

Institution: University of Oxford		
Unit of Assessment: 1 – Clinical Medicine		
Title of case study: INTERGROWTH-21 st Project: International standards to improve fetal and child health		
Period when the underpinning research was undertaken: 2009 - 2016		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Stephen Kennedy	Professor of Reproductive Medicine	1990 - present
José Villar	Professor of Perinatal Medicine	2008 - 2017
Aris Papageorgiou	Professor of Fetal Medicine	2009 - present
Period when the claimed impact occurred: 2014 – July 2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact The University of Oxford's INTERGROWTH-21st Project, involving nearly 70,000 mothers and babies worldwide, has produced clinical tools to diagnose impaired growth and development in pregnancy and infancy, which standardise care for mothers and their babies. These international standards replace multiple local reference charts and provide benchmarks for health professionals everywhere: for example, by establishing the standard for microcephaly that was recommended by the World Health Organization (WHO) and US Centers for Disease Control and Prevention during the 2016 Zika virus outbreak. For low-to-middle income countries, these standards have led to a reinterpretation of the number of deaths attributed to neonates born small for their gestational age. The INTERGROWTH-21st Preterm Postnatal Growth Standards and feeding protocol have also been implemented by 370 neonatal units globally. The standards are based on the INTERGROWTH-21st Project's landmark finding: healthy mothers have babies that grow in a similar way in utero and achieve a similar size at birth, irrespective of their ancestry, ethnicity or place of birth.		
2. Underpinning research The International Fetal & Newborn Growth Consortium for the 21st Century Project (INTERGROWTH-21st) is a large, multicentre, population-based research initiative, led by Professors Stephen Kennedy, José Villar and Aris Papageorgiou (University of Oxford). This work was done by a multidisciplinary network of more than 300 health care professionals and scientists from 35 institutions in 21 countries. Villar and Kennedy designed the studies, coordinated the network, managed the project, and analysed the data. Papageorgiou led the ultrasound and clinical dissemination components of the project. The project, involving nearly 70,000 mothers and babies worldwide, was established to assess human growth, development and associated behaviours from early pregnancy to two years of age under: i) healthy conditions (Phase I) and ii) various sub-optimal conditions (e.g., maternal infections, malnutrition and pregnancy complications) and other risk factors for adverse outcomes (Phase II, currently ongoing). The project's guiding principle was that the main		

adverse perinatal outcomes - fetal death, preterm birth and fetal growth restriction - are highly heterogeneous, inter-related syndromes that require targeted interventions focused on the underlying causes.

Phase I of the INTERGROWTH-21st Project, conducted between 2009 - 2016, consisted of five complementary studies designed to describe optimal human growth and development. The studies were based on the World Health Organization (WHO) prescriptive approach and took place across eight urban areas worldwide: these were geographically delimited to ensure the project was population-based [1]. The study team tracked fetal growth throughout pregnancy from <14 weeks gestation in a large cohort of healthy women and continued to monitor their infants prospectively until they were two years old. At both population and individual levels, the participants had the recommended health, nutritional and socio-economic status needed to produce international standards: the women were generally healthy, well-nourished, and well-educated, living freely in environments with minimal constraints on fetal growth, and receiving standardised, evidence-based antenatal care.

The principal findings of the project are that early human growth and development are similar across diverse geographical settings when mothers' nutritional and health needs are met, and environmental constraints on growth are low. These findings have a very strong public health message: healthy mothers have babies that grow in a similar way in utero and achieve a similar size at birth, irrespective of their ancestry, ethnicity, or place of birth [2].

These studies led to the construction of a set of international standards for monitoring mothers and babies, using the WHO recommended prescriptive approach [3, 4, 5]. These include tools for: 1) estimating gestational age in early and late pregnancy; 2) monitoring gestational weight gain; 3) measuring symphyseal-fundal height (SFH); 4) measuring fetal size and estimated fetal weight with ultrasound to monitor intrauterine growth; 5) evaluating newborn size at birth, and 6) monitoring the postnatal growth of preterm infants. Uniquely, the same healthy cohort was used to produce the entire set of tools - the largest population ever assembled for such a longitudinal study. This is also the first time that a uniform method to describe fetal health and growth up to two years of age had been developed.

The children whose intrauterine ultrasound growth data were used to construct the INTERGROWTH-21st Fetal Growth Standards remained healthy with satisfactory growth and motor development up to two years of age, supporting the use of this cohort to construct international standards.

The INTER-NDA tool, developed specifically for this project, was used to assess the sequence and timing of attainment of key neurodevelopmental milestones and associated behaviours among these children at two years of age, for implementation by non-specialists across international settings. The children's developmental patterns were similar across these geographically diverse populations in keeping with the associated low health, nutritional and environmental risks [6].

These international standards, which perfectly complement the existing WHO Child Growth Standards, provide a unique set of clinical tools for use across all healthcare systems to diagnose impaired growth and development and standardise the care of pregnant women and their infants across the world.

3. References to the research (University of Oxford authors in bold)

1. Villar J, Altman DG, Purwar M, Noble JA, Knight HE, Ruyan P, Cheikh Ismail L, Barros FC, Lambert A, Papageorgiou AT, Carvalho M, Jaffer YA, Bertino E, Gravett MG, Bhutta ZA, Kennedy SH; International Fetal and Newborn Growth Consortium for the 21st Century (2013). The objectives, design and implementation of the INTERGROWTH-21st Project, *BJOG* 120 Suppl 2:9-26, v. DOI: [10.1111/1471-0528.12047](https://doi.org/10.1111/1471-0528.12047). 131 citations WoS to 31/12/20

2. **Villar J, Papageorghiou AT, Pang R, Ohuma EO, Cheikh Ismail L, Barros FC, Lambert A, Carvalho M, Jaffer YA, Bertino E, Gravett MG, Altman DG, Purwar M, Frederick IO, Noble JA, Victora CG, Bhutta ZA, Kennedy SH**; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) (2014). The likeness of fetal growth and newborn size across non-isolated populations in the INTERGROWTH-21st Project: the Fetal Growth Longitudinal Study and Newborn Cross-Sectional Study. *Lancet Diabetes Endocrinol*; 2(10): 781-92. DOI: [10.1016/S2213-8587\(14\)70121-4](https://doi.org/10.1016/S2213-8587(14)70121-4). 133 citations WoS to 31/12/20
3. **Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Cheikh Ismail L, Lambert A, Jaffer YA, Bertino E, Gravett MG, Purwar M, Noble JA, Pang R, Victora CG, Barros FC, Carvalho M, Salomon LJ, Bhutta ZA, Kennedy SH, Villar J**; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) (2014). International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. *Lancet* 6;384(9946):869-79. DOI: [10.1016/S0140-6736\(14\)61490-2](https://doi.org/10.1016/S0140-6736(14)61490-2). 342 citations WoS to 31/12/20
4. **Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, Lambert A, Papageorghiou AT, Carvalho M, Jaffer YA, Gravett MG, Purwar M, Frederick IO, Noble AJ, Pang R, Barros FC, Chumlea C, Bhutta ZA, Kennedy SH**; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) (2014). International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet* 6;384(9946):857-68. DOI: [10.1016/S0140-6736\(14\)60932-6](https://doi.org/10.1016/S0140-6736(14)60932-6). 635 citations WoS to 31/12/20
5. **Villar J, Giuliani F, Bhutta ZA, Bertino E, Ohuma EO, Ismail LC, Barros FC, Altman DG, Victora C, Noble JA, Gravett MG, Purwar M, Pang R, Lambert A, Papageorghiou AT, Ochieng R, Jaffer YA, Kennedy SH** (2015). Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-up Study of the INTERGROWTH-21st Project. *Lancet Global Health* 3(11):e681-91. DOI: [10.1016/S2214-09X\(15\)00163-1](https://doi.org/10.1016/S2214-09X(15)00163-1). 102 citations WoS to 31/12/20
6. **Villar J, Fernandes M, Purwar M, Staines Urias E, Di Nicola P, Cheikh Ismail L, Ochieng R, Barros F, Albernaz E, Victora C, Kunawar N, Temple S, Giuliani F, Sandells T, Carvalho M, Ohuma E, Jaffer Y, Noble JA, Gravett M, Pang R, Lambert A, Bertino E, Papageorghiou AT, Garza C, Stein A, Bhutta Z & Kennedy SH** (2019). Neurodevelopmental milestones and associated behaviours are similar among healthy children across diverse geographical locations. *Nature Communications* 10:511. DOI: [10.1038/s41467-018-07983-4](https://doi.org/10.1038/s41467-018-07983-4).

Funding includes 'The International Fetal and Newborn Growth Consortium for the 21st Century' from the Bill & Melinda Gates Foundation, GBP5,946,463 to University of Oxford (OPP49038, 2008-2013), as project leader, as part of global budget of USD29,034,700; and further award for subsequent data analysis GBP359,987 (OPP1192091, 2015-2017).

4. Details of the impact

Global uptake of INTERGROWTH-21st Preterm Postnatal Growth Standards

In 2016, the team began the INTERPRACTICE-21st Project to scale up global implementation of the INTERGROWTH-21st Preterm Postnatal Growth Standards [5]. WHO and the US Centers for Disease Control and Prevention (CDC) have both recommended use of the INTERGROWTH-21st standards and feeding protocols [A]. As of 31 July 2020, 370 neonatal units around the world have implemented the standards and protocols in countries including Dubai, Haiti, Saudi Arabia, Sri Lanka, Thailand, and the USA. The standards and protocols have also been adopted by national paediatric and neonatal societies and Ministries of Health, for example the National Paediatric Society of Argentina and the Italian Society of Neonatology. The standards seek to reduce the overdiagnosis of extrauterine growth restriction, which results in overfeeding that can lead to obesity and cardiometabolic disease in adulthood. Monitoring preterm infants with the INTERGROWTH-21st standards, which describe optimal postnatal growth, reduces the risk of overfeeding. The feeding protocols detail how to feed a preterm infant, emphasising the use of human milk.

UK Clinical Guidelines

In 2018, following an analysis of evidence to prevent stillbirths, the Scottish Government recommended the use of the INTERGROWTH-21st Symphyseal-fundal Height (SFH) Standards and Fetal Growth Standards for monitoring pregnancies [3]. A letter in November 2018 from the Children and Families Directorate of the Scottish Government, to Chief Executives, Medical Directors and Nurse Directors [B] states that *"The expert Scottish Government led Stillbirth Group has reviewed current evidence around accuracy of charts and recommends the use of Intergrowth 21st SFH and ultrasound growth charts which are free to use and readily available"*

Use in perinatal patient data management and the Neonatology GIRFT project

The INTERGROWTH-21st standards, describing how a preterm infant should grow, have been integrated into BadgerNet, the pregnancy and neonatal unit data management system widely used across the NHS for the collection, storage and reporting of perinatal patient data. The raw data available in the BadgerNet system are being used by the Neonatology GIRFT Project to benchmark the extent to which preterm infants are growing optimally and to provide feedback to neonatal units on how well their patients are growing against the standards. The GIRFT Clinical Lead for Neonatology highlights how the data are being used: *"Thank you so much for providing GIRFT Neonatology with Z scores from both the INTERGROWTH-21st Newborn Size Standards and Preterm Postnatal Growth Standards for all premature babies admitted to neonatal units in England for the three year period 2016-19. I have used the data to develop some benchmarking metrics to review growth between admission and discharge for babies at different gestational ages"* [C].

Establishing international standards for microcephaly

During the 2016 Zika virus (ZIKV) outbreak in Brazil the use of the INTERGROWTH-21st standards redefined the definition of microcephaly and led to changes in global practice and guidelines. On 8 December 2015, the Brazilian Ministry of Health changed its definition of microcephaly from head circumference at birth ≤ 33 cm to ≤ 32 cm, irrespective of the baby's sex or gestational age at birth. In a letter to the Lancet in February 2016 a group of Brazilian epidemiologists argued to use the international INTERGROWTH-21st Newborn Size Standards as these are sex and gestational age specific standards for optimal size at birth. Their use, they stated, could reduce the number of suspected cases in Brazil from an anticipated 600,000 to 63,000 or 3,000 for cut-offs of -2SD or -3SD, respectively [D].

WHO published an interim Rapid Advice Guideline in February 2016 and an update in August 2016 [E], which included the recommendation to use the INTERGROWTH-21st Preterm Postnatal Growth Standards for pre-term neonates (and for term neonates if accurate gestational age is known) to interpret postnatal changes in head circumference until 64 weeks postmenstrual age. The CDC's ZIKV management guidelines also recommend the INTERGROWTH-21st Fetal Growth Standards to assess head circumference at three points during pregnancy [F]. The use of a more specific definition of microcephaly focuses screening efforts, reduces the need for further investigations, and would also reduce the burden and costs on the health system. Furthermore, it alleviates the emotional effects on parents of healthy infants who might have otherwise been given a false-positive result in the screening assessment [D]. The Brazilian Government subsequently adopted the standards for all pre-term babies born in the country.

Reinterpretation of existing newborn data in low-middle income countries (LMICs)

In a 2015 JAMA paper, the Child Health Epidemiology Reference Group at Johns Hopkins University concluded that using the INTERGROWTH-21st Newborn Size Standards rather than the US Birth Weight References reduced the prevalence of small for gestational age (SGA) in 16 LMIC cohorts without any effect on neonatal mortality [G], i.e. using the INTERGROWTH-21st standards resulted in a decrease in the percentage of neonatal deaths attributable to SGA. In a 2017 BMJ paper, the same group selected the INTERGROWTH-21st Newborn Size Standards [4] as the most reliable tool for estimating the true prevalence of SGA in LMICs worldwide [H].

The revised 2012 data, using the INTERGROWTH-21st definition, indicated that 23,300,000 infants were born SGA, with an estimated 606,500 attributable neonatal deaths, i.e. 21.9% of all neonatal deaths worldwide.

Healthcare professional uptake and training

For implementation purposes, the study team made the INTERGROWTH-21st clinical tools, publications, tables, charts, calculators, apps, and training resources freely downloadable [Ii]. Clinicians and health practitioners are further supported through a number of training resources [Iii]. Between July 2014 and May 2020 the resources have been downloaded from The Global Health Network website 231,726 times by users in 195 countries and territories, and 23,580 healthcare professionals have been trained using INTERGROWTH-21st e-learning modules [J].

In 2019, The Global Health Network conducted an online survey of website users (hospitals/health centres 57.0%; universities 19.9%; NGOs 15.1%; Health Ministries/ others 8.0%). The following percentages of these users had introduced the INTERGROWTH-21st standards into clinical practice in their institutions: pregnancy dating 43.2%; symphyseal-fundal height 31.6%; fetal growth by ultrasound 40.1%; newborn size 56.4%; gestational weight gain 34.9%, and preterm postnatal growth 50.6%. More than 100 health care professionals have been trained to deliver the INTERGROWTH-21st Neurodevelopment Package (INTER-NDA), which has been used to assess the neurodevelopment of over 15,000 2-year old children in 14 countries. The operation manuals and protocols for the INTER-NDA are freely available [Iiii].

5. Sources to corroborate the impact

- [A] Journal article: Papageorgiou AT et al. (2016) International standards for symphysis-fundal height based on serial measurements from the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project: prospective cohort study in eight countries. *BMJ* 355:i5662 DOI: [10.1136/bmj.i5662](https://doi.org/10.1136/bmj.i5662)
- [B] Letter from Scottish Government Children and Families Directorate to Chief Executives, Medical Directors and Nurse Directors directing implementation of Intergrrowth 21st standards, 8 November 2018
- [C] Letter from GIRFT Clinical Lead for Neonatology, 15 December 2020
- [D] Journal article: Victora CG et al (2016). Microcephaly in Brazil: how to interpret reported numbers? *Lancet* 387:621-624. DOI: [10.1016/S0140-6736\(16\)00273-7](https://doi.org/10.1016/S0140-6736(16)00273-7)
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