurred prospectively and consecutively at 9<sup>+0</sup> to 13<sup>+6</sup> weeks of gestation by LMP provided that: (1) the date was certain; (2) the agreement between LMP and CRL dating was  $\leq 7$  days; (3) they had a regular 24–32 day menstrual cycle, and (4) they had not been using hormonal contraception or breastfeeding in the preceding two months. The women, who were all well-educated and living in urban areas, reported the date and certainty of their LMP at their first antenatal clinic visit in response to specific questions.

A single ultrasound machine (Philips HD-9; Philips Ultrasound, Bothell, WA, USA) with an abdominal probe was the machine of choice to measure CRL. However, as the first contact with the study often occurred at several clinics in the geographical area, it was considered acceptable to use other, locally available, machines for the CRL measure at the first

antenatal visit only provided that they were evaluated and approved by the study team. All the ultrasonographers (n=39) at the eight study sites underwent rigorous training and standardisation specifically for the CRL measures.<sup>16</sup> In accordance with the study's quality control protocol, they also submitted images of the CRL measures, which were reviewed blindly by our collaborators at the Société Française pour l'Amélioration des Pratiques Echographiques (SFAPE). The ultrasonographers were only certified to measure CRL in the study if they demonstrated adequate knowledge of the study protocol and the quality of the images submitted for review was satisfactory.<sup>17</sup>

CRL was measured once using strict techniques and image criteria.<sup>18</sup> A >7 day discrepancy between the gestational ages based on LMP and CRL was a reason not to include the woman in the study. All women were then followed to delivery with standardised antenatal care evaluation and regular ultrasound scans every 5±1 weeks. The INTERGROWTH-21<sup>st</sup> Project was approved by the Oxfordshire Research Ethics Committee "C" (ref: 08/H0606/139), the research ethics committees of the individual participating institutions, as well as the corresponding regional health authorities where the project was implemented.

### *Statistical methods*

The sample size was based principally on the precision and accuracy of a single centile and regression based reference limits.<sup>18, 19</sup> We have shown that with a sample of 4000, we would obtain precision of 0.03SD at the 3rd or 97th centile. Further details on the precision obtained at the 5th or 10th centiles by sample size (ranging from a sample of 500 – 6000) are provided in a previous publication.<sup>20</sup> We determined a mean target sample of 500 women per site, after excluding complicated pregnancies and those lost to follow-up.<sup>20</sup> We expected that overall approximately 3% would be lost to follow-up, and that another 3% would be excluded (using criteria decided *a priori*) from the study population because of fetal/neonatal losses and congenital abnormalities. We also excluded mothers diagnosed with catastrophic or very severe medical conditions; those with severe unanticipated pregnancy-related conditions requiring hospital admission, and those identified during pregnancy who no longer fulfilled all the entry criteria.

The statistical methods used are described in detail elsewhere.<sup>21</sup> Briefly, data were first explored visually by a scatter plot of CRL by GA and vice versa. The relationship between GA and CRL is non-linear although the distribution of CRL is conditionally normal at any given GA. We applied fractional polynomial (FP) models to the data by fitting separate models to the mean and standard deviation (SD) of GA to account for increases in variance with greater CRL and gestation.<sup>22, 23</sup> Using equations of the mean and SD one can easily compute any desired centiles using the relation:

$$P^{\text{th}} \text{ centile} = \text{Mean CRL} \pm z \times \text{SD}$$

where  $z$  is the normal equivalent deviate ( $z$  score) corresponding to a particular centile, e.g.  $z = -1.88, -1.645, -1.28, 0, 1.28, 1.645, \text{ and } 1.88$  for the 3<sup>rd</sup>, 5<sup>th</sup>, 10<sup>th</sup>, 50<sup>th</sup>, 90<sup>th</sup>, 95<sup>th</sup> and 97<sup>th</sup> centiles, respectively; and the SDs in this equation are the predicted estimates from the regression analysis.

To overcome the effect of data truncation at the limits of recruitment at 9<sup>+0</sup> and 13<sup>+6</sup> weeks of gestation, we explored three alternative statistical approaches.<sup>21</sup> Truncation occurs when data are constrained by a restricted range of GA; such a restriction is commonly put in place for recruitment reasons, but also because fetal curling prevents accurate measurement beyond 13<sup>+6</sup> weeks.<sup>22</sup> In our analysis, all three statistical approaches gave very similar results, and we opted for one (simulation for small and large CRL) as it had the best fit at both the upper and lower ends of GA.

Fitted curves (3<sup>rd</sup>, 50<sup>th</sup>, and 97<sup>th</sup> centiles) from different models were assessed visually for a good fit and by comparing the deviances from each model. Goodness of fit was assessed by a scatter plot of the distribution of residuals in  $z$  scores by CRL and also by counting the number of observations below the 3<sup>rd</sup> and above the 97<sup>th</sup> centiles. Assessment of increasing variability with gestation, and smooth changes of both mean and SD across GA, were undertaken as part of the fractional polynomial approach.

## Results

Of the 13,108 pregnant women screened between May 2009 and July 2013 at the eight study sites, 4,607 (35%) met the clinical eligibility criteria and were enrolled in the study. All the women were closely followed up throughout pregnancy by the study team until delivery and hospital discharge. A total of 4,324 women had live singleton births in the absence of severe maternal conditions or congenital abnormalities detected by ultrasound or at birth. The sample size per country ranged from 311 in the USA to 640 in the UK. The overall maternal and pregnancy outcome characteristics are shown in Table 1. The CRL was measured in 56 women at <9<sup>+0</sup> weeks of gestation, resulting in 4,268 women who contributed data to the final analysis (Figure 1).

As we have reported elsewhere, the evaluation of the similarities in CRL across the eight populations was performed using variance component analysis, standardised site difference and sensitivity analysis. All three analytical strategies demonstrated that the populations were similar enough to justify pooling the data.<sup>25</sup>

The mean fetal size and SD increased with GA (Table 2, Figure 2). Their relationship to GA is defined by the two equations below in which GA is expressed in days of gestation:

$$\text{Mean CRL (mm)} = -50.6562 + 0.815118 \cdot \text{GA} + 0.00535302 \cdot \text{GA}^2$$

$$\text{SD of CRL (mm)} = -2.21626 + 0.0984894 \cdot \text{GA}$$

The data were then used to create a dating equation to allow GA estimation (as a dependent variable) in all women by measuring CRL (as an independent variable) (Fig 3, Table 3). The relationship is defined by the two equations below in which CRL is expressed in mm:

$$\text{GA (days)} = 40.9041 + 3.21585 \cdot \text{CRL}^{0.5} + 0.348956 \cdot \text{CRL}$$

$$\text{SD of GA (days)} = 2.39102 + 0.0193474 \cdot \text{CRL}$$

For the goodness of fit analysis, mean residuals by week of gestation expressed in z scores did not show any obvious pattern (-0.12, 0.00, -0.05, -0.06, 0.03 and 0.14 at 9, 10, 11, 12, 13 and 14 weeks of gestation, respectively).

## Discussion

We have studied a large, international cohort of women from eight diverse geographical locations worldwide, with minimal constraints on fetal growth at both population and individual level (i.e. a prescriptive approach to growth evaluation), so as to construct standards for CRL size and the corresponding GA estimation in the first trimester of pregnancy. These populations were judged to be similar enough to be pooled into a single cohort. This is the first time that an *international*, early fetal linear size standard and equation for GA estimation have been produced. When fully implemented they will allow for uniform, early pregnancy evaluation at all levels of health care across the world. Using the same standard to identify abnormal conditions early in pregnancy or make diagnoses is routine practice in most areas of medicine and long overdue for obstetric care.

Our study has a number of important methodological and conceptual strengths. Firstly, we included a diverse range of geographical locations and populations from different ethnic backgrounds around the world to make the findings as generalisable as possible. This is of special relevance today given the extent of multiethnic populations and children of admixed parents. Secondly, unified protocols were used for recruitment, clinical care until hospital discharge and data collection, and rigorous quality control processes were employed. Thirdly, the study was purposely prospective and population-based, and only included singleton pregnancies that were conceived naturally with a certain LMP. Fourthly, only healthy women sampled from preselected, geographically defined populations with low adverse perinatal outcome rates were selected. Lastly, all participants were studied to the end of pregnancy, but women were excluded if fetal/neonatal deaths, severe pregnancy

complications or congenital abnormalities occurred. This cohort of women, therefore, had the greatest potential for achieving optimal fetal growth.

The approach has allowed us to create an international *prescriptive standard* of early fetal growth. This is crucial for estimating GA because it is based on the assumption that the CRL values are from healthy fetuses that remained so for the remainder of the pregnancy. We based our strategy and rationale on the knowledge gained from our recent systematic review of existing charts for GA estimation, which showed that the overall quality of study design, statistical analysis and reporting was less than optimal.<sup>10</sup> Only 8 of the 29 previous studies identified and enrolled unselected or low-risk pregnancies, and while almost all the studies reported using some of the FGLS inclusion/exclusion criteria, no study used all of them. A comprehensive strategy for ultrasound quality control was not employed in any of the 29 studies. Many studies have also resulted from retrospective analysis of large databases of routinely collected clinical data. Such retrospective studies are at high risk of bias as the quality of the recorded data is variable and the ability to perform prospective ultrasound quality assurance is curtailed. In contrast, clinical application of our standard globally will allow fetal size centiles to be plotted uniformly, making comparisons of fetal size and gestational age across populations easier to interpret.

Furthermore, we compared our GA equation from the pooled eight different geographical and ethnic populations with the two studies selected during the systematic review with the lowest risk of methodological bias<sup>24, 25</sup> and that were conducted in populations with adequate medical care and nutrition conditions in developed countries making them potentially eligible for the INTERGROWTH-21<sup>st</sup> Project. Interestingly and reassuringly for the global introduction into clinical practice of our new international standards, only very small differences were seen that are of no clinical relevance in estimating GA from CRL values.

The first of these studies, carried out in 1973 in Scotland, was an analysis of 214 CRL measurements in 80 patients<sup>25</sup>; the second was a population-based study in the Netherlands between 2002 and 2006 with 2,079 individual CRL measurements.<sup>25</sup> The difference in both studies in the GA estimation was  $\pm 1$  day of gestation, except for CRL>80mm where the difference between the INTERGROWTH-21<sup>st</sup> equation and that by *Verburg et al* (2008)<sup>25</sup> approached and then exceeded 2 days at CRL>85mm. These striking similarities suggest that early linear fetal growth evaluated by CRL measures appears to be uniform both over time and among different ethnic populations once they have reached an adequate level of health, nutrition and socio-economic conditions, reinforcing the appropriateness of using international standards.



A potential limitation of our study was the use of multiple ultrasonographers as it has previously been argued that reference studies should be performed by a single operator in order to reduce inter-observer error. In our opinion, this is not appropriate: it produces small studies concentrated in a single practice; devalues the contribution of international, multicentre studies; reduces external validity, and fails to recognise that clinical services are delivered in most institutions by many members of staff. Rather, studies should account for the variability introduced by ultrasonographers by taking steps to improve the quality and consistency of measurements through standardisation, audit and quality control of all aspects of ultrasound.<sup>16, 17, 26</sup>

A disadvantage of GA estimation purely based on ultrasound measures of fetal anatomical parameters is that all biological variation in GA for a given value of CRL disappears - an assumption that is of course biologically implausible. This is not a problem peculiar to ultrasound but any other biological parameter being predicted by a single measure. We therefore suggest that all information collected at the time of the first antenatal visit (including the reported LMP and assessment of its reliability) should be taken into account when estimating GA or assessing fetal growth during future antenatal visits.<sup>30</sup> When a reliable LMP and ultrasound estimate concur, small adjustments in GA may mask inherent CRL measurement error. Conversely, an apparently reliable and accurate LMP with a substantial difference in GA estimation based on CRL should be considered as an indicator of possible growth disturbance or underlying pathology that needs to be monitored and corroborated.<sup>27</sup> Finally, it is important to emphasise that all estimates should be presented to women with the corresponding measure of variability, e.g. SD or percentiles, to provide a measure of the error of the estimation.

In short, we have presented, building on the experience of decades of ultrasound work conducted by others, international standards for evaluating fetal linear size in the first trimester and the corresponding new GA estimate equation from CRL values to be used across countries and populations. The new GA estimations are in close agreement with studies with low risk of methodological bias conducted in populations from developed countries, suggesting that when high methodological standards are met and populations adequately selected, early fetal growth is similar across populations. The adoption of these standards, through their introduction into ultrasound machines and fetal database systems, will standardise the evaluation of fetal growth across levels of care and facilitate comparisons internationally.

**Financial Disclosure Statement:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**Conflict of Interest Statement:** The authors have indicated they have no conflict of interest to disclose.

## Acknowledgements

This project was supported by a generous grant (no.49038) from the Bill & Melinda Gates Foundation to the University of Oxford, for which we are very grateful. We would also like to thank the Health Authorities in Pelotas, Brazil; Beijing, China; Nagpur, India; Turin, Italy; Nairobi, Kenya; Muscat, Oman; Oxford, UK and Seattle, USA, who facilitated the project by allowing participation of these study sites as collaborating centres. We are extremely grateful to Philips Healthcare for providing the ultrasound equipment and technical assistance throughout the project. We also thank MedSciNet U.K. Ltd for setting up the INTERGROWTH-21<sup>st</sup> web-site and for the development, maintenance and support of the on-line data management system.

We thank the parents and infants who participated in the studies and the more than 200 members of the research teams who made the implementation of this project possible. The participating hospitals included: Brazil, Pelotas (Hospital Miguel Piltcher, Hospital São Francisco de Paula, Santa Casa de Misericórdia de Pelotas, and Hospital Escola da Universidade Federal de Pelotas); China, Beijing (Beijing Obstetrics & Gynecology Hospital, Shunyi Maternal & Child Health Centre, and Shunyi General Hospital); India, Nagpur (Ketkar Hospital, Avanti Institute of Cardiology Private Limited, Avantika Hospital, Gurukrupa Maternity Hospital, Mulik Hospital & Research Centre, Nandlok Hospital, Om Women's Hospital, Renuka Hospital & Maternity Home, Saboo Hospital, Brajmonhan Taori Memorial Hospital, and Somani Nursing Home); Kenya, Nairobi (Aga Khan University Hospital, MP Shah Hospital and Avenue Hospital); Italy, Turin (Ospedale Infantile Regina Margherita Sant' Anna and Azienda Ospedaliera Ordine Mauriziano); Oman, Muscat (Khoula Hospital, Royal Hospital, Wattayah Obstetrics & Gynaecology Poly Clinic, Wattayah Health Centre, Ruwi Health Centre, Al-Ghoubra Health Centre and Al-Khuwair Health Centre); UK, Oxford (John Radcliffe Hospital) and USA, Seattle (University of Washington Hospital, Swedish Hospital, and Providence Everett Hospital).

Full acknowledgement of all those who contributed to the development of the INTERGROWTH-21<sup>st</sup> Project protocol appears at [www.intergrowth21.org.uk](http://www.intergrowth21.org.uk)

## References

1. Miller J, Turan S, Baschat AA. Fetal growth restriction. *Seminars in perinatology* 2008; **32**(4): 274-80.
2. Taipale P, Hiilesmaa V. Predicting delivery date by ultrasound and last menstrual period in early gestation. *Obstet Gynecol* 2001; **97**(2): 189-94.
3. Ananth CV. Menstrual versus clinical estimate of gestational age dating in the United States: temporal trends and variability in indices of perinatal outcomes. *Paediatr Perinat Epidemiol* 2007; **21 Suppl 2**: 22-30.
4. Callaghan WM, Dietz PM. Differences in birth weight for gestational age distributions according to the measures used to assign gestational age. *American journal of epidemiology* 2010; **171**(7): 826-36.
5. Lawn JE, Gravett MG, Nunes TM, Rubens CE, Stanton C, Group GR. Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data. *BMC Pregnancy Childbirth* 2010; **10 Suppl 1**: S1.
6. Lynch CD, Zhang J. The research implications of the selection of a gestational age estimation method. *Paediatr Perinat Epidemiol* 2007; **21 Suppl 2**: 86-96.
7. Nguyen TH, Larsen T, Engholm G, Moller H. Increased adverse pregnancy outcomes with unreliable last menstruation. *Obstet Gynecol* 2000; **95**(6 Pt 1): 867-73.
8. Health NCCfWsaCs. Antenatal care routine care for the healthy pregnant woman. [www.nice.org.uk/nicemedia](http://www.nice.org.uk/nicemedia) (accessed 19 September 2013).
9. Kalish RB, Thaler HT, Chasen ST, Gupta M, Berman SJ, Rosenwaks Z, Chervenak FA. First- and second-trimester ultrasound assessment of gestational age. *Am J Obstet Gynecol* 2004; **191**(3): 975-978.
10. Napolitano R, Dhami J, Ohuma EO, Ioannou C, Conde-Agudelo A, Kennedy SH, Villar J, Papageorgiou AT. Pregnancy dating by fetal crown-rump length: systematic review of charts. *BJOG*. 2014 Apr; **121**:556-65
11. Ioannou C, Talbot K, Ohuma E, Sarris I, Villar J, Conde-Agudelo A, Papageorgiou AT. Systematic review of methodology used in ultrasound studies aimed at creating charts of fetal size. *BJOG* 2012; **119**(12): 1425-39.

12. Garza C, de Onis M. Rationale for developing a new international growth reference. *Food Nutr Bull* 2004; **25**(1 Suppl): S5-14.
13. Villar J, Altman DG, Purwar M, Noble JA, Knight HE, Ruyan P, Cheikh Ismail L, Barros FC, Lambert A, Papageorghiou AT, Carvalho M, Jaffer YA, Bertino E, Gravett MG, Bhutta ZA, Kennedy SH; International Fetal and Newborn Growth Consortium for the 21st Century. The objectives, design and implementation of the INTERGROWTH-21st Project. *BJOG* 2013; **120 Suppl 2**: 9-26.
14. de Onis M, Garza C, Onyango AW, Martorell R. WHO Child Growth Standards. *Acta Paediatr* 2006; **450**: 1-101.
15. Eskenazi B, Bradman A, Finkton D, Purwar M, Noble JA, Pang R, Burnham O, Cheikh Ismail L, Farhi F, Barros FC, Lambert A, Papageorghiou AT, Carvalho M, Jaffer YA, Bertino E, Gravett MG, Altman DG, Ohuma EO, Kennedy SH, Bhutta ZA, Villar J; International Fetal and Newborn Growth Consortium for the 21st Century. A rapid questionnaire assessment of environmental exposures to pregnant women in the INTERGROWTH-21st Project. *BJOG* 2013; **120 Suppl 2**: 129-38.
16. Ioannou C, Sarris I, Hoch L, Salomon LJ, Papageorghiou AT; International Fetal and Newborn Growth Consortium for the 21st Century. Standardisation of crown-rump length measurement. *BJOG* 2013; **120 Suppl 2**: 38-41.
17. Sarris I, Ioannou C, Ohuma EO, Altman DG, Hoch L, Cosgrove C, Fathima S, Salomon LJ, Papageorghiou AT; International Fetal and Newborn Growth Consortium for the 21st Century. Standardisation and quality control of ultrasound measurements taken in the INTERGROWTH-21st Project. *BJOG* 2013; **120 Suppl 2**: 33-7.
18. Bellera CA, Hanley JA. A method is presented to plan the required sample size when estimating regression-based reference limits. *J Clin Epidemiol* 2007; **60**(6): 610-5.
19. Royston P. Constructing time-specific reference ranges. *Stat Med* 1991; **10**(5): 675-90.
20. Altman D, Ohuma E. Statistical considerations for the development of prescriptive fetal and newborn growth standards in the INTERGROWTH-21st Project. *BJOG* 2013; **120 Suppl 2**: 71-6.
21. Ohuma E, Papageorghiou AT, Villar J, Altman DG. Estimation of gestational age in early pregnancy from crown-rump length when gestational age range is truncated: the case study of the INTERGROWTH-21st Project. *BMC Medical Research Methodology* 2013; **13**.
22. Altman DG, Chitty LS. Design and analysis of studies to derive charts of fetal size. *Ultrasound in Obstetrics and Gynecology* 1993; **3**(6): 378-84.
23. Royston P, Altman DG. Regression Using Fractional Polynomials of Continuous Covariates: Parsimonious Parametric Modelling. *Journal of the Royal Statistical Society Series C (Applied Statistics)* 1994; **43**(3): 429-67.
24. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. *Br J Obstet Gynaecol* 1975; **82**(9): 702-10.
25. Verburg BO, Steegers EA, De Ridder M, Snijders RJ, Smith E, Hofman A, Moll HA, Jaddoe VW, Witteman JC. New charts for ultrasound dating of pregnancy and assessment of fetal growth:

longitudinal data from a population-based cohort study. *Ultrasound Obstet Gynecol* 2008; **31**(4): 388-96.

26. Papageorghiou AT, Sarris I, Ioannou C, Todros T, Carvalho M, Pilu G, Salomon LJ; International Fetal and Newborn Growth Consortium for the 21st Century. Ultrasound methodology used to construct the fetal growth standards in the INTERGROWTH-21st Project. *BJOG* 2013; **120 Suppl 2**: 27-32.

27. Mukri F, Bourne T, Bottomley C, Schoeb C, Kirk E, Papageorghiou AT. Evidence of early first-trimester growth restriction in pregnancies that subsequently end in miscarriage. *BJOG* 2008; **115**(10): 1273-8.

## **Appendix I: Members of the International Fetal and Newborn Growth Consortium for the 21<sup>st</sup> Century (INTERGROWTH-21<sup>st</sup>) and its Committees**

### **Scientific Advisory Committee**

M Katz (Chair from January 2011), MK Bhan, C Garza, S Zaidi, A Langer, PM Rothwell (from February 2011), Sir D Weatherall (Chair until December 2010).

### **Steering Committee**

ZA Bhutta (Chair), J Villar (Principal Investigator), S Kennedy (Project Director), DG Altman, FC Barros, E Bertino, F Burton, M Carvalho, L Cheikh Ismail, WC Chumlea, MG Gravett, YA Jaffer, A Lambert, P Lumbiganon, JA Noble, RY Pang, AT Papageorgiou, M Purwar, J Rivera, C Victora.

### **Executive Committee**

J Villar (Chair), DG Altman, ZA Bhutta, L Cheikh Ismail, S Kennedy, A Lambert, JA Noble, AT Papageorgiou.

### **Study Co-ordinating Unit**

J Villar (Head), S Kennedy, L Cheikh Ismail, A Lambert, AT Papageorgiou, M Shorten, L Hoch (until May 2011), HE Knight (until August 2011), EO Ohuma (from September 2010), C Cosgrove (from July 2011), I Blakey (from March 2011).

### **Data Analysis Group**

DG Altman (Head), EO Ohuma, J Villar.

### **Data Management Group**

DG Altman (Head), F Roseman, N Kunnawar, SH Gu, JH Wang, MH Wu, M Domingues, P Gilli, L Juodvirsiene, L Hoch (until May 2011), N Musee (until June 2011), H Al-Jabri (until October 2010), S Waller (until June 2011), C Cosgrove (until April 2013), EO Ohuma (from September 2010), D Yellappan (from November 2010), A Carter (from July 2011), D Muninzwa (from October 2011), D Reade (from June 2012), R Miller (from June 2012).

**Ultrasound Group**

AT Papageorgiou (Head), LJ Salomon (Senior external advisor), A Leston, A Mitidieri, F Al-Aamri, W Paulsene, J Sande, WKS Al-Zadjali, C Batiuk, S Bornemeier, M Carvalho, M Dighe, P Gaglioti, N Jacinta, S Jaiswal, JA Noble, K Oas, M Oberto, E Olearo, MG Owende, J Shah, S Sohoni, T Todros, M Venkataraman, S Vinayak, L Wang, D Wilson, QQ Wu, S Zaidi, Y Zhang, P Chamberlain (until September 2012), D Danelon (until July 2010), I Sarris (until June 2010), J Dhami (until July 2011), C Ioannou (until February 2012), CL Knight (from October 2010), R Napolitano (from July 2011), C Pace (from January 2011), V Mkrtychyan (from June 2012).

**Anthropometry Group**

L Cheikh Ismail (Head), WC Chumlea (Senior external advisor), F Al-Habsi, ZA Bhutta, A Carter, M Alija, JM Jimenez-Bustos, J Kizidio, F Puglia, N Kunnawar, H Liu, S Lloyd, D Mota, R Ochieng, C Rossi, M Sanchez Luna, YJ Shen, HE Knight (until August 2011), DA Rocco (from June 2012), IO Frederick (from June 2012).

**Neonatal Group**

ZA Bhutta (Head), E Albernaz, M Batra, BA Bhat, E Bertino, P Di Nicola, F Giuliani, I Rovelli, K McCormick, R Ochieng, RY Pang, V Paul, V Rajan, A Wilkinson, A Varalda (from September 2012).

**Environmental Health Group**

B Eskenazi (Head), LA Corra, H Dolk, J Golding, A Matijasevich, T de Wet, JJ Zhang, A Bradman, D Finkton, O Burnham, F Farhi.

**Participating countries and local investigators**

*Brazil:* FC Barros (Principal Investigator), M Domingues, S Fonseca, A Leston, A Mitidieri, D Mota, IK Sclowitz, MF da Silveira.

*China:* RY Pang (Principal Investigator), YP He, Y Pan, YJ Shen, MH Wu, QQ Wu, JH Wang, Y Yuan, Y Zhang.

*India:* M Purwar (Principal Investigator), A Choudhary, S Choudhary, S Deshmukh, D Dongaonkar, M Ketkar, V Khedikar, N Kunnawar, C Mahorkar, I Mulik, K Saboo, C Shembekar, A Singh, V Taori, K Tayade, A Somani.

*Italy:* E Bertino (Principal Investigator), P Di Nicola, M Frigerio, G Gilli, P Gilli, M Giolito, F Giuliani, M Oberto, L Occhi, C Rossi, I Rovelli, F Signorile, T Todros.

*Kenya:* M Carvalho (Principal Investigator), J Kizidio, R Ochieng, J Shah, W Stones, S Vinayak, N Musee (until June 2011), C Kisiang'ani (until July 2011), D Muninzwa (from August 2011).

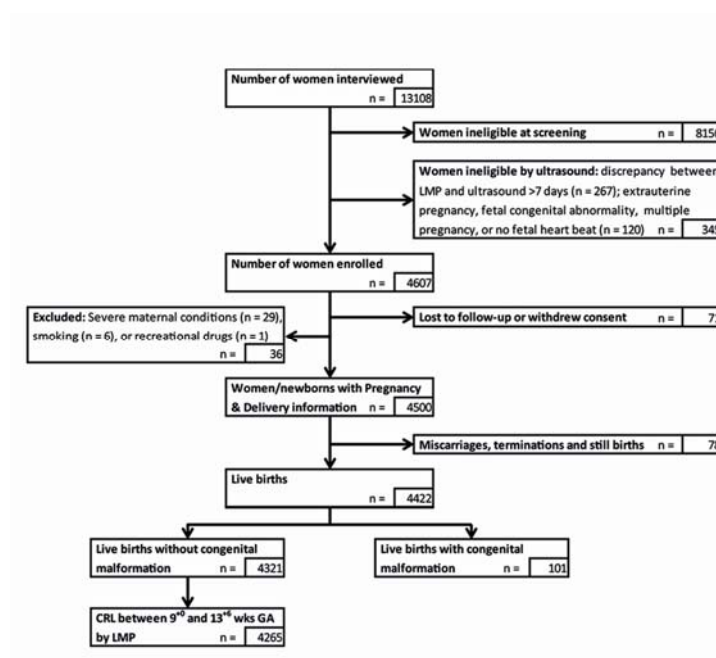
*Oman:* YA Jaffer (Principal Investigator), J Al-Abri, J Al-Abduwani, FM Al-Habsi, H Al-Lawatiya, B Al-Rashidiya, WKS Al-Zadjali, FR Juangco, M Venkataraman, H Al-Jabri (until October 2010), D Yellappan (from November 2010).

*UK:* S Kennedy (Principal Investigator), L Cheikh Ismail, AT Papageorgiou, F Roseman, A Lambert, S Lloyd, R Napolitano (from July 2011), C Ioannou (until February 2012), I Sarris (until June 2010),

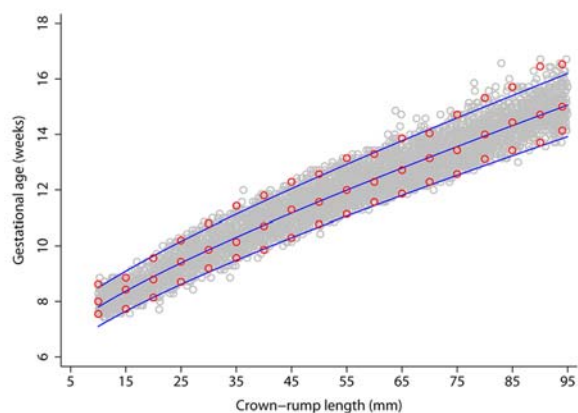
*USA:* MG Gravett (Principal Investigator), C Batiuk, M Batra, S Bornemeier, M Dighe, K Oas, W Paulsene, D Wilson, IO Frederick, HF Andersen, SE Abbott, AA Carter, H Algren, DA Rocco, TK Sorensen, D Enquobahrie, S Waller (until June 2011).



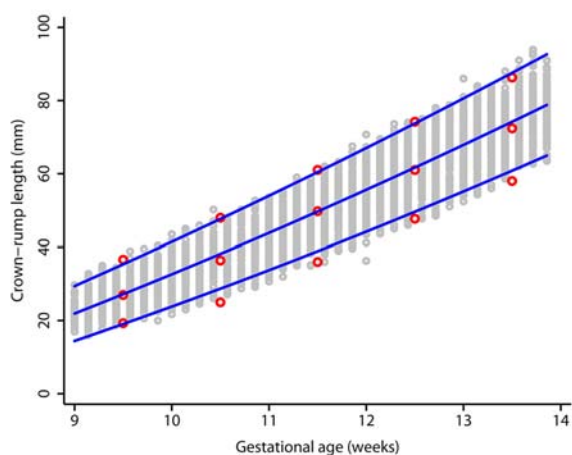
1) Flow diagram of the progress of women through the study. Congenital malformations diagnosed by ultrasound during pregnancy or at birth during clinical examination.



2) Fetal crown-rump length (CRL) (mm) size as a function of gestational age. Raw data (grey open circles) are plotted and the solid lines represent the mean, 3rd and 97th centiles ( $\pm 1.88$  SD). The red open circles represent the empirical means, 3rd and 97th centiles.



3) Estimation of gestational age (weeks) as a function of crown-rump length (CRL) (mm). The lines represent the mean, 3rd and 97th centiles ( $\pm 1.88$  SD) of gestational age for a given CRL value. The red open circles represent the empirical means, 3rd and 97th centiles.



**Table 1. Maternal and pregnancy characteristics of the 4,321 women enrolled in the Fetal Growth Longitudinal Study of the INTERGROWTH-21<sup>st</sup> Project who had a live singleton birth in the absence of severe maternal conditions or congenital abnormalities detected by ultrasound or at birth.**

Indicator	Mean (SD) or n (%)
Maternal age (years)	28.4 (3.9)
Maternal height (cm)	162.2 (5.8)
Paternal height (cm)	174.4 (7.3)
Maternal weight (kg)	61.3 (9.1)
Body Mass Index (kg/m <sup>2</sup> )	23.3 (3.0)
Gestational age at first visit (weeks)	11.8 (1.4)
Years of formal education (years)	15.0 (2.8)
Haemoglobin level before 15 weeks of gestation (g/dl)	12.5 (1.1)
Married/cohabiting, n (%)	4204 (97.3)
Nulliparous, n (%)	2955 (68.4)
Spontaneous initiation of labour, n (%)	2868 (66.4)
Caesarean section, n (%)	1541 (35.7)
Preterm (<37 <sup>+0</sup> weeks of gestation), n (%)	195 (4.5)
NICU admission >1 day, n (%)	240 (5.6)
Neonatal mortality, n (%)	7 (0.2)
Male sex, n (%)	2149 (49.7)
Birthweight (kg) (≥37 <sup>+0</sup> weeks of gestation only)	3.3 (0.4)
Birth head circumference (cm) (≥37 <sup>+0</sup> weeks of gestation only)	49.4 (1.9)
Birth length (cm) (≥37 <sup>+0</sup> weeks of gestation only)	33.9 (1.3)

All values are Mean (SD) for continuous variables and n (percentages) for categorical variables

NICU = Neonatal Intensive Care Unit

**Table 2. Sample size for each week of gestation reporting mean crown-rump length and standard deviation (mm).**

Gestational age (weeks)	n	CRL mm (mean)	CRL mm (Standard Deviation)
9 <sup>+0</sup> to 9 <sup>+6</sup>	554	27.47	4.83
10 <sup>+0</sup> to 10 <sup>+6</sup>	587	36.23	6.10
11 <sup>+0</sup> to 11 <sup>+6</sup>	972	49.39	6.62
12 <sup>+0</sup> to 12 <sup>+6</sup>	1279	60.78	7.07
13 <sup>+0</sup> to 13 <sup>+6</sup>	876	72.53	7.29

CRL = crown-rump length

**Table 3. Chart for pregnancy dating based on crown-rump length (CRL).**

	3 <sup>rd</sup> percentile		10 <sup>th</sup> percentile		50 <sup>th</sup> percentile		90 <sup>th</sup> percentile		97 <sup>th</sup> percentile	
CRL (mm)	Weeks	Days	Weeks	Days	Weeks	Days	Weeks	Days	Weeks	Days
15	7	5	7	6	8	3	8	6	9	1
16	7	5	8	0	8	3	9	0	9	1
17	7	6	8	1	8	4	9	1	9	2
18	8	0	8	1	8	5	9	1	9	3
19	8	0	8	2	8	6	9	2	9	4
20	8	1	8	3	8	6	9	3	9	4
21	8	2	8	3	9	0	9	4	9	5
22	8	2	8	4	9	1	9	4	9	6
23	8	3	8	5	9	1	9	5	10	0
24	8	4	8	5	9	2	9	6	10	0
25	8	4	8	6	9	3	9	6	10	1
26	8	5	9	0	9	3	10	0	10	2
27	8	6	9	0	9	4	10	1	10	3
28	8	6	9	1	9	5	10	1	10	3
29	9	0	9	2	9	5	10	2	10	4
30	9	0	9	2	9	6	10	3	10	5
31	9	1	9	3	10	0	10	3	10	5
32	9	2	9	3	10	0	10	4	10	6
33	9	2	9	4	10	1	10	5	11	0
34	9	3	9	5	10	2	10	5	11	0
35	9	3	9	5	10	2	10	6	11	1
36	9	4	9	6	10	3	11	0	11	2
37	9	5	9	6	10	3	11	0	11	2
38	9	5	10	0	10	4	11	1	11	3
39	9	6	10	1	10	5	11	2	11	4
40	9	6	10	1	10	5	11	2	11	4
41	10	0	10	2	10	6	11	3	11	5
42	10	0	10	2	10	6	11	4	11	5
43	10	1	10	3	11	0	11	4	11	6
44	10	1	10	3	11	1	11	5	12	0
45	10	2	10	4	11	1	11	5	12	0
46	10	3	10	5	11	2	11	6	12	1
47	10	3	10	5	11	2	12	0	12	2
48	10	4	10	6	11	3	12	0	12	2
49	10	4	10	6	11	4	12	1	12	3
50	10	5	11	0	11	4	12	1	12	3
51	10	5	11	0	11	5	12	2	12	4
52	10	6	11	1	11	5	12	3	12	5

53	10	6	11	1	11	6	12	3	12	5
54	11	0	11	2	11	6	12	4	12	6
55	11	0	11	3	12	0	12	4	12	6
56	11	1	11	3	12	1	12	5	13	0
57	11	2	11	4	12	1	12	6	13	1
58	11	2	11	4	12	2	12	6	13	1
59	11	3	11	5	12	2	13	0	13	2
60	11	3	11	5	12	3	13	0	13	2
61	11	4	11	6	12	3	13	1	13	3
62	11	4	11	6	12	4	13	1	13	4
63	11	5	12	0	12	4	13	2	13	4
64	11	5	12	0	12	5	13	3	13	5
65	11	6	12	1	12	6	13	3	13	5
66	11	6	12	1	12	6	13	4	13	6
67	12	0	12	2	13	0	13	4	14	0
68	12	0	12	2	13	0	13	5	14	0
69	12	1	12	3	13	1	13	5	14	1
70	12	1	12	3	13	1	13	6	14	1
71	12	2	12	4	13	2	14	0	14	2
72	12	2	12	4	13	2	14	0	14	2
73	12	3	12	5	13	3	14	1	14	3
74	12	3	12	5	13	3	14	1	14	4
75	12	4	12	6	13	4	14	2	14	4
76	12	4	13	0	13	4	14	2	14	5
77	12	5	13	0	13	5	14	3	14	5
78	12	5	13	1	13	6	14	4	14	6
79	12	6	13	1	13	6	14	4	14	6
80	12	6	13	2	14	0	14	5	15	0
81	13	0	13	2	14	0	14	5	15	1
82	13	0	13	3	14	1	14	6	15	1
83	13	1	13	3	14	1	14	6	15	2
84	13	1	13	4	14	2	15	0	15	2
85	13	2	13	4	14	2	15	0	15	3
86	13	2	13	5	14	3	15	1	15	3
87	13	3	13	5	14	3	15	1	15	4
88	13	3	13	6	14	4	15	2	15	4
89	13	4	13	6	14	4	15	3	15	5
90	13	4	14	0	14	5	15	3	15	6
91	13	5	14	0	14	5	15	4	15	6
92	13	5	14	1	14	6	15	4	16	0
93	13	5	14	1	14	6	15	5	16	0
94	13	6	14	1	15	0	15	5	16	1
5	13	6	14	2	15	0	15	6	16	1