

Which growth standards should be used to identify large- and small-for-gestational age infants of mothers with type 1 diabetes? A pre-specified analysis of the CONCEPTT trial

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Research article

Keywords: Large-for-gestational-age, small for gestational age, macrosomia, birth-weight, diabetes, pregnancy, CONCEPTT, growth standards, INTERGROWTH, GROW

Posted Date: July 9th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-27918/v2>

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Version of Record: A version of this preprint was published on January 29th, 2021. See the published version at <https://doi.org/10.1186/s12884-021-03554-6>.

Abstract

Background Offspring of women with type 1 diabetes are at increased risk of accelerated fetal growth which is associated with perinatal morbidity. Growth standards are used to identify large- or small- for gestational age (LGA, SGA) infants. Our aim was to examine which growth standards identify infants at risk of perinatal complications during the Continuous Glucose Monitoring in Type 1 Diabetes Pregnancy Trial (CONCEPTT).

Methods This was a pre-specified analysis of CONCEPTT involving 225 pregnant women from 31 international centres. Infants were weighed immediately at birth and GROW, INTERGROWTH and WHO centiles calculated. Unadjusted logistic regression identified the associations between different growth standards and perinatal outcomes including preterm delivery, Caesarean delivery, neonatal hypoglycaemia, hyperbilirubinaemia, respiratory distress, neonatal intensive care unit (NICU) admission and a composite neonatal outcome.

Results Accelerated fetal growth was common, with mean birthweight percentiles of 82.1, 85.7 and 63.9 and LGA rates of 62%, 67% and 30% using GROW, INTERGROWTH and WHO standards respectively. Corresponding rates of SGA were 2.2%, 1.3% and 8.9% respectively. All standards were associated with some but not all perinatal outcomes studied. Infants born >97.7th centile were at highest risk of complications.

Conclusions WHO standards underestimated birthweight centile. GROW and INTERGROWTH standards identified similar numbers of infants as LGA and SGA with GROW showing stronger associations with neonatal hypoglycaemia, hyperbilirubinaemia and NICU admission. Infants with suspected birthweight >97.7th centile according to any standard may require extra surveillance. Definitions of LGA and SGA should be re-evaluated in diabetic pregnancy.

Background

Birth weight is an important indicator of neonatal well-being^{1 2}. Infants who are small- or large-for-gestational-age (SGA or LGA; birth weight <10th or >90th percentile) experience higher risks of morbidity and mortality^{3 4}. Assessment of growth in offspring of mothers with type 1 diabetes (T1D) is vital as they are at high risk of accelerated growth resulting in perinatal complications⁵. Recent data suggests that despite improvements in care, infants of women with T1D remain at high risk of LGA (rates ~50%)⁵. LGA rates were also high in the CONCEPTT randomized controlled multicentre international trial of the use of continuous glucose monitoring (CGM) in comparison with capillary blood glucose monitoring in pregnant women with T1D⁶. LGA rates were significantly reduced in infants of women who used CGM (53% Vs 69% in home blood glucose monitoring group), likely due to improved glycaemic control⁷.

Currently there is controversy internationally about which growth standards to use. Customised (Gestation Related Optimum Weight; GROW) centiles⁸ were used in CONCEPTT for the comparison of

birthweight across international sites and diagnosis of LGA. GROW centiles are customised to maternal and neonatal factors including maternal ethnicity, height, weight, parity, neonatal sex and gestational age [7, 10]. Advocates of GROW suggest that customised centiles reduce over-investigation of normal fetuses and can more accurately predict stillbirth and perinatal mortality rates^{9 10}.

Other techniques based on data from the INTERGROWTH-21st study (20 486 infants across eight geographical areas) and the World Health Organisation (WHO) Multicentre Growth Reference Study (8500 infants across six geographical areas)^{11 12} are used internationally. Both standards assume <3.5% of the variability in growth is due to differences in ethnicity and population when circumstances are optimal (e.g healthy, well-nourished mothers)¹³. INTERGROWTH-21st standards focus on fetal growth and neonatal size at birth, while the WHO charts assess weight-for-age at 0-60 months¹².

Population studies comparing growth standards have focused on the identification of SGA in unselected antenatal populations^{9 10 14}. However, in infants of women with T1D, LGA is five times more common than in the background maternity population⁵. Identification of these infants may improve outcomes by increasing surveillance and targeting interventions to those at highest risk¹⁵. However, the optimal method for growth assessment in infants of women with T1D diabetes is unclear and thus our aim was to examine which of the growth standards identified infants at highest risk of perinatal complications.

Methods

The recruitment, rationale and methodology of CONCEPTT is described in detail elsewhere⁶. In brief, women with T1D were recruited before or during pregnancy and randomized to real-time continuous glucose monitoring or capillary glucose monitoring alone. Women in the capillary glucose monitoring group also had short periods of masked continuous glucose monitoring, to allow comparison of glycaemic control between groups. Women were followed-up until delivery with collection of information about birth outcomes. Local policies in the study sites were used to determine the optimal timing and method of delivery.

Pre-specified neonatal outcomes for the CONCEPTT study included miscarriage, stillbirth, neonatal death, birth injury, shoulder dystocia, preterm delivery, neonatal hypoglycaemia requiring intravenous dextrose, hyperbilirubinaemia, respiratory distress syndrome, neonatal intensive care unit admission requiring a duration of at least 24 hours, total length of hospital stay, birthweight, macrosomia (birthweight ≥ 4 kg), LGA (>90th centile) and SGA (<10th centile) based on customised centiles. Definitions for CONCEPTT outcomes are given in Appendix S2 and were standardised across all the CONCEPTT sites. This data was collected using participant's medical records. A composite neonatal endpoint incorporated pregnancy loss (miscarriage, stillbirth, or neonatal death), birth injury, neonatal hypoglycaemia, hyperbilirubinaemia, respiratory distress syndrome, or neonatal intensive care admission >24 hours. This pre-specified secondary analysis includes data from pregnant and pre-pregnant recruits who became pregnant during the 6-month pre-pregnancy trial and who gave birth to a liveborn infant. Therefore, in the current study, the

composite neonatal endpoint incorporated birth injury, neonatal hypoglycaemia, hyperbilirubinaemia, respiratory distress syndrome, or neonatal intensive care admission >24 hours but not pregnancy loss.

Calculation of Birth weight Centiles

Gestational age at delivery was based upon ultrasound measurements in early pregnancy (approximately 12 weeks). Maternal height and weight required for the GROW calculation was measured by trained staff at the baseline study visit. As the CONCEPTT study recruited women in early pregnancy, this was considered broadly similar to pre-pregnancy weight.

GROW centiles were calculated using version 8 (2017) of the GROW calculator using data about maternal self-reported ethnicity, parity, height, weight, gestational age at birth and neonatal sex⁸. INTERGROWTH centiles were calculated using the windows app (available at <https://intergrowth21.tghn.org/intergrowth-21st-applications/>; accessed 31/03/2019) using information about infant sex, weight and age (0-60 months). WHO centiles were calculated using data about infant sex, weight and gestational age at birth using the igrowup package for Stata (available at <http://www.who.int/childgrowth/software/en/>; accessed 31/03/2019). Some studies have previously reported standard deviation (SD) based birthweight categorisation. To allow comparison between centile-based methods and SD-based methods, we also included SD-based definitions for LGA (+1 and 2 SDs) using methods which were commonly used in the literature. Calculation of SGA using definitions <5th and <2.5th percentile resulted in too few infants to permit meaningful analysis.

Statistical Analysis

Continuous data were described as mean (SD) and categorical data as n (%) as appropriate. Data regarding birthweight were analysed as percentiles. Logistic regression was used to identify the ability of birthweight categories according to different growth standards to predict neonatal categorical outcomes. Unadjusted odds ratios were reported for the associations between birth weight centile category and perinatal outcomes. We used odds ratios instead of risk ratios, as the predictor variable, LGA or SGA, is not a true 'exposure' but rather reflects a manifestation of a pathological process which could also be associated with other pregnancy outcomes. We considered that the best performing growth standard to be that which was significantly associated with the most suboptimal perinatal outcomes.

Results

225 women and infants were included in this analysis, including 200 from the pregnancy arm and 25 from the pre-pregnancy arm who became pregnant during the trial. Baseline characteristics and pregnancy outcomes are detailed in Table 1. Most women were over 30 years old (mean age 31.4 years), overweight (mean BMI 25.8 kg/m²), of European or Mediterranean ethnicity (86.2%) and approximately half used insulin pump therapy (48.9%). They had T1D of 16.5 years' duration with suboptimal glucose control (HbA_{1c} 6.9%; 51.8 mmol/mol) in early pregnancy as defined by the trial eligibility criteria, which

required HbA_{1c} \geq 6.5% (48 mmol/mol) in early pregnancy. Their infants were born at 37.0 weeks of gestation, predominantly by Caesarean section (68.9%).

Large-for-gestational-age (LGA) rates varied (Table 2. GROW: 62.2%; INTERGROWTH 66.7%; WHO 29.8%) and there were differences in mean centile (Table 1. GROW: 82.1; INTERGROWTH 85.7; WHO 63.9 centiles). Other measures of birth weight are shown in table 2. Other common perinatal complications included neonatal hypoglycaemia (25.3%), hyperbilirubinaemia (27.6%), respiratory distress (8.4%) which all contributed to frequent NICU admissions >24 hr (36.9%). Birth injury and shoulder dystocia were uncommon, (1/225 (0.4%) for each) and only occurred in infants who were considered LGA by all criteria. LGA according to GROW, INTERGROWTH and WHO criteria were associated with increased risks of perinatal complications (Table 2). While each growth standard was associated with some complications, no growth standard identified all complications studied. Caesarean section was most strongly associated with LGA, according to all three growth standards. Increased birthweight according to GROW displayed more significant associations with perinatal outcomes than INTERGROWTH (i.e. with preterm delivery, neonatal hypoglycemia or hyperbilirubinemia).

Most perinatal complications demonstrated a U-shaped relationship with the birth centile (figure 1). Neonatal hypoglycaemia was most frequent in infants born extremely large for gestational age (ELGA; $>97.7^{\text{th}}$ centile). No significant differences in rates of preterm delivery, NICU admission, hyperbilirubinaemia and respiratory distress were observed in smaller infants ($<25^{\text{th}}$ centile; figure 1) but there were few infants in this group (Table 2). GROW and INTERGROWTH standards performed similarly and identified similar numbers with LGA (slightly higher for INTERGROWTH) and SGA (slightly higher for GROW). These standards performed consistently regardless of sex, ethnicity and timing of delivery (see supporting tables S1-S3). The positive and negative predictive values of the neonatal outcomes and their associated sensitivity and specificity are varied depending on outcome (supporting table S4). The WHO standards do not take gestational age at birth into account and therefore underestimate size in preterm infants. This resulted in a linear association between WHO centile and preterm delivery (Figure 1).

Discussion

This study demonstrates that GROW and INTERGROWTH growth standards perform comparably in type 1 diabetes pregnancy and are both able to identify infants at increased risk of perinatal complications. LGA defined according to GROW centiles ($>90^{\text{th}}$ and/or $>97.7^{\text{th}}$ centile) showed stronger associations with preterm delivery, neonatal hypoglycaemia, hyperbilirubinaemia and NICU admission.

WHO standards were also able to predict outcomes, but do not incorporate gestational age at delivery, fail to adequately describe size at birth in preterm infants. For term infants, the WHO criteria gave a true birth centile, but for preterm infants, the WHO criteria gave a low centile, which reflected their prematurity, not their comparative size at birth. This measure of prematurity means that the WHO criteria were still able to predict outcomes, despite giving an unreliable birth centile, which demonstrates the importance of preterm delivery in relation to multiple neonatal complications. However, the inability to reliably attribute a

birth weight centile is a substantial limitation in pregnancies of women with T1D, where rates of preterm delivery are high (40% in this study; 46% in clinical data ⁵).

As only a small proportion of the antenatal population has T1D diabetes, CONCEPTT represents one of the largest randomised trials with detailed data on perinatal outcomes, making it useful to assess fetal growth, maternal glycaemia and infant risk. Customised (GROW) centiles were reported for CONCEPTT, but the effect of the intervention was also seen using INTERGROWTH standards. Although accelerated fetal growth is common in T1D pregnancies, the rates of LGA in the CONCEPTT infants were higher than expected (66% in CONCEPTT compared to ~46% in a UK population using similar methodology ⁵). The reasons for this are unclear, particularly as the CONCEPTT population had better glycaemic control compared to the UK clinical population ⁵.

A central aspect to the controversy about GROW and INTERGROWTH centiles involves the perceived importance of maternal factors to the growth of the infant, and ethnicity in particular. A limitation of the CONCEPTT trial is that while it international, 86% of women recruited were of European / Mediterranean origin, which reduced the opportunity to look in depth at growth standard performance in different ethnicities. A further issue is that women who choose to participate in studies are often affluent, well-nourished and educated, and may not represent mothers with different socioeconomic circumstances. Although we have identified that infants <25th centile displayed a trend to be at highest risk of multiple complications, very few infants fall into this category which makes detailed assessment of SGA in diabetic pregnancy very challenging.

The potential value of accurate growth standards is enormous, as identifying LGA or SGA infants offers the opportunity to treat perinatal complications. However, controversy surrounding the performance of different growth standards has been a barrier to improving care. Proponents of the GROW customised approach believe that incorporating maternal variables results in a more accurate representation of size at birth ^{10 16}. Conversely, proponents of the INTERGROWTH-21st study state that variables such as ethnicity make little difference to size at birth, in a well –nourished population with access to adequate antenatal care¹³. A major focus for growth standards has been on the identification of infants who are SGA with a view to reducing stillbirth rates¹⁰.

In this study, standard-deviation-based criteria for the diagnosis of LGA have been assessed. Although a birth weight z score >1 is considered consistent with LGA, this definition is different to standard centile-based definitions (>90th centile)¹⁷. Different approaches to the LGA diagnosis contribute to difficulty in comparing populations internationally ¹⁸⁻²⁰.

In this population, the standard definition of SGA identified few infants (1.3-1.8% both with GROW and INTERGROWTH standards). Although SGA is uncommon in type 1 diabetes pregnancy, it is likely that infants born <10th centile do not represent all those with growth restriction. Better understanding of the causes and early identification of growth restriction in diabetic pregnancy should be a research priority.

Larger data sets that examine the risks of this group are required, due to the small numbers in this category examined here.

A fundamental aim of antenatal care in T1D pregnancies involves careful control of maternal factors (e.g. glycaemia) to normalise fetal growth. GROW standards showed stronger associations with neonatal complications but this standard requires additional data to calculate, which may make it less feasible to guide routine care decisions. Significant odds ratios for INTERGROWTH standards were associated with Caesarean delivery, neonatal hypoglycaemia, NICU admission and the composite outcome in the >97.7th centile group. GROW identified fewer infants as LGA compared to INTERGROWTH standards.

WHO growth standards performed poorly here, as there was no adjustment made for infants born preterm. This limitation highlights this system may miss infants at risk, especially those born preterm¹². Fewer infants identified as LGA using the WHO standards compared to GROW and INTERGROWTH, but those identified were undeniably at high risk of complications. Therefore LGA infants not born near term using WHO standards are at risk of not being identified, giving fewer opportunities for intervention preventing complications.

GROW and INTERGROWTH approach preterm growth differently. GROW centiles are based upon the Hadlock formula for certain gestational ages, suggesting that the growth of preterm and term infants should be exactly the same at any timepoint²¹. The INTERGROWTH standards do not make this assumption but are based on the size of preterm infants at birth. Although this approach seems more scientifically justifiable, as growth abnormalities may contribute to preterm birth, the INTERGROWTH standards were based upon data from real preterm babies, a relatively rare clinical occurrence in a healthy population, there were fewer infants in the very preterm categories which may introduce more uncertainty (details at <https://www.intergrowth21.org.uk/protocol.aspx?lang=1> accessed 11/09/2018)²². More studies in very preterm infants are needed to identify which growth standard might perform best in this group²³.

Despite maternal diabetes being a risk factor of perinatal morbidity, there has been relatively little assessment of different growth standards in this population. Kase and colleagues reported that customised centiles identified more infants as SGA/LGA compared to population centiles in diabetic pregnancies²⁴. Narchi and Skinner had similar findings but concluded there was no evidence of a difference in mortality or morbidity between the infants identified by customised vs population growth standards²⁵. The current study adds to the literature by highlighting differences between the common growth standards in a population comparable to clinical populations of women with type 1 diabetes in pregnancy. We had no women with ideal glucose control in early pregnancy (HbA1c<48 mmol/mol) as these women were excluded from the CONCEPTT trial. However, population based studies confirm that only 15% of women with T1D with a HbA1c level <6.5% (48mmol/mol⁵) and thus the data presented here would represent the vast majority of women (85%) with T1D. Future studies should identify optimal growth standard for use even in women with optimal pre-pregnancy Hba1c and in larger cohorts.

Conclusions

WHO growth standards do not incorporate gestational age at birth and therefore are unsuitable for use in diabetic pregnancy, where preterm delivery is commonplace. However, GROW and INTERGROWTH standards are both suitable and GROW showed stronger associations with outcomes. Infants born >97.7th centile had the highest risks of suboptimal perinatal outcomes in this study. Future work should assess if definitions of LGA and SGA should be altered for diabetes pregnancy.

Abbreviations

LGA; large for gestational age, SGA; small for gestational age, CONCEPTT; Continuous Glucose Monitoring in Type 1 Diabetes Pregnancy Trial, NICU; neonatal intensive care unit, T1D; type 1 diabetes, CGM; continuous glucose monitoring, GROW; Gestation Related Optimum Weight, WHO; World Health Organisation, SD; standard deviation, BMI; body mass index.

Declarations

Ethics approval and consent to participate

The CONCEPTT study was approved by the Research Ethics Committee East of England (Essex) under reference 12/EE/0310 in 2012. All participants provided written informed consent. Further ethical approval was not required for this analysis.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Claire Meek has no relevant conflicts of interest to declare. She currently receives support from the Diabetes UK Harry Keen Intermediate Clinical Fellowship (17/0005712) and the EFSD-Novo Nordisk Foundation Future Leader's Award (NNF19SA058974).

Denice Feig has received honoraria for speaking engagements from Medtronic and has been on an Advisory Board for Novo Nordisk.

Rosa Corcoy has no conflict of interest to declare.

Elizabeth Asztalos (EA) has no conflict of interests to declare.

Laura Kusinski has no conflict of interest to declare.

Esther López has no conflict of interest to declare.

Helen Murphy has received honoraria for speaking engagements from Medtronic, Roche, Novo Nordisk, Eli-Lilly and is a member of the Medtronic European Advisory Board.

CLM is the guarantor of this work and, as such, has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

The trial is funded by Juvenile Diabetes Research Foundation (JDRF) grants #17-2011-533, and grants under the JDRF Canadian Clinical Trial Network, a public-private partnership including JDRF and FedDev Ontario and supported by JDRF #80-2010-585. The funders provided solely the finance required for this study and had no role in the trial design, data collection, data analysis or data interpretation. Medtronic supplied the CGM sensors and CGM systems at reduced cost. They also had no role in trial design, collection, handling, analysis or interpretation of data.

HRM conducts independent research supported by the National Institute for Health Research (Career Development Fellowship, CDF-2013-06-035), and is supported by Tommy's charity. CLM is supported by the Diabetes UK Harry Keen Intermediate Clinical Fellowship (DUK-HKF 17/0005712) and the EFSD-Novo Nordisk Foundation Future Leader's Award (NNF19SA058974).

Authors' contributions

CLM designed the study, analysed and interpreted the data, wrote and revised the manuscript. HRM identified the study question, contributed to data analysis, reviewed and revised the manuscript and contributed to the discussion. DSF, EL and RC contributed to study design, data collection, data collation and reviewed and revised the final manuscript. EA and LCK contributed to the discussion and reviewed the final manuscript. All authors gave approval of the final version of the manuscript prior to publication.

Acknowledgements

The authors would like to thank all the women with type 1 diabetes who participated in the CONCEPTT trial. We also acknowledge the invaluable support from the 31 clinical care teams and the CONCEPTT Steering Committee: Denice S Feig, Helen R Murphy, Elisabeth Asztalos, Jon F R Barrett, Rosa Corcoy, Alberto de Leiva, Lois E Donovan, J Moshe Hod, Lois Jovanovic, Erin Keely, Craig Kollman, Ruth McManus, Kellie E Murphy, Katrina Ruedy and George Tomlinson.

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Tables

Table 1

Maternal Infant Characteristics. BMI: body mass index; GROW: gestation related optimum weight; NICU: neonatal intensive care unit; WHO: World Health Organisation. Composite outcome: birth injury, neonatal hypoglycaemia, hyperbilirubinaemia, respiratory distress syndrome, or neonatal intensive care admission. Diabetes complications defined as any retinopathy, neuropathy or nephropathy.

	Mean (SD) or n (%)
	n = 225
MATERNAL CHARACTERISTICS	
Maternal age, years	31.4 (4.5)
BMI at enrolment, kg/m ²	25.8 (4.6)
Ethnicity European/ Mediterranean origin	194 (86.2)
Primiparous	89 (39.6)
Duration of diabetes, years	16.5 (7.7)
Diabetes complications	58 (25.8)
Hypertension pre-pregnancy	15 (6.7)
HbA1c at randomisation mmol/mol	51.8 (6.6)
HbA1c at randomisation %	6.9 (0.6)
Smoking	20 (8.9)
Insulin pump	110 (48.9)
INFANT CHARACTERISTICS	
Sex (% male)	115 (51.1)
Gestational age at delivery	37.0 (1.6)
BIRTHWEIGHT MEASURES	
Birthweight g	3583.6 (705)
Macrosomia > = 4 kg	59 (26.2)

	Mean (SD) or n (%)
	n = 225
GROW centile	82.1 (25.9)
INTERGROWTH centile	85.7 (20.8)
WHO centile	63.9 (32.0)
OBSTETRIC AND PERINATAL OUTCOMES	
Caesarean section	155 (68.9)
Preterm delivery	89 (39.6)
Neonatal hypoglycaemia requiring intravenous dextrose	57 (25.3)
NICU admission	83 (36.9)
Hyperbilirubinaemia	62 (27.6)
Respiratory distress	19 (8.4)
Composite neonatal outcome	107 (47.6)

Table 2: Association of adverse neonatal outcomes with low and high birthweights after GROW, INTERGROWTH and WHO criteria. Unadjusted odds ratios and 95% confidence intervals are reported in comparison to all other pregnancies. Neonatal hypoglycaemia included only infants who required IV dextrose. GROW: gestation related optimum weight; NICU: neonatal intensive care unit; WHO: world health organisation. Composite outcome: birth injury, neonatal hypoglycaemia, hyperbilirubinaemia, respiratory distress syndrome, or neonatal intensive care admission. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

	n	Caesarean delivery	Preterm delivery	Neonatal hypoglycaemia	NICU Admission	Hyper-bilirubinaemia	Respiratory Distress	Composite Outcome
Birthweight >84.1st centile (mean +1 sd)								
GROW >84.1 st centile	146/225 (64.9%)	2.31 (1.29 to 4.14)**	1.11 (0.63 to 1.94)	1.94 (0.98 to 3.82)	1.70 (0.94 to 3.05)	1.81 (0.95 to 3.47)	2.15 (0.69 to 6.71)	1.98 (1.13 to 3.47)*
INTERGROWTH >84.1 st centile	167/225 (74.2%)	2.78 (1.49 to 5.18)***	1.10 (0.59 to 2.03)	1.62 (0.78 to 3.40)	1.28 (0.68 to 2.40)	1.27 (0.64 to 2.52)	1.33 (0.42 to 4.19)	1.40 (0.77 to 2.56)
WHO >84.1 st centile	82/225 (36.4%)	2.50 (1.32 to 4.76)**	0.35 (0.19 to 0.63)***	1.52 (0.82 to 2.81)	0.98 (0.56 to 1.72)	0.70 (0.38 to 1.31)	0.79 (0.29 to 2.16)	1.00 (0.58 to 1.72)
Birthweight >90th centile (mean +1.28 sd)								
GROW >90 th centile	140/225 (62.2%)	2.29 (1.28 to 4.08)**	1.34 (0.76 to 2.33)	2.25 (1.14 to 4.42)*	1.85 (1.04 to 3.30)*	1.89 (1.00 to 3.59)*	2.43 (0.78 to 7.58)	2.24 (1.29 to 3.91)**
INTERGROWTH >90 th centile	150/225 (66.7%)	2.19 (1.22 to 3.95)**	0.97 (0.55 to 1.71)	1.98 (0.99 to 3.96)	1.81 (0.99 to 3.30)	1.63 (0.85 to 3.13)	1.97 (0.63 to 6.17)	1.87 (1.06 to 3.29)*
WHO >90 th centile	67/225 (29.8%)	3.03 (1.47 to 6.25)**	0.33 (0.17 to 0.63)***	1.72 (0.91 to 3.24)	1.03 (0.57 to 1.85)	0.76 (0.40 to 1.48)	0.61 (0.19 to 1.90)	1.10 (0.62 to 1.95)
Birthweight >97.7th centile (mean +2 sd)								
GROW >97.7 th centile	95/225 (42.2%)	3.16 (1.68 to 5.93)***	1.76 (1.02 to 3.03)*	3.17 (1.70 to 5.91)***	2.18 (1.25 to 3.79)**	1.85 (1.03 to 3.35)*	2.00 (0.77 to 5.17)	2.22 (1.30 to 3.81)**
INTERGROWTH >97.7 th centile	92/225 (40.9%)	2.92 (1.56 to 5.49)***	1.13 (0.66 to 1.95)	3.10 (1.66 to 5.77)***	1.88 (1.09 to 3.27)*	1.27 (0.71 to 2.30)	1.68 (0.65 to 4.31)	1.99 (1.16 to 3.41)*
WHO >97.7 th centile	28/225 (12.4%)	1.41 (0.57 to 3.49)	0.57 (0.24 to 1.36)	3.58 (1.59 to 8.09)**	2.19 (0.98 to 4.87)	0.86 (0.35 to 2.14)	1.36 (0.37 to 4.99)	1.84 (0.82 to 4.12)
Birthweight <10th centile (<1.28 sd below mean)								
GROW <10 th centile	5/225 (2.2%)	1.83 (0.20 to 16.66)	2.34 (0.38 to 14.28)	0.73 (0.08 to 6.69)	2.63 (0.43 to 16.04)	4.09 (0.67 to 25.11)	2.81 (0.30 to 26.45)	1.67 (0.27 to 10.21)
INTERGROWTH <10 th centile	3/225 (1.3%)	insufficient events	3.10 (0.28 to 34.75)	insufficient events	3.48 (0.31 to 38.99)	5.40 (0.48 to 60.65)	5.67 (0.49 to 65.56)	2.23 (0.20 to 24.93)
WHO <10 th centile	20/225 (8.9%)	1.90 (0.61 to 5.90)	7.23 (2.33 to 22.44)***	1.29 (0.47 to 3.54)	3.58 (1.37 to 9.38)**	2.35 (0.92 to 5.98)	4.55 (1.44 to 14.34)**	3.68 (1.29 to 10.52)*
Birthweight <25th centile (<0.675 sd below mean)								
GROW <25 th centile	13/225 (5.8%)	2.60 (0.56 to 12.04)	1.85 (0.60 to 5.70)	0.52 (0.11 to 2.42)	1.07 (0.34 to 3.40)	1.70 (0.53 to 5.41)	2.09 (0.43 to 10.19)	0.67 (0.21 to 2.13)
INTERGROWTH <25 th centile	7/225 (3.1%)	1.13 (0.21 to 5.99)	2.09 (0.46 to 9.55)	0.48 (0.06 to 4.09)	2.35 (0.51 to 10.75)	3.68 (0.80 to 16.93)	4.73 (0.85 to 26.23)	1.49 (0.33 to 6.81)
WHO <25 th centile	37/225 (16.4%)	1.49 (0.66 to 3.36)	6.48 (2.88 to 14.57)***	1.31 (0.60 to 2.85)	3.05 (1.48 to 6.30)**	2.35 (1.13 to 4.88)*	3.42 (1.25 to 9.39)*	3.12 (1.46 to 6.69)**

Figures

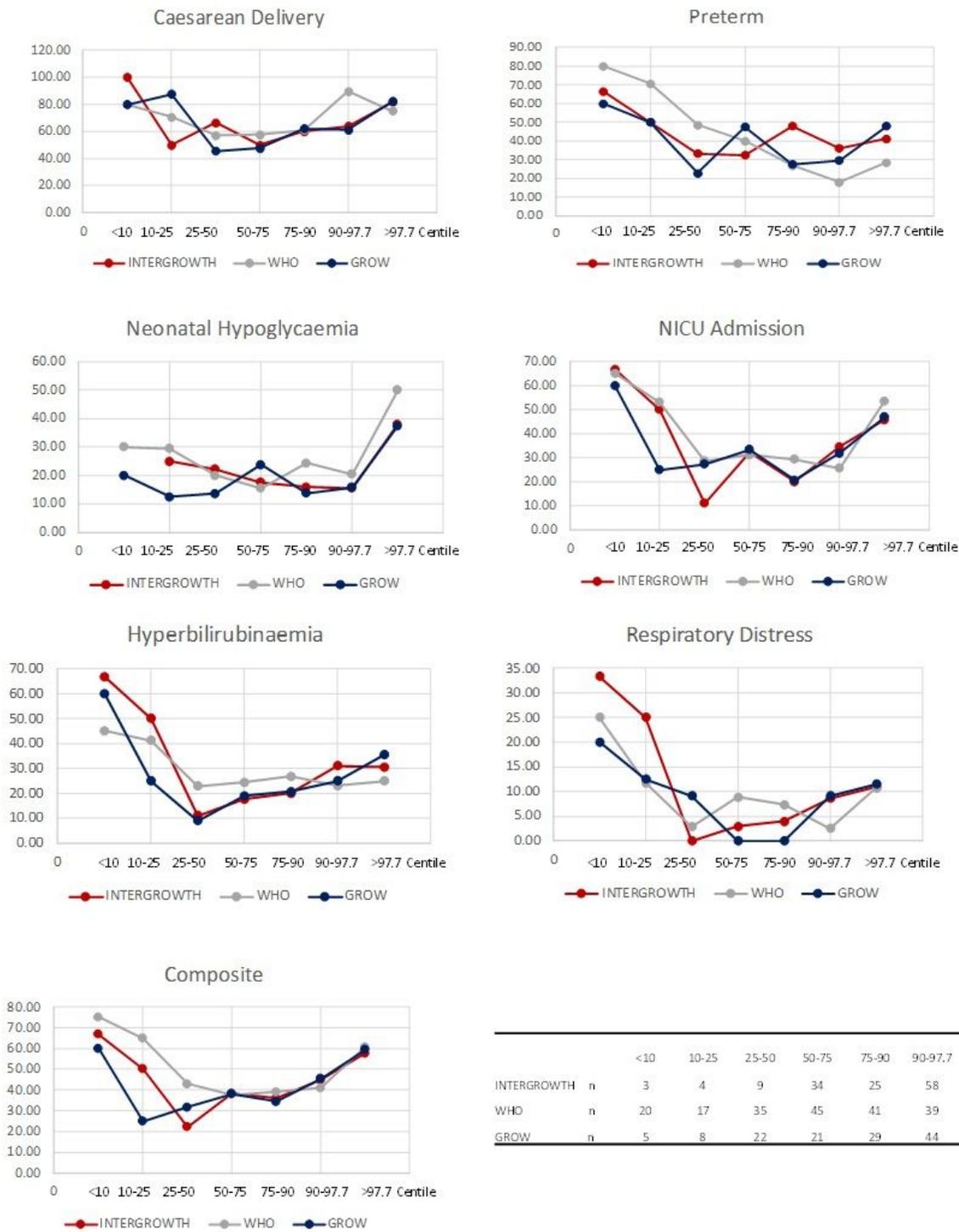


Figure 1

Rates (%) of caesarean delivery, preterm delivery, neonatal hypoglycaemia, hyperbilirubinaemia, respiratory distress, NICU admission and the composite neonatal outcome according to birth centile

category based on GROW, INTERGROWTH and WHO standards. Numbers in each category are given at the bottom right of this figure.

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