

INTERGROWTH-21st – Time to standardise fetal measurement in Australia

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Introduction

Fetal measurements have been a contentious issue in ultrasound departments worldwide for decades. With a plethora of literature on measuring planes, mathematical formulae, local charts, and differences in fetal size due to various factors, deciding which charts to use can be confusing.

Australia has not been immune to this issue. In 2001, ASUM recommended the use of the Campbell Westerway charts for CRL, BPD, OFD, HC, AC, FL & HL, which were formulated from an Australian population. Despite this recommendation, there are currently at least eight fetal growth charts in clinical use around Australia.¹ Unfortunately, it is not uncommon to find different charts on different machines within the same department, which is confusing for follow-up growth studies, and affects parents, clinicians and researchers alike. For example, a baby diagnosed as small for gestational age (SGA) by one practitioner is later that day found to be 'normal' with a different reference chart at the referral hospital. This makes counselling challenging: why does this difference exist? Is it due to the chart or the quality of scanning? Is the baby at risk or not? The issue illustrates the problem of a lack of uniform ultrasound reporting, which may be particularly noticeable in countries like Australia where scans are commonly performed in small private practices.

In general terms, fetal growth can be assessed using charts that are:

- 1 Derived from the observed distributions of fetal size for gestational age in a defined population
- 2 Customised on the basis of maternal characteristics such as maternal parity, height and ethnicity including an estimate of fetal weight based on Hadlock's proportionality equation
- 3 Standards derived from a healthy population purposely selected to reflect optimal growth, based on observed measurements of fetuses that are free from adverse constraints on growth and which are independent of time or place.

SGA is most commonly defined as the 10th centile of estimated fetal weight (EFW) or abdominal circumference (AC). It must be realised that the apparent 'prevalence' of SGA will

always be close to the 10th centile when reference or customised charts are used. This is despite the fact that the prevalence of other perinatal conditions differs greatly around the world: for example, differences in rates of pre-eclampsia or gestational diabetes are readily accepted, without a call for local definitions, demonstrating the illogical nature of insisting on an SGA prevalence that is "fixed" at 10%.

So which fetal biometry charts should be used from the hundreds available around the world? After over five decades of obstetric ultrasound there has been no implementation of an international standard. Contrast this with the consensus on optimal growth in paediatrics. Since the 1970s, it has been observed that growth in children depends more on their environment and nutritional state, than ethnic origin.² In 1996, the WHO Multicentre Growth Reference Study (MGRS) was established to prove whether this hypothesis was indeed correct for babies born in diverse populations around the world. Across six countries, researchers followed the growth and development of 8406 healthy, breast-fed babies until 5 years of age.³ They demonstrated that, under such conditions, growth was remarkably similar in childhood.⁴ This led to the release of the WHO Child Growth Standards in 2006 and these have subsequently been adopted in over 130 countries.⁵ In Australia, national unification of child growth monitoring occurred in 2012, when the NHMRC recommended the WHO Child Growth Standards for use in all infants aged 0 to 2 years of age.⁶

The current situation in fetal medicine

Identifying babies experiencing poor or excessive growth in utero is challenging. Despite ASUM recommending the Campbell Westerway charts in 2000,⁷ there has been no consensus on fetal growth monitoring, no publication of an 'Australian standard', and consequently several charts have been used. For most practitioners, the choice of fetal growth chart is determined either by their institutional protocol, professional society, imaging software program, or the default chart installed by the ultrasound machine manufacturer. However, charts differ

Intergrowth vs. Westerway charts

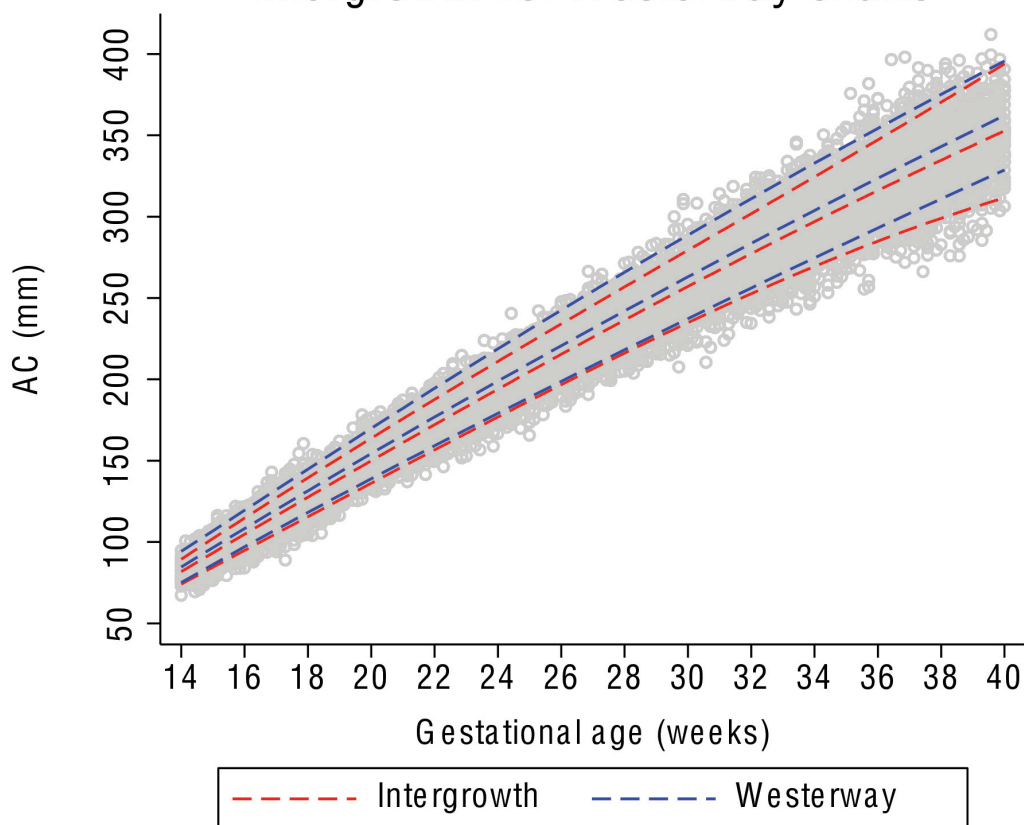


Figure 1: Abdominal circumference.

greatly not only in the centile thresholds and trajectories, but also the quality of the studies upon which they were based: two comprehensive systematic reviews evaluated the quality of published ultrasound charts for fetal dating with crown-rump length⁸ and fetal growth monitoring.⁹ Across the 112 studies identified, there were several important potential sources of methodological bias including: failure to define gestational age accurately; inconsistent population definitions and inclusion and exclusion criteria; lack of image standardisation protocols, and retrospective analysis of images captured for clinical purposes. This resulted in a large amount of variation in centile thresholds when different charts were used: for example, the 10th centile for AC at 36 weeks' gestation ranged from 276 to 292 mm even among the best studies.

The INTERGROWTH-21st Project

In 2008, the INTERGROWTH-21st Consortium was established to determine if under optimal circumstances, fetal growth was similar enough between populations to justify an international standard, directly analogous to the WHO Child Growth Standards.¹⁰ The Consortium, led by a team at the University of Oxford, comprised a global collaborative network of over 300 researchers and clinicians. The INTERGROWTH-21st Project was implemented in eight countries from 2009 to 2014. All study protocols and primary findings are available online (intergrowth21.org). Briefly, eight diverse urban populations living in demarcated geographical areas were selected where: environments were free from major known pollutants; altitude

was less than 1600 m; most women accessed antenatal and delivery care in institutions; mean birth weight was greater than 3100 g; rates of low birth weight (< 2500 g) were less than 10%, and perinatal mortality was less than 20 per 1000 births.¹⁰ The study sites were: Pelotas, Brazil; Shunyi County Beijing, China; Central Nagpur District, India; Turin, Italy; Nairobi, Kenya; Muscat, Oman; Oxford, UK, and Seattle, USA.

Within these populations, mothers were screened for eligibility to enter the Fetal Growth Longitudinal Study (FGLS), a component of the INTERGROWTH-21st Project that aimed to monitor growth and development from early pregnancy until infancy. In FGLS, fetal biometry was measured by ultrasound using a highly standardised, blinded and scientifically rigorous protocol designed to minimise intra- and inter-observer bias.¹¹⁻¹³ Measurements were repeated every five weeks until birth. At birth, the same rigour was applied to measure the weight, length and head circumference of all newborns in the entire population.¹⁴

The statistical approaches to determine whether the measurements from the eight study sites could be pooled to produce standards were the same as those used in the WHO MGRS. The analysis demonstrated that only 1.9% to 3.5% of the variation observed between linear fetal growth and newborn size at birth, was due to inter-site differences.¹⁵ Therefore, as previously observed with infant and child growth patterns, fetal growth and newborn size at birth are remarkably similar around the world when constraints on growth are minimal. At 12 months of postnatal age, height for age z scores in the FGLS

Intergrowth vs. Westerway charts

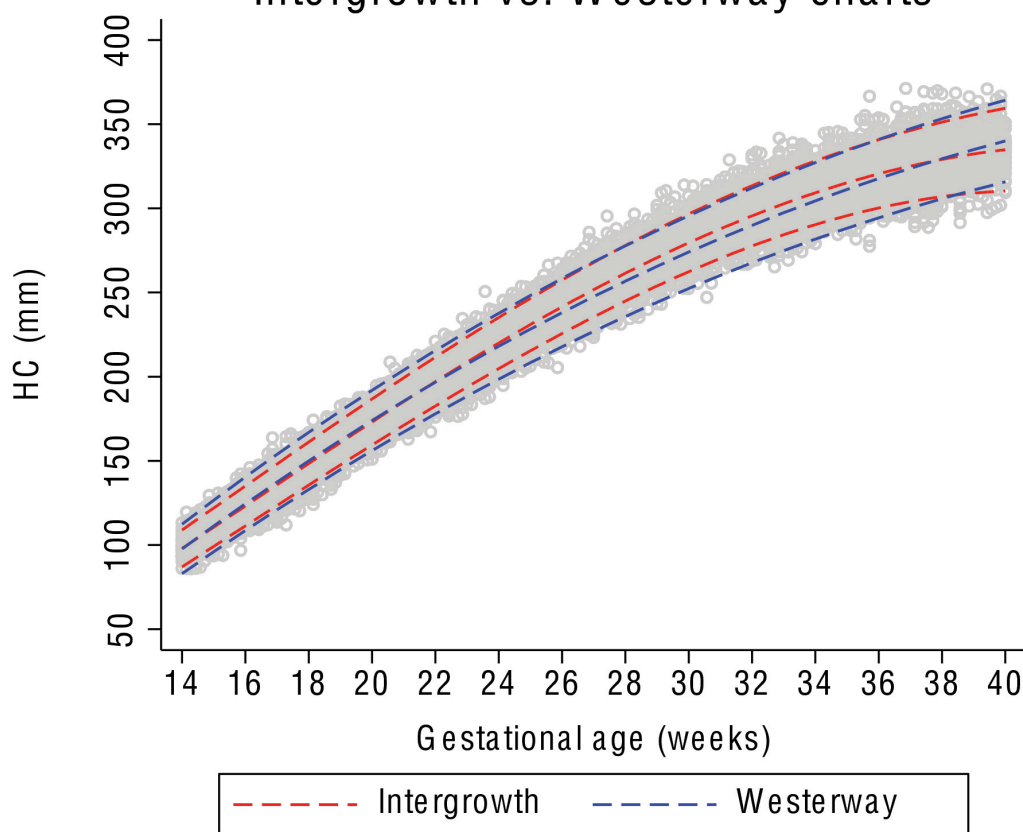


Figure 2: Head circumference.

children aligned almost exactly with the distribution observed in the WHO MGRS children. This meant that the data from all sites could be pooled in order to create international fetal and newborn growth standards, describing not how fetuses have grown in a particular location or at a particular time, but how they *should* grow.

Relevance for the Australian population

The INTERGROWTH-21st Fetal Growth Standards represent the most scientifically robust data available on fetal growth monitoring and align exactly with the WHO standards endorsed in Australia for use in infants. Questions that now arise include: How applicable are the FLGS standards for pregnancies in Australia? How do the new standards compare to growth charts currently in use and how should the standards be interpreted in clinical practice?

The ethnic and racial mix in Australia is perhaps greater than anywhere else on Earth. In the 2011 census, 30% of Australians were born overseas, with some of the highest proportions originally from the UK, China, India and Italy: all INTERGROWTH-21st countries. Of those born in Australia, 30% have one or both parents born overseas.¹⁶ The INTERGROWTH-21st standards should be highly appealing to a country like Australia, where concepts such as ‘race’ are becoming less relevant with each generation.

Comparing the INTERGROWTH-21st standards to the Campbell Westerway Charts recommended by ASUM demonstrates that the charts are generally similar (Graphs 1–3).

There is slight variation for the BPD as it was measured “outer to outer” in FGLS instead of “outer to inner” of the parietal bone. The largest difference is seen with the femur length where the apparently shorter femurs in the INTERGROWTH-21st study may be explained by technical issues, as it has been previously shown that the narrowed beam width in newer ultrasound machines shortens measurements in the lateral direction.¹⁷

Implications for and introduction into clinical practice

Clinically it is important to be able to define a cohort at high-risk of fetal growth restriction as these pregnancies have higher rates of morbidity and mortality. Fetal biometry is only one tool to detect babies at risk of perinatal or longer-term complications. A number of research questions still need to be addressed. A first step could be to consider fetal growth phenotypes beyond estimated weight for gestational age. In the the INTERGROWTH-21st populations as a whole, there was strong evidence of phenotypic differences at birth, i.e. stunting, wasting and overweight, with different neonatal outcomes. This is likely going to be an important area of research in the future as we begin to understand more about the patterns and longer-term consequences of intrauterine growth.

Given the international nature and scale of INTERGROWTH-21st, the attention to image quality, and the similarities of growth observed between the babies in FGLS and MGRS nearly 20 years earlier, there is now robust evidence to support the hypothesis that ethnicity plays a minimal role in early human growth. It makes no biological sense to measure a baby differently in utero

Intergrowth vs. Westerway charts

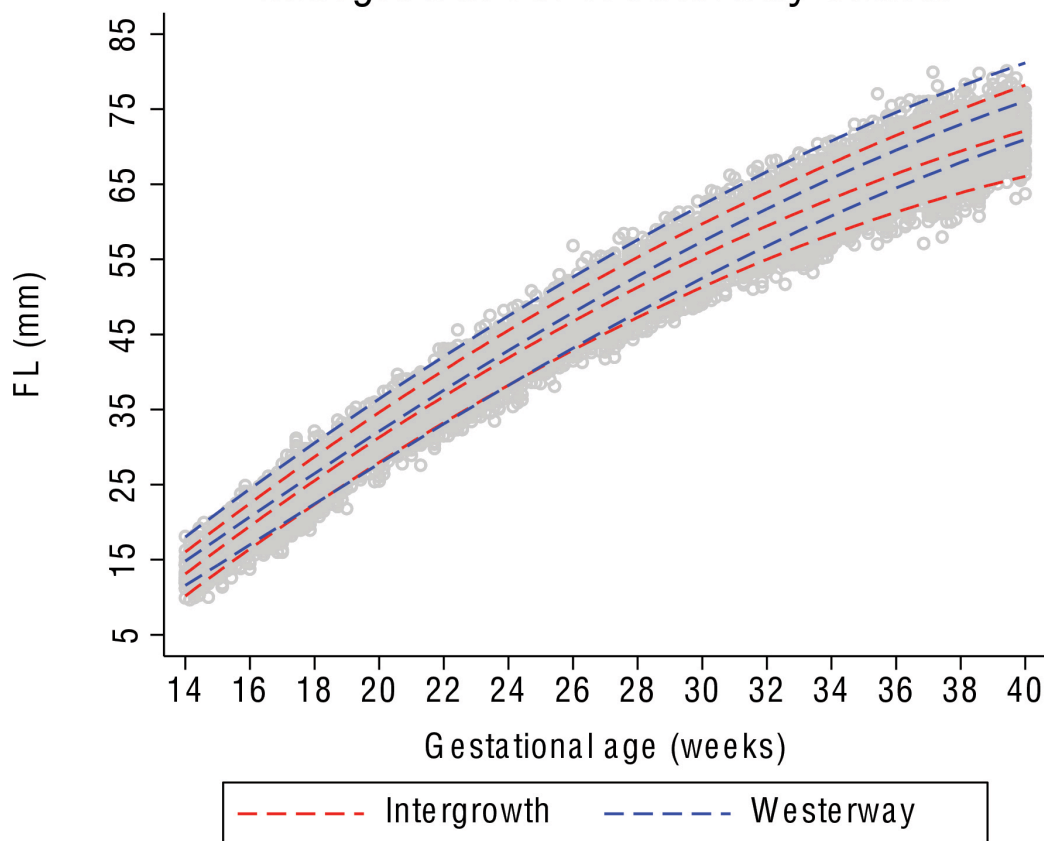


Figure 3: Femur length.

and after birth. This brings into question the role of ethnicity that has been proposed in some customised charts.

The questions for clinicians are not whether the standards are applicable to Australian babies, but whether these charts can be used to identify and manage pregnancies that have evidence of abnormal growth. Should women living in circumstances that do not match the ‘ideal’ environment of the INTERGROWTH-21st centres be expected to have constitutionally identical fetuses? Are INTERGROWTH-21st centiles appropriate trigger points for pathways of pregnancy management and will these interventions lead to a reduction in morbidity and mortality related to abnormal fetal growth? These questions don’t have answers at this stage.

At the 2015 ASUM Annual Scientific Meeting in Sydney, Professor Aris Papageorghiou will give a number of presentations on the INTERGROWTH-21st Project. There will also be a panel of Australian experts to discuss and debate the implementation of the INTERGROWTH-21st maternal weight gain, early pregnancy dating, fetal growth and newborn size for gestation age standards into clinical practice in Australia.

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