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Conceptual basis for prescriptive growth standards from conception to early childhood: present and future

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Background Healthy growth in utero and after birth is fundamental for lifelong health and wellbeing. The World Health Organization (WHO) recently published standards for healthy growth from birth to 6 years of age; analogous standards for healthy fetal growth are not currently available. Current fetal growth charts in use are not true standards, since they are based on cross-sectional measurements of attained size under conditions that do not accurately reflect normal growth. In most cases, the pregnant populations and environments studied are far from ideal; thus the data are unlikely to reflect optimal fetal growth. A true standard should reflect how fetuses and newborns 'should' grow under ideal environmental conditions.

Objective The development of prescriptive intrauterine and newborn growth standards derived from the INTERGROWTH-21st Project provides the data that will allow us for the first time to establish what is 'normal' fetal growth.

Methods The INTERGROWTH-21st study centres provide the data set obtained under pre-established standardised criteria, and details of the methods used are also published.

Design Multicentre study with sites in all major geographical regions of the world using a standard evaluation protocol.

Results These standards will assess risk of abnormal size at birth and serve to evaluate potentially effective interventions to promote optimal growth beyond securing survival.

Discussion The new normative standards have the potential to impact perinatal and neonatal survival and beyond, particularly in developing countries where fetal growth restriction is most prevalent. They will help us identify intrauterine growth restriction at earlier stages of development, when preventive or corrective strategies might be more effective than at present.

Conclusion These growth standards will take us one step closer to effective action in preventing and potentially reversing abnormal intrauterine growth. Achieving 'optimal' fetal growth requires that we act not only during pregnancy but that we optimize the maternal uterine environment from the time before conception, through embryonic development until fetal growth is complete. The remaining challenge is how 'early' will we be able to act, now that we can better monitor fetal growth.

Keywords Fetal and neonatal growth, growth standards, INTERGROWTH-21st Project.

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Relevance of intrauterine and early growth

Estimates of child mortality in 2008, show that >40% of the deaths in children under 5 years old occur in neonates.[1] Most of these were directly or indirectly related to abnormal fetal growth. In addition, preterm babies ($<37^{+0}$ weeks) currently account for one in every four neonatal deaths.[1] Low birthweight (LBW; <2500 g), a cruder measure, is associated with increased mortality from birth asphyxia, lung disease and infections (pneumonia, sepsis and diarrhoea), which together account for approximately 60% of all neonatal deaths.[2]

Intrauterine growth is an important determinant of linear growth and adult stature; so it potentially impacts on the

growth of future generations.[3] Intrauterine growth is also related to school performance and adult productivity. Thus it is a key factor in human capital formation, especially in developing countries.[4] Abnormal birthweight, by itself is associated with significant adverse outcomes such as cardiovascular disease, stroke, diabetes and some forms of cancer.[5] These observations support the concept of the early origin of adult diseases, coined as the Developmental Origins of Health and Disease, which in its current version proposes that events taking place in the intrauterine environment, starting even before conception, induce epigenetic changes (modifications in DNA and histones that affect gene expression without modification of the code itself) that may, under certain environmental conditions, be detrimental later in life.[6]

Why do we need a fetal growth standard?

Traditionally, fetal nutritional status has been assessed using indirect methods that are simple and inexpensive. The simplest clinical method is abdominal palpation during pregnancy but this is very imprecise and inaccurate. Standardised methods to assess fundal height have been developed and tested, showing good sensitivity and specificity to predict LBW for gestational age.[7] However, the precision of fundal height measurement is limited, thus it remains as a method to screen for abnormal fetal growth in primary-care settings.[8,9] More recently, ultrasound imaging has provided a tool to assess fetal size and organ structures with greater sensitivity and specificity. Unfortunately, the precision of ultrasound estimates is also a problem given the high inter-practitioner and intra-practitioner variability among nonstandardised practitioners.[10]

Another challenging issue is the estimation of true gestational age. In clinical studies, it is possible to estimate gestational age with reasonable accuracy by ultrasound scans in early pregnancy, although this is based on a growth parameter that may already have been adversely affected. Conversely, larger population-based studies tend to collect gestational data with less accuracy (i.e. gestational age based on last menstrual period or later ultrasound measurements).

More importantly, current fetal growth and newborn references are based on selected samples with limitations in the methodologies used. Populations have been exposed to a series of sociodemographic, cultural and nutritional conditions that have a profound impact on patterns of diet and physical activity, thereby modifying causes of death and disability.[11] In the case of newborn growth standards by gestational age, current World Health Organization (WHO) recommendations are based on a population of births from California, USA, in the 1970s[12] and, therefore, are unlikely to reflect present conditions or complement the important, new, WHO Multicentre Growth Reference Study (MGRS) infant growth standards.[13] Hence, no truly global, gestational-age-specific standards from 'contemporary healthy populations' are currently available. The INTERGROWTH-21st Project, if it achieves its objectives, once implemented at scale, will close this gap.[14] It reflects a truly global population not only in terms of ethnic backgrounds, and social, cultural and environmental conditions, but also in terms of the staging of the epidemiological and nutritional transition.

Furthermore, fetal growth references presently being used are not truly attained growth standards because they were generated using cross-sectional data, i.e. size parameters such as head circumference collected at various gestational ages, and seldom in a standardised manner. As a consequence, they can be used to make comparisons for specific gestational ages but they have serious limitations if the purpose is to assess, i.e. make a value judgement regarding the adequacy of a given growth trajectory or the potential consequences for fetal and neonatal health. To describe growth trajectories adequately, i.e. provide estimates of growth velocity, references should be based on longitudinal data (i.e. ideally with several repeated measurements). From a biological viewpoint, it also may be relevant to assess whether growth has deviated from its normal progression, independently of actual size at any given time. For example, a fetus moving from the 50th to the 30th centile of the normal size distribution should be a matter of concern, although these centiles would not be considered abnormal or 'at risk' when assessed at a single time-point. The INTERGROWTH-21st fetal and newborn standards will provide both classical birth data and longitudinal information corresponding to fetal growth charts derived from ultrasound measurements taken from the same population under rigorous methodological conditions (i.e. rates of growth between two specific periods). Velocity charts built using repeated ultrasound measurements at selected time-points during gestation may be useful to disentangle biological processes underlying fetal growth faltering, as well as to detect subtle insults that do not necessarily affect size at a given time-point but are still meaningful.

Reviewing the impact that the current worldwide obesity and diabetes epidemic has on fetal outcomes serves to illustrate the urgent need and possible advantages of monitoring organ growth. Pregnancy under obesogenic conditions affects placental and fetal growth and development. Excess birthweight, in this case largely as a result of excess body fat, has been linked to increased risk of later obesity and other metabolic disturbances affecting diabetes and cardiovascular risk.[15,16] However, birthweight alone may not fully reflect the impact of the metabolic state during pregnancy because, if diabetes coexists with vascular compromise leading to placental insufficiency, birthweight will be lower than anticipated. If nutrient supply is limited, fetal peripheral insulin resistance serves to

maintain brain glucose supply while limiting peripheral adipose tissue gain; therefore, sparing brain growth has a clear survival advantage. This justifies the decision of the INTERGROWTH-21st Project to use fetal head circumference as the primary parameter to compare fetal growth across the populations evaluated. Present substudies within the INTERGROWTH-21st Project, aimed at creating a three-dimensional ultrasound bank of organ volume data, should shed light on how the fetus accommodates to changes in substrate flow. The organ growth standards to be produced by INTERGROWTH-21st might allow us to assess the effect that alterations in the maternal diet have on fetal adaptation to changes in the quality and quantity of the energy supplied.

So far, we have detailed a series of issues that are relevant to the development of 'optimal' fetal growth references; however, what differentiates a growth standard from a reference chart is its prescriptive nature. On the one hand, fetal growth references describe how growth has taken place in a particular population and not what growth should be under ideal conditions. They are built using samples selected under a very limited set of conditions that are consistent with the absence of disease. However, they do not provide a judgment of what fetal growth is under optimal conditions or what the trajectory of a given individual fetus should be. Standards on the other hand are prescriptive, they describe growth under optimal conditions, and provide an indication of which practices promote optimal growth. Standards are built using samples within a population that are considered optimal in terms of conditions that support physiological growth. In addition, individuals included in the sample are carefully screened to verify that they fulfil the requisites to achieve their full growth potential. Growth standards should also be validated using functional outcomes that indicate short-term (i.e. survival, morbidity) and long-term (i.e. adult stature, mental development, cardiovascular, metabolic health) health and wellbeing, although it would be impractical to wait for the latter before releasing the standards.[17] However, the INTERGROWTH-21st Project will provide morbidity, diet, growth and development data for infants up to 2 years of age in the longitudinal study, which represents a significant improvement on existing fetal growth charts currently in use.

However, if we accept the prescriptive approach, a reasonable question is whether we use a single national or ethnicity-specific reference, or if we need a truly international standard. The generation of a standard from multiple local data sets is supported by observations that fetal and neonatal growth may vary among populations. However, it is now accepted that ethnic differences contribute only a small part (approximately 3%) of the total variation in growth among well-nourished children; most of the variance is related to environmental conditions such as health, nutrition and socio-economic status.[17] The WHO MGRS that generated a set of international growth standards for children aged 0–5 years, was a real-life evaluation of the relative importance of ethnicity in early life growth.[13] In that study, the growth of representative samples from six different countries (Brazil, Ghana, India, Norway, Oman and the USA) was carefully monitored. Results show that differences in linear growth during the first 5 years of life were minimal under optimal conditions, indicating that ethnicity did not affect early growth in a significant manner.[18] The development of international standards for the fetus and newborn is appealing because it will complement the existing WHO infant and child growth standards that provide normative data to 5 years of age. Finally, ethnicity-specific standards are impractical to implement today because of the high degree of admixture in the pregnant population.

The INTERGROWTH-21st prescriptive approach to define optimal fetal growth represents great progress. It provides us with well-timed fetal measures because gestational age is confirmed by an early ultrasound scan at $<14^{+0}$ weeks. It also provides six serial ultrasound assessments of: a) placental localisation, fetal presentation and amniotic fluid volume index; b) head circumference and two head diameters, namely biparietal diameter and occipito-frontal diameter; c) abdominal circumference, transverse abdominal diameter and anterior–posterior abdominal diameter, and d) femur length—all obtained under uniquely strict quality control measures to ensure the validity and precision of the data collected. Hence, for the first time, we will have sequential longitudinal data from a prescriptive population study that serves to characterise whole body as well as brain, liver and long-bone growth. The fetal growth standards that will emerge from the INTERGROWTH-21st Project represent a quantum leap in terms of evaluating the effect of early life events on later growth, health and wellbeing.

A critical issue in the generation of these standards has been how to define optimal fetal environmental conditions. This is further complicated by the fact that fetal nutrition depends not only on maternal conditions but also on the integrity and functional state of the fetus—placenta unit. In the future, we will understand the determinants of fetal growth more comprehensively. In the meantime, it is reasonable to define what is optimal by working with well-to-do populations without any sociodemographic (i.e. maternal education, assets, age), health (i.e. gestational diabetes, history of stillbirths), nutritional (i.e. adequate height and weight) or environmental (i.e. smoke, pollutants) exposures currently associated with restricted fetal growth.

It is vital to consider sociodemographic variables, at both population and individual levels, when defining optimal growth because they account for an important part of the variability in pregnancy health outcomes worldwide and

influence fetal growth in multiple ways. For example, education influences health behaviour such as smoking, alcohol and drug consumption, as well as perceptions of health and risks and susceptibility to infections, while assets and income determine household sanitary conditions, quality of the diet and access to health care. These are just a few of the critical conditions affected by socio-economic status.[19] Maternal age is another important factor to consider in achieving optimal growth potential. There is a strong correlation between maternal age at conception and fetal loss or death, independent of previous reproductive outcomes. Women >35 years old have a higher risk of spontaneous miscarriage and stillbirths compared with younger women.[20] The reasons for this increased risk are not fully elucidated but may include failure of the uterine vasculature with advancing age to support changing haemodynamics and adequate placental function.[21]

Adequate maternal health is required to develop fetal growth standards. Diseases such as maternal diabetes, severe urinary tract infection or pre-eclampsia have a clear impact on fetal growth as a whole. However, other diseases may affect the development of specific organs or their functions. It is essential to recruit mothers who are free of significant clinical disease and to monitor their pregnancies carefully to ensure that they remain healthy. Meeting nutritional standards in terms of weight gain and diet are key to supporting optimal fetal growth,[22] as it is well established that there is an appropriate prepregnancy, maternal weight and height status.

Other environmental exposures influence the fetal environment and development. Maternal smoking, even if passive, is associated with an increased risk of fetal and perinatal mortality, preterm delivery and LBW.[23] Several components of cigarette smoke such as nicotine and carbon monoxide alter fetal growth and placental function, thereby compromising the viability of the fetus.[23] More recently, maternal smoking, particularly in the first trimester, has been also linked to increased risk of childhood obesity. This is likely to be a result of modifications of appetite regulatory hormones such as leptin or direct effects on adipogenesis.[24] Avoidance of air pollutants and other contaminants found in water and food is also relevant in terms of optimising fetal growth. Air pollution has not yet been causally related to preterm delivery or intrauterine growth restriction; however, there is growing evidence suggesting a link, and a causal relationship with LBW has now been demonstrated.[25] Water contaminants such as arsenic or cadmium lead to adverse pregnancy outcomes, fetal loss and LBW.[26,27] Exposure to heavy metals during pregnancy such as lead and mercury is also associated with adverse pregnancy outcomes.[28]

All these conditions may be beyond the control of the investigators but they should be recorded so that they can be considered in the analysis of potential differences found across sites. For example, in some geographical regions, industrial pollution, traffic and occupational exposures have become so widespread, that it may be difficult if not impossible to find a population free from exposure to many contaminants. The process of describing precisely the established conditions of the population (inclusion and exclusion criteria), in which optimal growth was defined, is an essential aspect in support of the external validity of the study.

What purpose will fetal and newborn growth standards serve?

The new fetal and neonatal growth standards bring important public health gains as well as significant challenges. The description of optimal patterns of fetal growth allows for more timely detection of 'true' intrauterine growth restriction. It provides a unique opportunity for preventive measures, which may reverse the identified risks. It will also facilitate testing the efficacy and safety of therapeutic actions and determining the optimal timing of delivery. Altogether, this should result in important improvements in child survival and, in turn, human capital accrual.

These standards will also assist in the timely detection of accelerated departures from the normal growth trajectory. In view of the current obesity epidemic, it is expected that this will increasingly become a problem, even in developing countries. The application of the standards at an individual level may provide an opportunity to prevent fetal overweight. At a population level, they will serve to monitor trends in nutritional status at birth both in terms of population distributions (i.e. means and standard deviations) and high-risk populations (i.e. the percentage of newborns below or above a specific cut-off point). The application of the standards at a population level will also help in evaluating the performance of maternal and perinatal programmes, in terms of prevention and clinical care. This should be particularly relevant for developing countries, which are presently most affected by LBW and premature birth, and are increasingly at greatest risk for the consequences of the 'new' obesity and its associated chronic diseases.

In addition, a detailed description of the trajectories of size (and eventually organ development) will advance our understanding of the implications of prenatal life on health and disease. Moreover, the combined use of these standards will clearly describe how prenatal growth trajectories relate to early postnatal growth, with a particular emphasis on premature babies; information for this group up to now has been scarce. The new fetal and neonatal standards, however, must be implemented on a sufficiently large scale and the information obtained from their implementation used to evaluate and revise maternal and neonatal care programmes.

Challenges ahead

The release of the new standards requires careful planning and implementation. Health workers, at all levels, need to be trained to obtain the information correctly and, more importantly, to use it in clinical decision-making and actions. Practices and norms may need to be revised and modified in accordance with the INTERGROWTH-21st standards. Adequate planning time needs to be allocated to these issues to secure success in translating the new standards into better practices. We will all be challenged to find interventions to correct the abnormal growth patterns identified at later stages. We will be able to answer what proportion of fetal growth is conditioned by embryonic development and thus will need to face the challenge of how much can be done to correct fetal growth after 10–13 weeks.

We predict that embryonic development, between fertilisation and the establishment of the placenta, will become an important area of research. The evidence to date indicates that the periconception period is critical for normal fetal growth and development: for example, folate supplementation during this period has a marked effect in preventing neural tube defects.[29] Equally, placental tissue from newborns conceived by in vitro fertilisation is associated with altered DNA methylation patterns,[30] suggesting that an 'abnormal', early embryo environment can alter epigenetic programming.

Meeting the challenge of achieving 'optimal' fetal growth would include addressing embryonic and placental growth and development. The new fetal growth reference moves us closer to this goal.

Disclosure of interests

None.

Contribution to authorship

RU wrote the manuscript with contributions from all authors who read and approved the final version.

Details of ethics approval

The INTERGROWTH-21st Project was approved by the Oxfordshire Research Ethics Committee 'C' (reference: 08/H0606/139), and the research ethics committees of the individual participating institutions and corresponding health authorities where the Project was implemented.

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References

1 World Health Organization, and UNICEF. *Countdown to 2015 Decade Report (2000–2010):tacking stock of maternal, newborn and child survival*. Washington, DC: WHO/UNICEF, 2010.
2 Black RE, Allen LH, Bhutta ZA, Caulfield LE, De Onis M, Ezzati M, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 2008;371:243–60.
3 Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, et al. Maternal and child undernutrition: consequences for adult health and human capital. *Lancet* 2008;371:340–57.
4 Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, et al. Child development: risk factors for adverse outcomes in developing countries. *Lancet* 2007;369:145–57.
5 Barker DJ, editor. *Mothers, babies and health in later life*. Edinburgh: Churchill Livingstone, 1998.
6 Gluckman PD, Hanson MA, Beedle AS. Early life events and their consequences for later disease: a life history and evolutionary perspective. *Am J Hum Biol* 2007;19:1–19.
7 Belizan JM, Villar J, Nardin JC, Malamud J, De Vicurna LS. Diagnosis of intrauterine growth retardation by a simple clinical method: measurement of uterine height. *Am J Obstet Gynecol* 1978;131:643–6.
8 Bailey SM, Sarmandal P, Grant JM. A comparison of three methods of assessing inter-observer variation applied to measurement of the symphysis-fundal height. *Br J Obstet Gynaecol* 1989;96:1266–71.
9 Neilson JP. Symphysis–fundal height measurement in pregnancy. *Cochrane Database Syst Rev* 2000;(2):CD000944.
10 Bricker L, Neilson JP, Dowswell T. Routine ultrasound in late pregnancy (after 24 weeks' gestation). *Cochrane Database Syst Rev* 2008;4:CD001451.
11 Popkin BM. An overview on the nutrition transition and its health implications: the Bellagio meeting. *Public Health Nutr* 2002;5:93–103.
12 Williams RL, Creasy RK, Cunningham GC, Hawes WE, Norris FD, Tashiro M. Fetal growth and perinatal viability in California. *Obstet Gynecol* 1982;59:624–32.
13 De Onis M, Garza C, Victora CG, Onyango AW, Frongillo EA, Martines J. The WHO Multicentre Growth Reference Study: planning, study design, and methodology. *Food Nutr Bull* 2004;1Suppl:S15–26.
14 Villar J, Altman DG, Purwar M, Noble JA, Knight HE, Ruyan P, et al. for the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). The objectives, design and implementation of the INTERGROWTH-21st Project. *BJOG* 2013; DOI: 10.1111/1471-0528.12047.
15 Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics* 2005;115:e290–6.
16 Catalano PM, Hauguel-De MS. Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? *Am J Obstet Gynecol* 2011;204:479–87.

17 Garza C, De Onis M. Rationale for developing a new international growth reference. *Food Nutr Bull* 2004;1Suppl:S5–14.
18 World Health Organization (WHO). *WHO Child Growth Standards: methods and development: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age*. Geneva: WHO, 2006.
19 Kramer MS, Seguin L, Lydon J, Goulet L. Socio-economic disparities in pregnancy outcome: why do the poor fare so poorly? *Paediatr Perinat Epidemiol* 2000;14:194–210.
20 Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *BMJ* 2000;320:1708–12.
21 Fretts RC, Schmittdiel J, McLean FH, Usher RH, Goldman MB. Increased maternal age and the risk of fetal death. *N Engl J Med* 1995;333:953–7.
22 Institute of Medicine (IOM) US. *Nutrition during Pregnancy Part I: weight gain Part II: nutrient supplementation*. Washington DC: IOM, 1990.
23 Dechanet C, Anahory T, Mathieu Daude JC, Quantin X, Reyftmann L, Hamamah S, et al. Effects of cigarette smoking on reproduction. *Hum Reprod Update* 2011;17:76–95.
24 Von Kries R, Toschke AM, Koletzko B, Slikker W, Jr. Maternal smoking during pregnancy and childhood obesity. *Am J Epidemiol* 2002; 156:954–61.
25 Sram RJ, Binkova B, Dejmek J, Bobak M. Ambient air pollution and pregnancy outcomes: a review of the literature. *Environ Health Perspect* 2005;113:375–82.
26 Kippler M, Tofail F, Gardner R, Rahman A, Hamadani JD, Bottai M, et al. Maternal Cadmium Exposure During Pregnancy and Size at Birth: a Prospective Cohort Study. *Environ Health Perspect* 2012; 120:284–9.
27 Rahman A, Vahter M, Ekstrom EC, Rahman M, Golam Mustafa AH, Wahed MA, et al. Association of arsenic exposure during pregnancy with fetal loss and infant death: a cohort study in Bangladesh. *Am J Epidemiol* 2007;165:1389–96.
28 Jones L, Parker JD, Mendola P. Blood lead and mercury levels in pregnant women in the United States, 2003–2008. *NCHS Data Brief* 2010;52:1–8.
29 De-Regil LM, Fernandez-Gaxiola AC, Dowswell T, Pena-Rosas JP. Effects and safety of periconceptional folate supplementation for preventing birth defects. *Cochrane Database Syst Rev* 2010;10: CD007950.
30 Katari S, Turan N, Bibikova M, Erinle O, Chalian R, Foster M, et al. DNA methylation and gene expression differences in children conceived *in vitro* or *in vivo*. *Hum Mol Genet* 2009;18: 3769–78.

