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Fetal Growth Velocity Standards from the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project

Eric O. Ohuma, PhD, José Villar, MD, Yuan Feng, PhD, Luo Xiao, PhD, Laurent Salomon, MD, Fernando C. Barros, MD, Leila Cheikh Ismail, PhD, William Stones, MD, Yasmin Jaffer, MD, Manuela Oberto, MD, J Alison Noble, PhD, Michael Gravett, MD, Wu Qingqing, MD, Cesar G. Victora, MD, Ann Lambert, PhD, Paola Di Nicola, MD, Manorama Purwar, MD, Zulfiqar A. Bhutta, PhD, Stephen H. Kennedy, MD, Aris T. Papageorghiou, for the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st Project)

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F y of the INTERGROWTH-21st Project

Eric O OHUMA PhD[1,2*], José Villar MD[3,4], YUAN Feng PhD[5], LUO Xiao PhD[5], Laurent SALOMON MD[6], Fernando C BARROS MD[7], Leila CHEIKH ISMAIL PhD[8], William STONES MD [9], Yasmin JAFFER MD[10], Manuela OBERTO MD[11], J Alison NOBLE PhD[12], Michael GRAVETT MD[13], WU Qingqing MD[14], Cesar G VICTORA MD[15], Ann LAMBERT PhD[3], Paola DI NICOLA MD[16], Manorama PURWAR MD[17], Zulfiqar A BHUTTA PhD[18], Stephen H KENNEDY MD[3,4], Aris T PAPAGEORGHIOU[3,4.] for the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st Project)

[1] Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine Research Building, Old Road Campus, Roosevelt Drive, Headington, Oxford OX3 7FZ, UK
[2]Maternal, Adolescent, Reproductive & Child Health (MARCH) Centre, London School of Hygiene &Tropical Medicine (LSHTM), London, UK
[3]Nuffield Department of Women's & Reproductive Health, University of Oxford, UK
[4]Oxford Maternal & Perinatal Health Institute, Green Templeton College, University of Oxford, Oxford, UK
[5]Department of Statistics, North Carolina State University, Raleigh, NC 27695, USA
[6]Department of Obstetrics and Fetal Medicine, Hôpital Necker Enfants Malades, Université Paris Descartes, Paris, France
[7]Programa de Pós-Graduação em Saúde e Comportamento, Universidade Católica de Pelotas, Pelotas, Brazil
[8]Clinical Nutrition and Dietetics Department, University of Sharjah, Sharjah, United Arab Emirates
[9]Faculty of Health Sciences, Aga Khan University, Nairobi, Kenya
[10]Department of Family & Community Health, Ministry of Health, Muscat, Sultanate of Oman
[11]S.C. Ostetricia 2U, Città della Salute e della Scienza di Torino, Italy
[12]Department of Engineering Science, Institute of Biomedical Engineering, University of Oxford, Oxford, UK
[13]Departments of Obstetrics & Gynecology and of Public Health, University of Washington, Seattle 98195 WA USA
[14]Department of Ultrasound, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China
[15]Programa de Pós-Graduação em Epidemiologia, Universidade Federal de Pelotas, Pelotas, Brazil
[16]Dipartimento di Scienze Pediatriche e dell' Adolescenza, Terapia Intensiva Neonatale Ospedale TINO, Torino
[17]Nagpur INTERGROWTH-21st Research Centre, Ketkar Hospital, Nagpur, India
[18]Center for Global Child Health, Hospital for Sick Children, Toronto, Canada

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Corresponding author*

Eric Ohuma, BSc (Hons), MSc, D.Phil, CStat
Senior Medical Statistician
Centre for Tropical Medicine and Global Health
Nuffield Department of Medicine
The Peter Medawar Building, University of Oxford,
South Parks Road, Oxford, OX1 3SY, UK
Email: eric.ohuma@ndm.ox.ac.uk

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Fetal Growth Velocity Standards from the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project

Short title:

Fetal Growth Velocity Standards

AJOG at a glance

A. Why was the study conducted

To identify fetuses at risk of adverse outcomes because actual rates of skeletal and organ growth differ across time, and insults at different time-points during pregnancy almost certainly have differential effects on growth.

B. What are the key findings

We present fetal velocity standards using fetal data collected prospectively in a rigorous scientific manner from low-risk women, whose newborns have been followed until 2 years of age. We provide an App that can easily be used in clinical practice to evaluate changes in fetal size as conditional velocity for a more refined assessment of fetal growth than is possible at present

C. What does this study add to what is already known

These standards may be valuable if one wants to study the pathophysiology of fetal growth comprehensively. They perfectly complement our existing fetal growth standards (distance), which are already being used clinically in many settings.

A

BACKGROUND: Human growth is susceptible to damage from insults, particularly during periods of rapid growth. Identifying those periods and the normative limits that are compatible with adequate growth and development are the first key steps towards preventing impaired growth.

OBJECTIVE: To construct international fetal growth velocity increment and conditional velocity standards from 14 to 40 weeks' gestation based on the same cohort that contributed to the INTERGROWTH-21st Fetal Growth Standards.

STUDY DESIGN: Prospective, longitudinal study of 4,321 low-risk pregnancies from eight geographically diverse populations in the INTERGROWTH-21st Project with rigorous standardization of all study procedures, equipment, and measurements that were performed by trained ultrasonographers. Gestational age was accurately determined clinically and confirmed by ultrasound measurement of crown-rump length at <14 weeks' gestation. Thereafter, the ultrasonographers, who were masked to the values, measured the fetal head circumference (HC), biparietal diameter (BPD), occipitofrontal diameter (OFD), abdominal circumference (AC) and femur length (FL) in triplicate every 5 weeks (within 1 week either side) using identical ultrasound equipment at each site (4-7 scans per pregnancy). Velocity increments across a range of intervals between measures were modelled using fractional polynomial regression.

RESULTS: Peak velocity was observed at a similar gestational age: 16- and 17-weeks' gestation for HC (12.2 mm/week), and 16 weeks' gestation for AC (11.8 mm/week) and FL (3.2 mm/week). However, velocity growth slowed down rapidly for HC, BPD, OFD and FL, with an almost linear reduction towards term that was more marked for FL. Conversely, AC velocity remained relatively steady throughout pregnancy. The change in velocity with gestational age was more evident for HC, BPD, OFD and FL than for AC when the change was expressed as a percentage of fetal size at 40 weeks' gestation. We have also shown how to obtain accurate conditional fetal velocity based on our previous methodological work.

CONCLUSION: The fetal skeleton and abdomen have different velocity growth patterns during intrauterine life. Accordingly, we have produced international Fetal Growth Velocity Increment Standards to complement the INTERGROWTH-21st Fetal Growth Standards so as to monitor fetal wellbeing comprehensively worldwide. Fetal growth velocity curves may be valuable if one wants to study the pathophysiology of fetal growth. We provide an App that can easily be used in clinical practice to evaluate changes in fetal size as conditional velocity for a more refined assessment of fetal growth than is possible at present (https://lxiao5.shinyapps.io/fetal_growth/).

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In

Fetal anthropometric measurements, assessed by ultrasound scanning during pregnancy, are taken as an indirect means of assessing fetal size. Values are plotted on one of the many reference charts available, which have been developed using a variety of methods and varying scientific rigor.[1, 2] Size measures at the extreme ends, e.g. below the 3rd, 5th or 10th centiles or above the 90th, 95th or 97th centiles, of an often locally derived reference distribution, are typically interpreted as markers of growth impairment for the purpose of identifying fetuses at increased risk of adverse perinatal outcomes.

However, size and growth are not synonymous terms – a fact that is frequently ignored or misunderstood.[3-6] Size is an individual measure taken at a specific point in time; repeated size measures represent distant variations in size. In contrast, growth is a change in a measure per unit of time – hence, a dynamic process.[3, 7] Specific charts for each objective should have been purposely derived from several anthropometric measures obtained longitudinally from the same fetuses and expressed as distance or velocity measures.[5, 8-10] Charts should conform to the recommendations of the World Health Organization (WHO) for monitoring human growth and be based on the ‘prescriptive’ approach, i.e. they should be international standards, derived from healthy populations that have minimal nutritional, environmental or socio-economic constraints on growth.[11]

To our knowledge, the only published international fetal growth charts that conform completely to the WHO prescriptive recommendations are those constructed using data from the INTERGROWTH-21st Fetal Growth Longitudinal Study (FGLS).[12-14] However, the use of such ‘distance’ growth charts in clinical practice may not be sufficient to identify fetuses at risk of adverse outcomes because: 1) actual rates of skeletal and organ growth differ across time and 2) insults at different time-points during pregnancy almost certainly have differential effects on the growth and development of the skeleton and individual organs.[15] It should, therefore, be self-evident that the concept of the differential growth velocity of fetal structures is in conflict with the practice of using single summary indicators of fetal growth, such as estimated fetal weight (EFW). To illustrate the point, poor placental nutrient transfer in the second trimester of pregnancy leads to early onset fetal growth restriction (FGR) including impaired skeletal growth,[16] whilst in later pregnancy it leads to depletion of fetal fat stores.[17]

Thus, to complement the existing international INTERGROWTH-21st Fetal Growth (*Distance)* Standards,[12] we present here international Fetal Growth (*Velocity Increment and Conditional Velocity)* Standards, based on the same serial ultrasound measures obtained from the FGLS cohort. We also provide an easy to use App that enables assessment of velocity increment and conditional velocity for fetal head circumference (HC), biparietal diameter (BPD), occipitofrontal di [illegible] (FL) (https://lxiao5.shinyapps.io/fetal_growth/). The App is freely available with the other INTERGROWTH-21st tools at (https://intergrowth21.tghn.org/standards-tools/).

Materials & Methods

Design

INTERGROWTH-21st was a multicenter, population-based project, carried out between 2009 and 2016, in eight delimited urban areas: Pelotas, Brazil; Turin, Italy; Muscat, Oman; Oxford, UK; Seattle, WA, USA; Shunyi County, a suburban district of the Beijing municipality, China; the central area of the city of Nagpur (Central Nagpur), Maharashtra, India; and the Parklands suburb of Nairobi, Kenya.[12] At each study site, we recruited women with no clinically relevant obstetric, gynecological or medical history, who initiated antenatal care $<14^{+0}$ weeks' gestation by menstrual dates and met the entry criteria of optimal health, nutrition, education and socio-economic status. This resulted in a group of educated, affluent, clinically healthy women, with adequate nutritional status, who by definition were at low risk of FGR and preterm birth. A detailed description of the entry criteria and definitions has been published previously.[12]

The last menstrual period (LMP) was used to calculate gestational age provided that: a) the date was certain; b) the woman had a regular 24-32 day menstrual cycle; c) she had not been using hormonal contraception or breastfeeding in the preceding 2 months, and d) any discrepancy between the gestational ages based on LMP and crown-rump length (CRL), measured by ultrasound at 9^{+0} to 13^{+6} weeks from the LMP was ≤7 days, using the formula described by Robinson & Fleming.[18] To ensure that CRL measures were interpreted consistently, the Robinson & Fleming formula was loaded into all the study ultrasound machines; whenever another machine had to be used locally for CRL measurement, a conversion table extracted from the same formula was provided. The CRL technique was also standardized across sites and all ultrasonographers were uniformly trained.[19]

FGLS was one of the nine component studies of the INTERGROWTH-21st Project, which has been described in detail elsewhere.[12-14, 20] Briefly, FGLS involved performing serial examinations with the same ultrasound machine (Philips HD-9, Philips Ultrasound, USA) every 5 weeks (within 1 week either side) after an initial scan <14 weeks' gestation that confirmed the certain clinical dates; hence, the possible ranges of scan visits were at 14-18, 19-23, 24-28, 29-33, 34-38 and 39-42 weeks' gestation. At each visit after 14 weeks' gestation, the fetal measures obtained were HC, BPD, OFD, AC and FL. Each parameter was measured in triplicate from three separately obtained images of each structure. These studies have provided robust evidence of the similarities in skeletal growth from early pregnancy to 2 years of age in the infants of healthy w[illegible] to neurodevelopment[14, 20]

The measurement protocol, including masking the ultrasonographer to the values, and the unique training, standardization and quality control procedures have been reported elsewhere [21-24]. In brief, ultrasonographers were recruited based on their technical experience, motivation, reliability and ability to speak the local language(s). They underwent rigorous training consisting of acquiring theoretical knowledge and familiarity with the study protocol, ultrasound machine and operations manual, data collection and quality control measures. Centralized hands-on training and initial standardization were also conducted.[12] In addition, site-specific standardization was conducted at regular intervals by the Ultrasound Quality Control Unit, based in Oxford, to ensure proper use of the ultrasound equipment, calibration and adherence to the protocol. A quality control system was implemented throughout the study based on: 1) assessing the distributions of the three masked measurements taken for HC, BPD, OFD, AC and FL at each scan and 2) the Ultrasound Quality Control Unit taking a random 10% sample of all ultrasound images, assessing their quality using a validated scoring system and remeasuring them.[24] Only after three measurements of each structure were recorded was each average value revealed to the ultrasonographer for clinical purposes. The reproducibility of the fetal ultrasound measurements has been previously reported. [25]

The cohort enrolled in FGLS was followed up to 2 years of age and evaluated for their skeletal growth, nutrition, health and the WHO gross motor milestones.[20, 26]

The INTERGROWTH-21st Project was approved by the Oxfordshire Research Ethics Committee "C" (reference: 08/H0606/139), the research ethics committees of the individual participating institutions, and the corresponding regional health authorities where the project was implemented. Participants provided written consent to be involved in the study. All documentation, protocols, data collection forms and clinical tools are freely available on the INTERGROWTH-21st website (https://intergrowth21.tghn.org/).

Statistical methodology

The decision to pool the data from all the study sites to construct fetal velocity increment standards was based on our detailed, previously published analyses of the same data,[14] using the strategy recommended in the WHO Multicentre Growth Reference Study,[27] that produced the WHO Child Growth Standards.[28] Our overall aim was to produce velocity increments that change smoothly with gestational age and maximize simplicity, without compromising model fit; we have, in [illegible]ical considerations for the analysis of the FGLS data are described in detail elsewhere.[29, 30]

Velocity increment

Velocity increment was calculated as the difference between two ultrasound measures denoted by Y_1 and Y_2, divided by the time interval between them, i.e., t_1, and t_2, respectively.[31-34] The velocity increment rate of growth per week is therefore:

Velocity increment = $(Y_2 – Y_1) / (t_2 – t_1)$ mm/week.

Velocity increments per week were modelled as a function of gestational age at the mid-time-point between any pair of observations on a continuous scale using fractional polynomial regression.[35] To account for increasing variability with gestational age, the mean and standard deviation (SD) were modelled separately using fractional polynomial regression [35] of the best fitting powers for HC, BPD, OFD, AC and FL. To determine velocity increments, we analyzed pairs of observations taken during the course of the serial ultrasound examinations performed every 5 weeks (within 1 week either side).

Goodness of fit incorporated visual inspection of overall model fit by comparing empirical centiles (calculated per complete week of gestation, e.g. 38 weeks = 38^{+0} to 38^{+6}) to the fitted centiles, using quantile-quantile (q-q) plot of the residuals, plots of residuals vs. fitted values, and the distribution of fitted Z-scores across gestational ages.

The fitted models were used to obtain velocity centiles on the relative change over each gestational week. Velocity increments were computed as the average relative change for the average week-specific measurement. These velocities were determined across gestational ages from 16 to 40 weeks, and for each fetal biometry.

Conditional velocity

In the context of this paper, we considered conditional velocity as the rate of growth (often referred to as growth velocity) which evaluates velocity, based on the change in relative attained size between two time-points.[34, 36] A velocity Z-score of zero denotes perfect tracking whereas one above or below zero represents faster or slower growth than expected between the specified times. However, an important consideration is the well-known phenomenon of regression to the mean [37] as many, but not all, small fetuses will on average ‘catch-up’ and many, but not all, large fetuses will ‘catch-down’.[38] Regression to the mean has far-reaching implications,[37, 39, 40] not often accounted for, especially when assessing velocity. The correlation coefficient is a direct measure of regression to the mean.[38, 39, 41] The conditional standard deviation scores (cSDS) account for regression to the mean by adjusting for the correlation between the two time-points.[38]

Th [illegible] s of the correlation between any pair of fetal HC, BPD, OFD, AC or FL measures between 14 and 40 weeks' gestation has recently been published.[42] In brief, to account for non-normality of fetal measurements, we applied a two-stage approach. The first stage involved finding a suitable transformation of the raw fetal measurements as the marginal distributions of ultrasound measurements were non-normal using LMS transformation [43] of three parameters (location, scale, and skewness using Box-Cox Cole-Green distribution [43]) and four parameters (location, scale, skewness, and kurtosis using Box-Cox *t*-distribution [44] and Box-Cox power exponential distribution [45]) to standardised deviations (Z-scores). In the second stage, a correlation model for a Gaussian process is fitted, yielding a correlation for any pair of observations made between 14 and 40 weeks of gestation. To model correlations, parametric and non-parametric models were used. Four exponential parametric models were applied and because growth measurements might have non-ignorable measurements errors, a nugget effect term for the exponential model was also explored, as well as two non-parametric models for modelling correlation. Further details are presented in a pervious report. [42].

We used the correlation coefficients from this work to calculate the fetal conditional velocity for HC, BPD, OFD, AC and FL using the cSDS approach.[38]

The FGLS data were converted to Z-scores using the published international INTERGROWTH-21st Fetal Growth (*Distance)* Standards derived from the same data.[12] Let fetal biometry Z-scores be denoted by Z_1 and Z_2 at time-points t_1 and t_2, and correlation coefficient r_{12} between them. The cSDS between the two time-points is given by:

$$\text{cSDS} = (Z_2 - r_{12} \times Z_1) / \sqrt{(1 - r_{12}^2)}, \quad \text{Equation 1}$$ [38]

where $t_1 < t_2$, Z_1 is the Z-score at t_1, Z_2 is the Z-score at t_2, and r_{12} is the correlation coefficient between Z_1 and Z_2 [38].

All analyses were performed in STATA, version 11.2, software (StataCorp LP, College Station, Texas, USA) and R statistical software.

Results

Overall results

In the original FGLS, a total of 4,321 women had live singleton births in the absence of severe maternal conditions or congenital abnormalities detected by ultrasound or at birth; this forms the included study sample. The median number of ultrasound scans (excluding the dating scan) was 5.0 (mean = 4.9, SD = 0.8, range from 4 to 7) and 97% of women had ≥ 4 scans (mean = 5.0, SD

= ame population was used for the present analysis.

The high protocol adherence meant that the intervals between adjacent measurements were mostly 4- (n=3,836), 5- (n=8,871), or 6- (n=2,411) weeks, or intervals involving a combination or multiples of the 4-, 5- and 6-week intervals: 8- (n=721), 9-(n=2,817), 10- (n=5,186), 11- (n=1,932), and 12- (n=356) weeks. In total, 20,030 fetal measures were used to construct the Fetal Growth Velocity Standards.

A scatter plot of increments in raw HC, AC, BPD, OFD and FL data (mm/week) and the fitted 3^{rd}, 50^{th} and 97^{th} smoothed centiles according to gestational age (weeks) is shown in Figure 1 and Supplementary Figure 1.

The baseline characteristics of the study cohort across the eight urban areas have previously been shown to be very similar, which was expected because women were selected using the same clinical and demographic criteria (supplementary Table 1). The pregnancy and perinatal events for the complete cohort, which confirmed their status as healthy women at low risk of impaired fetal growth have also been published before.[12] In addition, the infant cohort remained healthy with adequate growth, motor development and associated behaviours up to 2 years of age, [20, 46] supporting its appropriateness for the construction of the INTERGROWTH-21^{st} Fetal Growth (*Distance)* Standards[12] and associated Preterm Postnatal Growth Standards.[47]

Velocity increments

The rate of growth for HC was highest at 16- and 17-weeks' gestation (12.2 mm/week), and the velocity slowed down with an almost linear reduction (9.7 mm/week at 28 weeks versus 6.1 mm/week at 35 weeks' gestation) towards term (Figure 1, Table 1A). For BPD, peak velocity was observed at 19- and 20-weeks' gestation (3.2 mm/week) (Supplementary Figure 1, Table 1B). OFD had an earlier observed peak velocity at 16 weeks' gestation (4.51 mm/week) (Supplementary Figure 1, Table 1C). A similar pattern of growth was seen with the other skeletal measure (FL). The rate of FL growth was highest very early in pregnancy at 16 weeks' gestation: mean 3.2 mm/week, reduced to 2.2mm/week at 28 weeks and 1.8 mm/week at 34 weeks' gestation (Figure 1, Table 1D). FL velocity decreased linearly with increasing gestational age.

Conversely, the velocity growth for AC (consisting of abdominal organs and subcutaneous fat) was relatively steady across most gestational ages, from 16 weeks (mean 11.8 mm/week), to 10.4 mm/week at 28 weeks, to 9.7 mm/week at 34 weeks' gestation. This pattern is clearly different from that of HC (Figure 1, Table 1E).

Figure 2 shows the velocity increment growth presentations of fetal HC, AC, and FL relative to the expected attained size at 40 weeks' gestation according to the published international

IN 33 weeks / 33.4 cm at 40 weeks) of the HC size at term has been reached by 33 weeks' gestation (Figure 2).

The change in velocity with gestational age was more clearly seen in the skeletal markers for HC, BPD, OFD and FL compared with AC when expressed as a percentage of size at 40 weeks' gestation [12] (Figure 2 and Supplementary Figure 2). AC gain is steady at around 3% per week (range: 2.7%, 3.4%) of the total size at term; HC gain is close to 4% of the term size per week at 16 weeks and <1% after 36 weeks' gestation (range: 0.8%, 3.7%). FL gain is highest in early pregnancy and decreases linearly with advancing gestational age (range: 2%, 4.5%).

Tables 1A-E present the predicted 3rd, 5th, 10th, 50th, 90th, 95th and 97th centiles for velocity increments between 14 and 40 weeks' gestation for HC, BPD, OFD, AC and FL respectively to match the previously published Fetal Growth *(Distance)* Standards.[12] The corresponding equations for the mean and SD from the fractional polynomial regression models for each measure are presented in Table 2, allowing for calculations by readers of any desired centiles or Z-scores according to gestational age. For example, centiles can be calculated as mean ± Z×SD, where Z is -1.88, -1.645, -1.28, 0, 1.28, 1.645 and 1.88 for the 3rd, 5th, 10th, 50th, 90th, 95th and 97th centiles, respectively. Printable charts and related tools will be available free of any charge at http://www.intergrowth.org.uk.

Conditional velocity

We randomly selected measures across different gestational ages and used the fitted correlations and observed Z-scores [12] to illustrate conditional velocity (cSDS) for a single fetus according to gestational age. For demonstration purposes, we show in Figures 3A-D, four hypothetical fetal HC growth scenarios likely to be observed during pregnancy: a fetus that exhibits the expected average rate of growth throughout pregnancy (Scenario A); a fetus whose longitudinal pattern of growth exhibits possible microcephaly (Scenario B); a fetus whose pattern of growth is within 2 SD of an established fetal HC standard (Scenario C); and a fetus whose longitudinal pattern of growth exhibits possible macrosomia (Scenario D).

These calculations and visual illustrations are embedded in the R-shiny application (App) (https://lxiao5.shinyapps.io/shinycalculator/). In addition, the App converts fetal measures to Z-scores according to the international Fetal Growth *(Distance)* Standards of the INTERGROWTH-21st Project;[12] enables correlations to be calculated between any pair of fetal biometry measures to calculate conditional velocity (cSDS), and calculates velocity increments for HC, BPD, OFD, AC and FL (https://lxiao5.shinyapps.io/shinycalculator/).

Comment

Principal findings

We have described growth velocity increment and estimated velocity standards, as well as conditional velocity, using highly standardized ultrasound measures of the skeleton and abdominal organs/fat of fetuses from the FGLS cohort of the INTERGROWTH-21st Project. This is the same cohort from which not only the INTERGROWTH-21st Fetal Growth *(Distance)* Standards were developed,[12] but also the international standards for: i) Symphysis-Fundal Height,[48] ii) Gestational Weight Gain,[49] iii) Early and Late Pregnancy Dating,[50] iv) Estimated Fetal Weight,[51] v) Newborn Body Composition,[52] and vi) the Postnatal Growth of Preterm Infants.[47] Hence, the new velocity standards allow, for the first time, distance and velocity growth *in utero* to be assessed using longitudinal growth trajectories from the same international populations of pregnant women at low risk for adverse health, nutritional and environmental factors, i.e. prescriptive populations.

In addition, for the first time in the obstetric ultrasound literature, we followed up the cohort until 2 years of age and showed that the mean skeletal growth of the infants participating in FGLS was well within the WHO Child Growth Standards (50th centile for HC, 49th centile for length, and 58th centile for weight). These findings strongly suggest that the fetal growth velocity increments described here are likely to be observed in healthy populations worldwide.

Results

Our results show that peak growth velocity is observed between 16- and 17-weeks' gestation for the fetal skeleton (HC and FL) and abdomen (AC); however, the observed patterns were markedly different. OFD had an earlier peak velocity at 16 weeks compared to 19- and 20- weeks' gestation for BPD, which implies that the fetal head may have a rate of growth that promotes a slightly disproportionate shape to accommodate certain brain structures.

Growth velocity slowed down rapidly for HC and FL and at an almost linear rate in the case of FL; by contrast, it remained steady throughout pregnancy for AC. In addition, there was larger variability in the AC velocity values, compared to those for HC and FL, especially in the second half of pregnancy. Taken together, the findings show that overall skeletal growth is a biological process that has the highest rate of growth in the first part of pregnancy; linear skeletal growth (FL) is even more pronounced.

How do our results compare with previously published studies? For HC, Deter and colleagues, using the Rossavik growth model in a cohort of 20 fetuses,[53] reported an earlier peak velocity at 14 weeks (14 mm/week), which decreased to 9 mm/week at 30 weeks and 5 mm/week at 38 weeks' gestation.[54] Similarly, for AC, peak velocity was earlier (12 mm/week at 14 weeks and reduced to 11 mm/week at 30 weeks of gestation), Todros and colleagues, applying a growth model similar to Rossavik's in 4,758 fetuses of physiological pregnancies found that the peak velocity was at around 16 weeks' gestation for both HC and BPD (63). Similarly, Guihard-Costa and colleagues reported multiphasic patterns of growth velocity with a common peak of velocity at about 16 weeks of gestation, and no sex differences in growth velocity [55]. Bertino and colleagues reported similar findings to ours: in 238 fetuses, peak velocity was reached at 17.3 weeks' gestation with a rapid increase in the early part of the second trimester, which then decreased up until the end of pregnancy.[56]

A number of studies using different selection criteria, hospital populations, ultrasound equipment and methodologies have reported a decrease in FL linear growth velocity by gestational age.[57-59] However, it is important to bear in mind that the populations studied were not equivalent and that FL is measured differently by modern equipment; hence, the values are not entirely comparable.[60] This is an important issue because hospitals are still using FL charts based on equipment that is no longer in use, which increases the risk of misclassifying fetuses.

Recently, Grantz and colleagues studied the relationship between fetal growth velocity and self-reported maternal ethnicity.[61] The findings were similar to the present study: FL velocity was between 3.4 to 3.5 mm/week at 16 weeks (3.2 mm/week in our study), 2.2 mm/week at 28 weeks (2.2 mm/week in our study), and 1.8 to 1.9 mm/ week at 34 weeks' gestation (1.8 mm/week in our study). Therefore, as the INTERGROWTH-21st Project has clearly demonstrated, fetal linear skeletal growth velocity seems to be very similar regardless of the mother's geographical location, country of origin or self-reported ethnicity, which adds considerable support to the concept that growth amongst healthy, low-risk fetuses is universal.[62]

AC, which is an indicator of abdominal organ growth (mostly liver and subcutaneous fat), is strongly influenced by the underlying nutritional status of the population being studied. In developed countries and in countries suffering from the "double burden of malnutrition", where a large proportion of the population is in the midst of the obesity epidemic, it is becoming increasingly clear that overweight/obesity is often initiated *in utero*.[63] Hence, comparing AC growth in previous studies[56, 64] with the FGLS cohort of healthy, low-risk women, is a less relevant question given that fetal AC values in unselected populations are influenced by the distribution of maternal fat-related markers, i.e. the fetal AC may be larger in obese women than in those with a normal BMI.[65]

Interestingly, Grantz and colleagues, in a US population, reported AC velocity values early in pregnancy that were very similar to our study: 11.7 to 12.2 mm/week at 16 weeks (11.8 mm/week in our study) and 10.3 to 10.9 mm/week at 28 weeks' gestation (10.4 mm/week in our study.[61] However, in the third trimester, there was clear evidence of AC over-growth: 10.1 to 10.8 mm/week at 34 weeks' gestation versus 9.7 mm/week in our study. In short, fat may be deposited in the fetal abdomen faster in some populations compared to others resulting in over-weight, despite similar skeletal growth velocities.

Clinical implications

Our analysis of skeletal and abdominal velocity increments, expressed as a percentage of attained fetal size at 40 weeks' gestation, also showed differential growth velocity patterns. This finding has important clinical consequences because of how EFW is utilized in obstetric practice. Based on the present findings and taking into account basic analytic principles, summary measures such as EFW should not be used if there is evidence of biological heterogeneity among the parameters to be combined. Thus, the observation that similar EFW estimations can be obtained from different permutations of HC, AC and FL values may explain the large errors often seen in EFW values regardless of which equation is used.[66, 67]

The biological significance of the heterogeneity in the velocity and timing of fetal growth is best appreciated by examining how an intrauterine insult, such as infection with the Zika virus (ZIKV), can have varying effects at different stages of pregnancy. Infection in the first trimester has clearly been associated with massive disruption to brain development and a decrease in the rate of head growth, resulting in microcephaly.[68] However, brain damage can also arise from infection late in pregnancy despite head size remaining within 'normal' limits.[69, 70] Certainly, in our dataset, 90% of the HC at term has been reached by 33 weeks' gestation, i.e. HC values at birth and at 33 weeks' gestation are very similar. Therefore, ZIKV infection after 33 weeks' gestation may still lead to brain damage but the effect on skull size will be limited, which means that diagnosing ZIKV infection based solely on the presence of microcephaly at birth will be associated with a false negative rate. Interestingly, we can extend this type of comparison into childhood. The mean HC of the same cohort at 2 years of age was 47.8 cm; although we acknowledge differences in measurement techniques, on average, two-thirds of a 2 year-old child's HC is attained by 33 weeks' gestation.

Strengths and limitations

The present findings could have important implications for clinical practice as improved assessment of fetal growth patterns could potentially lead to more personalized antenatal care. In other words, the use of the standards described here could help to distinguish healthy from disturbed fetal growth for both the management of individual pregnancies and for screening purposes. However, there are practical challenges. A similar approach has been advocated in the past for monitoring child growth; however, it has not been adopted in routine practice largely because the calculations are complex and the results are difficult to interpret. To illustrate the point, the choice of interval length between measures affects the results: the shorter the interval, the higher the variability in growth and measurement error compared with the actual growth. Guihard-Costa and colleagues recommend a 3-week interval as the minimal time interval in which the growth rate may be statistically significant, taking into account the number of cases, the minute fluctuations of growth rate in short periods and the individual variability of growth velocity [55]. However, extending the time interval loses the benefit of assessing velocity especially during the third trimester when the peak of growth has passed for skeletal markers, AC variability is very large and birth is soon likely to occur. Frequent ultrasound measurements are also not presently recommended for routine antenatal care and have implications for cost, staff numbers and workload. Our robust statistical modelling work of the correlation of fetal biometry measurements using a two-stage approach addressed at least some of these limitations by enabling the calculation of fetal biometry correlations for any pair of observations between 14 and 40 weeks, and is independent of time interval.[42]

To facilitate the use of the standards described here, we have provided an easy to use R shiny App (freely available at https://lxiao5.shinyapps.io/fetal_growth/) for assessing conditional velocity if repeat ultrasound measures are clinically indicated. We believe that both distance and velocity assessments of fetal growth would help clinicians to detect fetuses at risk of a growth abnormality. There are clinical advantages of assessing growth using conditional velocity. For instance, a fetus may not meet its growth trajectory, yet not fall below a cut-off centile (such as the 10th); however, a size chart would not identify that fetus as small for gestational age, despite its evident poor growth over time.

Research implications

The present findings offer new avenues for both clinical and life sciences research. It may now be possible to identify more refined fetal growth phenotypes (or 'fetotypes'), matching those described for the neonate, which may be associated with certain child health outcomes. Hence, we encourage health professionals worldwide to join us in determining the clinical significance of deviations from optimal skeletal and fat-dependent growth by conducting research to establish if routine fetal growth velocity assessment can improve health outcomes.[71] External assessment of the findings in daily practice, including the implications of growth above or below the standards are areas for future research. The potential pathophysiologic significance of the growth velocity patterns identified here should also prompt a renewed focus on research into the underlying cellular and molecular mechanisms responsible for fetal growth.

Conclusions

In summary, we have shown that fetal growth velocity increment is highest in the early part of the second trimester, and decreases with gestational age for skeletal structures, and that there is a clear continuous pattern throughout pregnancy for fat-related markers such as AC. Lastly, we have constructed international Fetal Growth *Velocity Increment* Standards and conditional velocity to complement the set of tools produced by the INTERGROWTH-21st Project.[12] A free, simple-to-use, online clinical tool is presented here enabling calculation of fetal growth velocity throughout pregnancy.

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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 (from July 2011), D Muninzwa (from October 2011), EO Ohuma (from September 2010), D Yellappan (from November 2010), A Carter (from July 2011), D Reade (from June 2012), R Miller (from June 2012).

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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: W Stones and M Carvalho (Co- Principal Investigators), J Kizidio, R Ochieng, J Shah, , 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 Papageorghiou, F Roseman, A Lambert, EO Ohuma, 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).

Table 1A: Smoothed centiles for fetal head circumference velocity increment (mm/week) according to gestational age

Gestational age (weeks)	FHC						
	C3	C5	C10	C50	C90	C95	C97
16	10.6	10.8	11.1	12.2	26.1	32.4	35.2
17	10.5	10.7	11.1	12.2	26.0	32.3	35.2
18	10.4	10.6	11.0	12.2	25.8	32.2	35.1
19	10.2	10.5	10.8	12.1	25.5	32.0	34.8
20	10.0	10.3	10.7	12.0	25.1	31.7	34.5
21	9.8	10.1	10.5	11.8	24.7	31.3	34.1
22	9.5	9.8	10.2	11.6	24.2	30.8	33.5
23	9.2	9.5	9.9	11.4	23.6	30.2	32.9
24	8.9	9.2	9.6	11.2	22.9	29.5	32.1
25	8.5	8.8	9.3	10.9	22.1	28.7	31.2
26	8.1	8.4	8.9	10.5	21.2	27.8	30.2
27	7.6	7.9	8.4	10.1	20.3	26.7	29.1
28	7.1	7.4	7.9	9.7	19.2	25.6	27.9
29	6.6	6.9	7.4	9.2	18.0	24.3	26.5
30	5.9	6.3	6.8	8.7	16.7	23.0	25.0
31	5.3	5.7	6.2	8.1	15.3	21.5	23.4
32	4.6	5.0	5.5	7.5	13.8	19.8	21.6
33	3.9	4.2	4.8	6.8	12.2	18.1	19.7
34	3.1	3.4	4.0	6.1	10.5	16.2	17.6
35	2.2	2.6	3.2	5.3	8.7	14.1	15.4

36	1.3	1.7	2.3	4.5	6.7	12.0	13.0
37	0.4	0.8	1.4	3.7	4.6	9.7	10.5
38	-0.6	-0.2	0.4	2.7	2.5	7.2	7.9

Table 1B: Smoothed centiles for fetal biparietal diameter velocity increment (mm/week) according to gestational age

Gestational age (weeks)	BPD						
	C3	C5	C10	C50	C90	C95	C97
16	2.4	2.5	2.6	3.2	3.7	3.9	4.0
17	2.4	2.5	2.7	3.2	3.8	3.9	4.0
18	2.4	2.5	2.7	3.2	3.8	3.9	4.0
19	2.4	2.5	2.7	3.2	3.8	4.0	4.1
20	2.4	2.5	2.7	3.2	3.8	4.0	4.1
21	2.4	2.5	2.7	3.2	3.8	3.9	4.1
22	2.4	2.5	2.7	3.2	3.8	3.9	4.0
23	2.3	2.5	2.6	3.2	3.7	3.9	4.0
24	2.3	2.4	2.6	3.1	3.7	3.9	4.0
25	2.2	2.3	2.5	3.1	3.6	3.8	3.9
26	2.2	2.3	2.4	3.0	3.6	3.7	3.8
27	2.1	2.2	2.3	2.9	3.5	3.6	3.8
28	2.0	2.1	2.2	2.8	3.4	3.5	3.7
29	1.8	1.9	2.1	2.7	3.3	3.4	3.5
30	1.7	1.8	2.0	2.6	3.1	3.3	3.4
31	1.6	1.7	1.8	2.4	3.0	3.2	3.3
32	1.4	1.5	1.7	2.3	2.8	3.0	3.1
33	1.2	1.3	1.5	2.1	2.7	2.8	3.0
34	1.0	1.1	1.3	1.9	2.5	2.7	2.8
35	0.8	0.9	1.1	1.7	2.3	2.4	2.6
36	0.6	0.7	0.9	1.5	2.1	2.2	2.3
37	0.3	0.4	0.6	1.2	1.8	2.0	2.1
38	0.1	0.2	0.4	1.0	1.6	1.7	1.8

Table 1C: Smoothed centiles for fetal occipito-parietal diameter velocity increment (mm/week) according to gestational age

Gestational age (weeks)	OFD C3	C5	C10	C50	C90	C95	C97
16	3.9	4.0	4.1	4.5	4.9	5.0	5.1
17	3.8	3.9	4.0	4.5	4.9	5.0	5.1
18	3.7	3.8	3.9	4.4	4.9	5.0	5.1
19	3.6	3.7	3.9	4.4	4.9	5.0	5.1
20	3.5	3.6	3.8	4.3	4.9	5.0	5.1
21	3.4	3.5	3.6	4.2	4.8	5.0	5.1
22	3.2	3.3	3.5	4.1	4.8	4.9	5.0
23	3.1	3.2	3.4	4.0	4.7	4.9	5.0
24	2.9	3.0	3.2	3.9	4.6	4.8	4.9
25	2.7	2.9	3.1	3.8	4.5	4.7	4.9
26	2.5	2.7	2.9	3.7	4.4	4.6	4.8
27	2.3	2.5	2.7	3.5	4.3	4.5	4.7
28	2.1	2.3	2.5	3.3	4.2	4.4	4.6
29	1.9	2.0	2.3	3.2	4.0	4.3	4.4
30	1.6	1.8	2.1	3.0	3.9	4.1	4.3
31	1.4	1.6	1.8	2.8	3.7	4.0	4.1
32	1.1	1.3	1.6	2.5	3.5	3.8	4.0
33	0.8	1.0	1.3	2.3	3.3	3.6	3.8
34	0.5	0.7	1.0	2.1	3.1	3.4	3.6
35	0.2	0.4	0.7	1.8	2.9	3.2	3.4
36	-0.1	0.1	0.4	1.5	2.6	2.9	3.1
37	-0.5	-0.3	0.1	1.2	2.4	2.7	2.9
38	-0.8	-0.6	-0.3	0.9	2.1	2.4	2.6

Table 1D: Smoothed centiles for fetal length velocity increment (mm/week) according to gestational age

Gestational age (weeks)	FL						
	C3	C5	C10	C50	C90	C95	C97
16	2.7	2.8	2.9	3.2	3.6	3.7	3.7
17	2.6	2.7	2.8	3.1	3.5	3.6	3.6
18	2.5	2.6	2.7	3.0	3.4	3.5	3.5
19	2.4	2.5	2.6	2.9	3.3	3.4	3.4
20	2.3	2.4	2.5	2.8	3.2	3.3	3.3
21	2.2	2.3	2.4	2.7	3.1	3.2	3.3
22	2.1	2.2	2.3	2.6	3.0	3.1	3.2
23	2.0	2.1	2.2	2.6	2.9	3.0	3.1
24	1.9	2.0	2.1	2.5	2.9	3.0	3.0
25	1.8	1.9	2.0	2.4	2.8	2.9	3.0
26	1.7	1.8	1.9	2.3	2.7	2.9	2.9
27	1.7	1.7	1.9	2.3	2.7	2.8	2.9
28	1.6	1.6	1.8	2.2	2.6	2.7	2.8
29	1.5	1.6	1.7	2.1	2.6	2.7	2.8
30	1.4	1.5	1.6	2.0	2.5	2.6	2.7
31	1.3	1.4	1.5	2.0	2.4	2.6	2.6
32	1.2	1.3	1.4	1.9	2.4	2.5	2.6
33	1.1	1.2	1.3	1.8	2.3	2.5	2.5
34	1.0	1.1	1.3	1.8	2.3	2.4	2.5
35	0.9	1.0	1.2	1.7	2.2	2.3	2.4
36	0.8	0.9	1.1	1.6	2.1	2.3	2.4
37	0.7	0.8	1.0	1.5	2.1	2.2	2.3
38	0.6	0.7	0.9	1.4	2.0	2.2	2.3

Table 1E: Smoothed centiles for abdominal circumference velocity increment (mm/week) according to gestational age

Gestational age (weeks)	AC						
	C3	C5	C10	C50	C90	C95	C97
16	9.4	9.7	10.1	11.8	13.4	13.9	14.2
17	9.1	9.5	9.9	11.6	13.3	13.8	14.1
18	8.9	9.2	9.7	11.5	13.2	13.7	14.0
19	8.7	9.1	9.6	11.3	13.1	13.6	13.9
20	8.5	8.9	9.4	11.2	13.0	13.5	13.9
21	8.3	8.7	9.2	11.1	12.9	13.5	13.8
22	8.1	8.5	9.0	11.0	12.9	13.5	13.8
23	7.9	8.3	8.9	10.9	12.9	13.4	13.8
24	7.7	8.1	8.7	10.8	12.8	13.4	13.8
25	7.5	7.9	8.5	10.7	12.8	13.4	13.8
26	7.3	7.7	8.3	10.6	12.8	13.5	13.9
27	7.0	7.5	8.1	10.5	12.8	13.5	13.9
28	6.8	7.2	7.9	10.4	12.8	13.5	14.0
29	6.5	7.0	7.7	10.3	12.8	13.6	14.0
30	6.3	6.8	7.5	10.2	12.8	13.6	14.1
31	6.0	6.5	7.3	10.1	12.9	13.7	14.2
32	5.7	6.2	7.0	10.0	12.9	13.7	14.3
33	5.4	5.9	6.8	9.9	12.9	13.8	14.4
34	5.0	5.6	6.5	9.7	13.0	13.9	14.5
35	4.7	5.3	6.3	9.6	13.0	14.0	14.6
36	4.3	5.0	6.0	9.5	13.0	14.1	14.7
37	3.9	4.6	5.7	9.4	13.1	14.2	14.8
38	3.5	4.2	5.3	9.2	13.2	14.3	15.0

Figure legends

Figure 1: Increments in fetal head circumference (FHC), abdominal circumference (AC), and femur length (FL) (mm/week) according to gestational age (weeks) for all of the sites combined. The fitted 3rd, 50th and 97th centiles are superimposed.

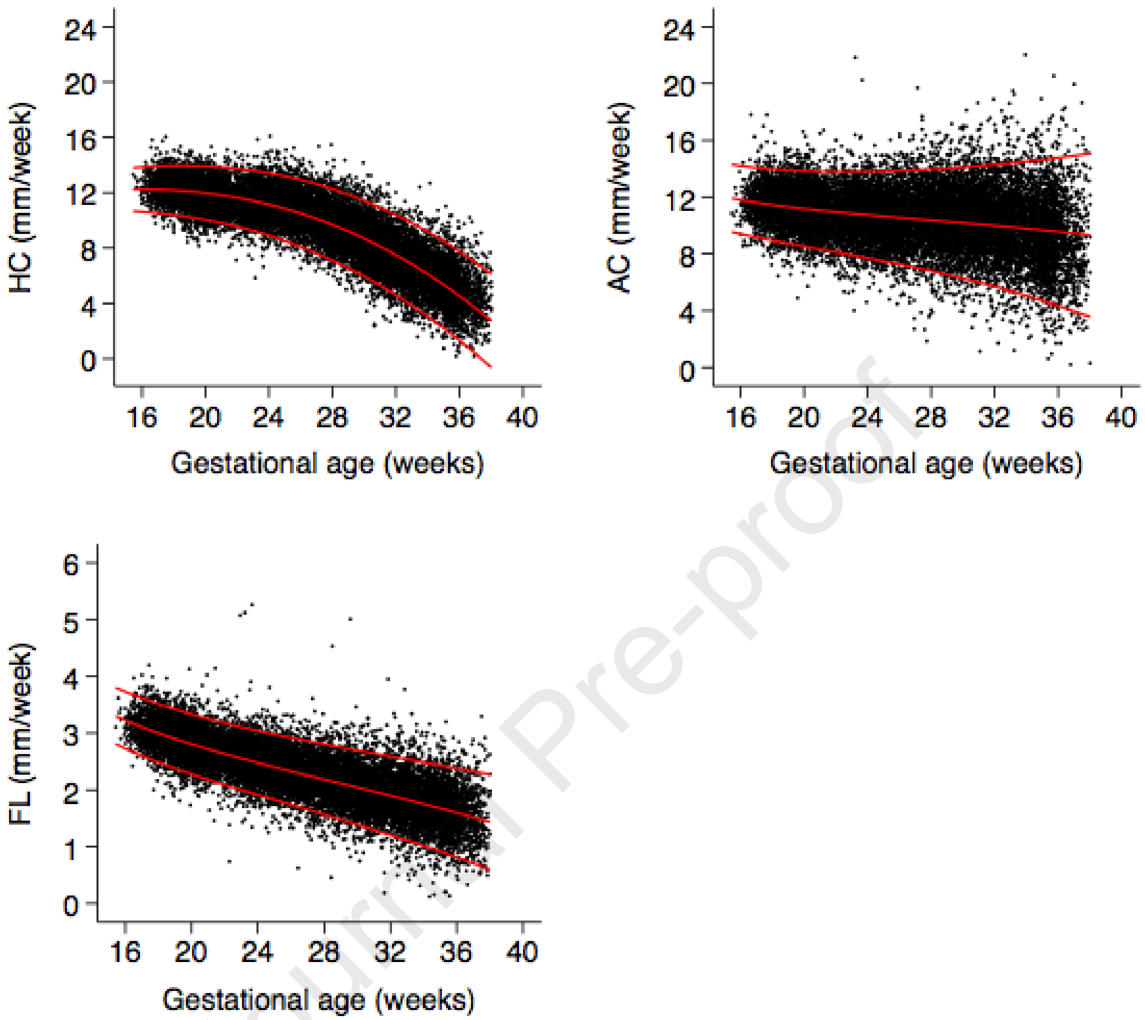
Figure 2: Median velocity increments in fetal head circumference (FHC) (green), abdominal circumference (AC) (red), and femur length (FL) (blue) according to gestational age expressed as a percentage of the attained fetal size at 40 weeks' gestation according to the published international INTERGROWTH-21st Fetal (Distance) Growth Standards.[1]

Figure 3: Screenshots of the fetal velocity app showing four example plots of longitudinal fetal growth evaluation based on observed and predicted measurements for a fetus representing: Figure 3A – normal fetus based on head circumference; Figure 3B – possible microcephaly based on head circumference; Figure 3C – a fetus within 2 standard deviations; Figure 3D – possible case of macrosomia based on abdominal circumference. All measurements are compared to the published international INTERGROWTH-21st Fetal (Distance) Growth Standards.[1]

Supplementary Figure 1: Increments in biparietal diameter (BPD) and occipito-frontal diameter (OFD) (mm/week) according to gestational age (weeks) for all of the sites combined. The fitted 3rd, 50th and 97th centiles are superimposed.

Supplementary Figure 2: Median velocity increments in biparietal diameter (BPD) (green) and occipito-frontal diameter (OFD) (red) according to gestational age expressed as a percentage of the attained fetal size at 40 weeks' gestation according to the published international INTERGROWTH-21st Fetal (Distance) Growth Standards.[1]

1. PAPAGEORGHIOU AT, OHUMA EO, ALTMAN DG, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet 2014;384:869-79.


HC (mm/week)
AC (mm/week)
FL (mm/week)
Gestational age (weeks)
Gestational age (weeks)
Gestational age (weeks)

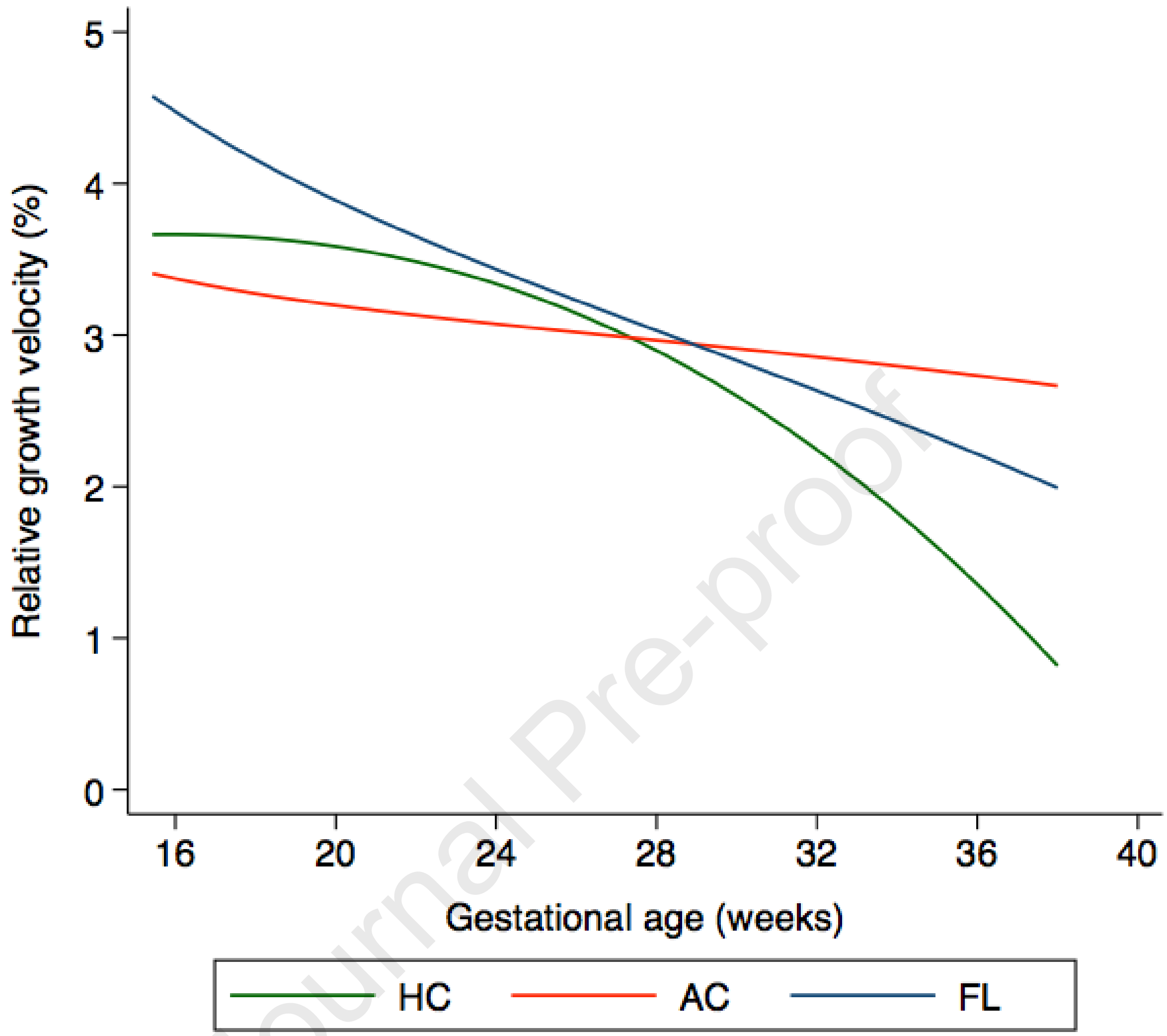

5
4
3
2
1
0
Relative growth velocity (%)
16
20
24
28
32
36
40
Gestational age (weeks)
HC
AC
FL

Figure 3: Screenshots of the fetal velocity app showing four example plots of longitudinal fetal growth evaluation based on observed and predicted measurements for a fetus representing: Figure 3A – normal fetus based on head circumference; Figure 3B – possible microcephaly based on head circumference; Figure 3C – a fetus within 2 standard deviations; Figure 3D – possible case of macrosomia based on abdominal circumference. All measurements are in reference to the international fetal growth standards of the INTERGROWTH-21st Project.

Figure 3A

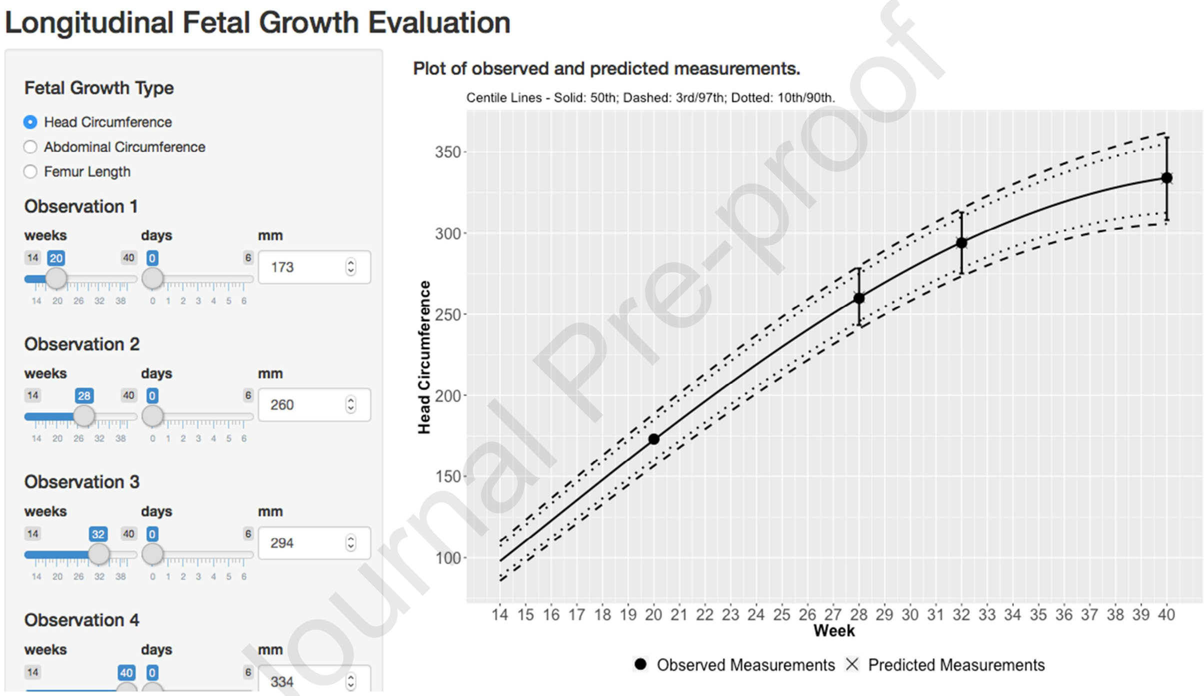


Figure 3B

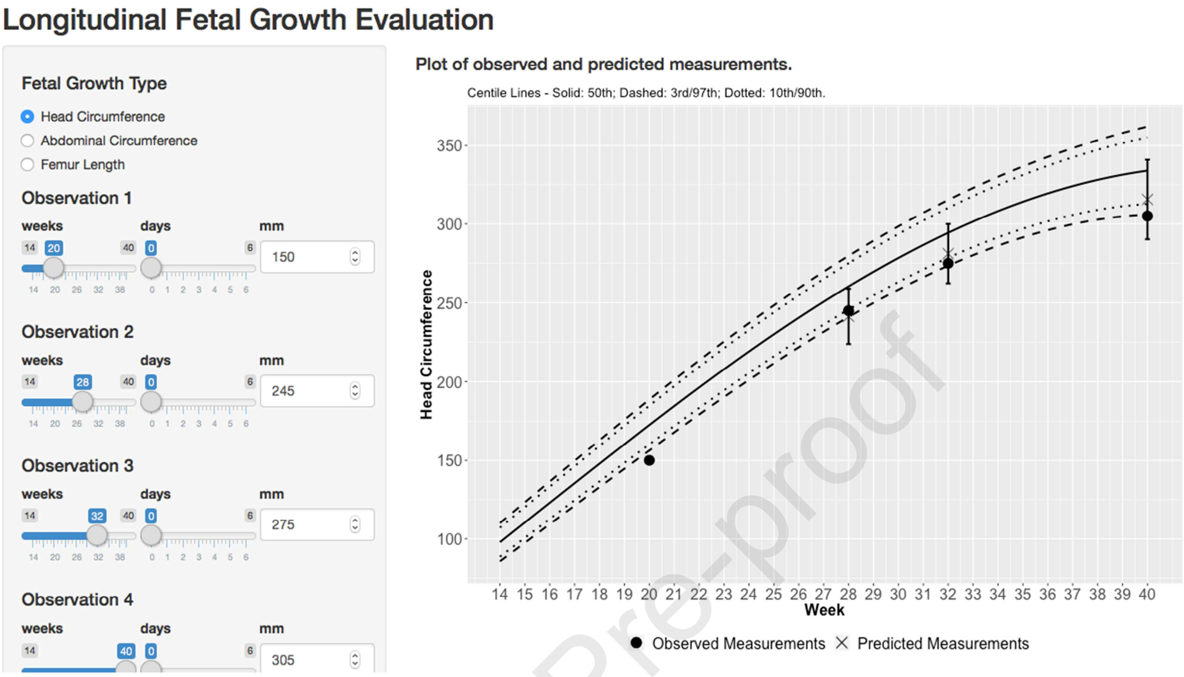


Figure 3C

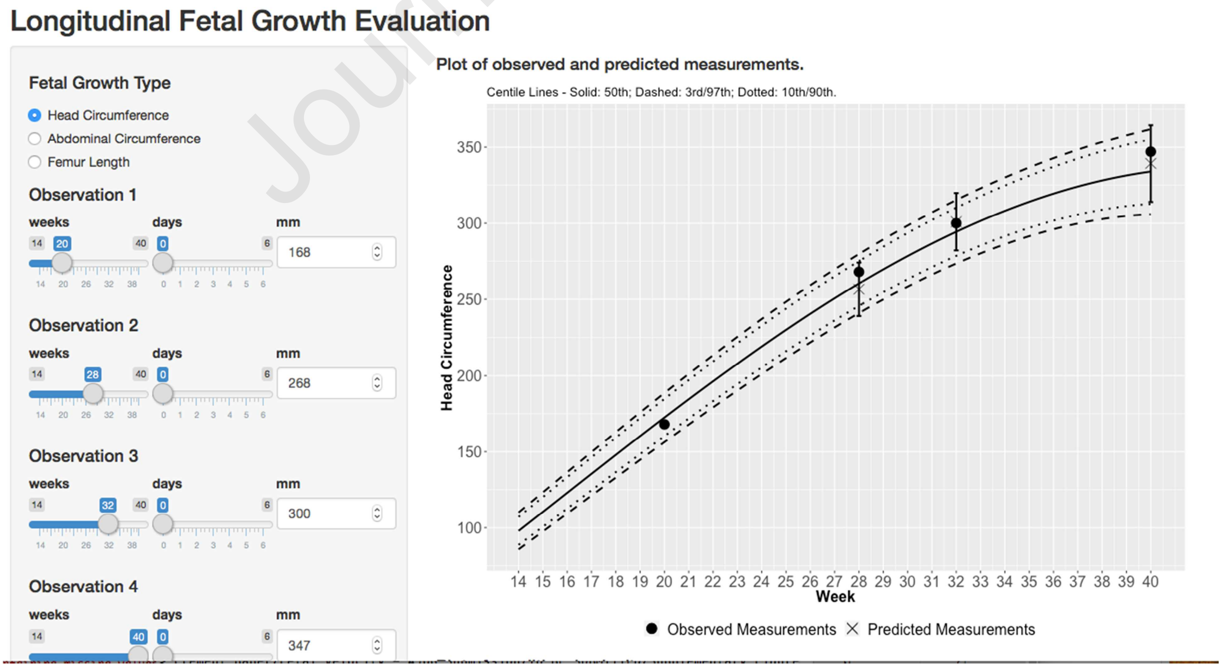
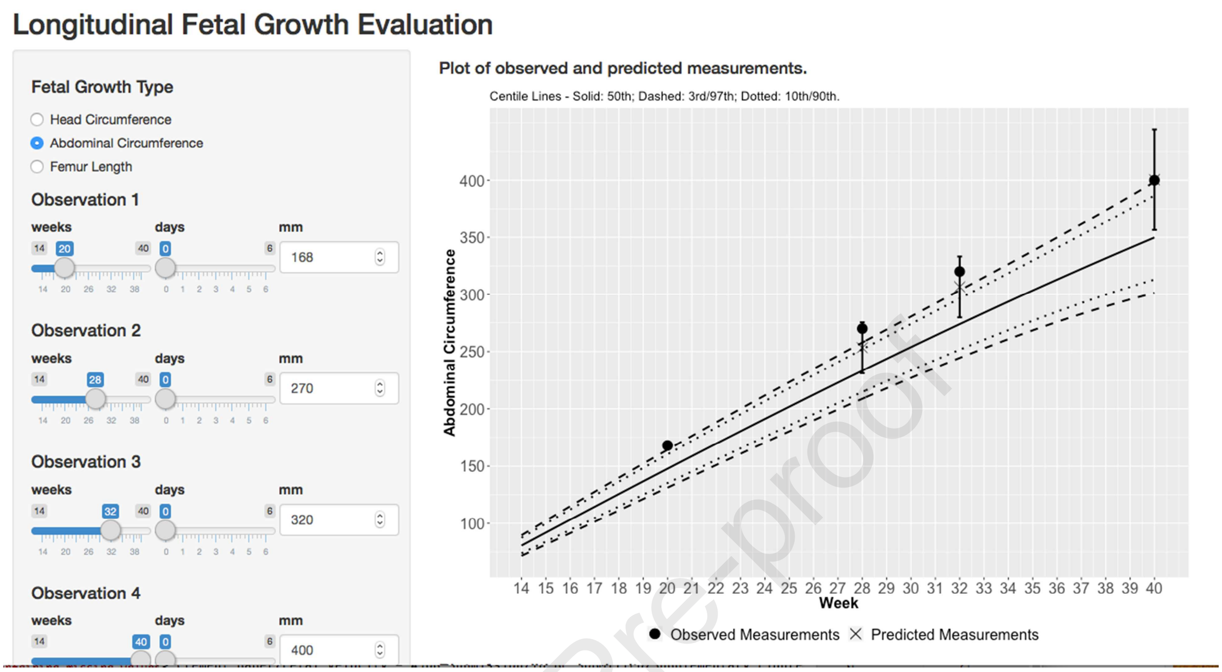
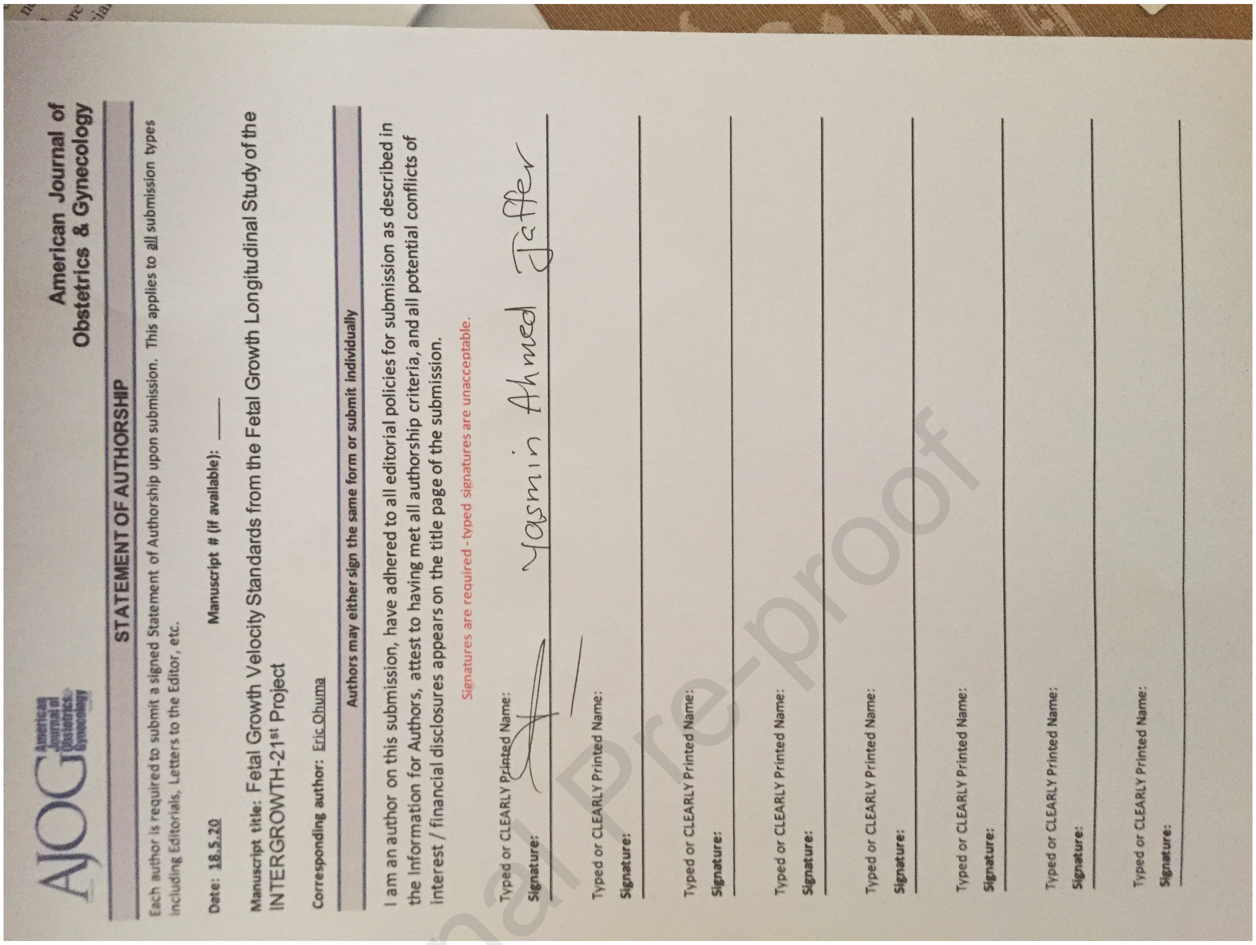


Figure 3D


Longitudinal Fetal Growth Evaluation
Fetal Growth Type
Head Circumference
Abdominal Circumference
Femur Length
Observation 1
weeks
days
mm
168
Observation 2
270
Observation 3
320
Observation 4
400
Plot of observed and predicted measurements.
Centile Lines - Solid: 50th; Dashed: 3rd/97th; Dotted: 10th/90th.
Abdominal Circumference
Week
Observed Measurements
Predicted Measurements


AJOG American Journal of Obstetrics & Gynecology

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Corresponding author: Eric Ohuma

Authors may either sign the same form or submit individually

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Signature:

Typed or CLEARLY Printed Name:
Signature:

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