Identifying small-for-gestational-age preterm infants from the Finnish Medical Birth Register using eight growth charts

Authors

Alice HOCQUETTE[1], Anna PULAKKA[2], Johanna METSÄLÄ[2], Katriina HEIKKILÄ[2], Jennifer ZEITLIN[1], Eero KAJANTIE[2,3,4,5]

Affiliations

1. Université de Paris, CRESS, INSERM, INRA, F-75004 Paris, France

2. Population Health Unit, Finnish Institute for Health and Welfare, Helsinki and Oulu, Finland

3. PEDEGO Research Unit, MRC Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland

4. Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

5. Children's Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

Corresponding author

Alice HOCQUETTE

INSERM Equipe EPOPé, Maternité Port Royal

53 avenue de l'Observatoire, 75014 Paris, France

alice.hocquette@inserm.fr

Telephone : 06 32 98 83 22

Fetal growth restriction (FGR) is a major risk factor for infant mortality and morbidity and adverse lifelong developmental, mental and physical health outcomes.[1] It is usually studied using small for gestational age (SGA), which is most commonly defined as a weight under the 10th percentile based on growth charts. Identifying infants with SGA is necessary for research on the long-term consequences of perinatal pathologies and particularly important for children born preterm. Early onset FGR, which has been associated with preterm birth, incurs higher risks than later onset FGR and is a prognostic factor for poor cognitive development, respiratory morbidity and metabolic disorders.[2]

Growth charts to identify SGA infants use different conceptual approaches and methods, reflecting on-going debate on three key questions. First, should charts be constructed from birthweights or fetal weights estimated from ultrasound measurements (abdominal and head circumference and femur length)? Preterm infants are more likely to have growth anomalies and charts established from birthweights will have have lower percentiles than intrauterine charts established from estimated fetal weights in on-going pregnancies. Therefore, the 10^{th} percentile will be lower and some infants at risk for complications due to poor growth may be missed.[3] Second, is it possible to develop universal standards for healthy growth or should charts be based on national references? Third, do customised charts, which adjust growth trajectories for individual maternal and fetal factors that physiologically affect growth, including sex and maternal height, provide added value?

Our aim was to describe the differences in SGA classifications when using national and international intrauterine and birthweight charts in Finland.

We included live infants born with a birthweight ≥500 grams, or a GA ≥22 weeks, recorded in the Finnish Medical Birth Register in 2006-2016. The data collected included birthweight, GA in weeks and days, calculated from last menstrual period and confirmed by ultrasound, sex and variables for deriving customised charts (maternal height, pre-pregnancy weight,

parity and smoking). We used two SGA definitions: birthweight <10th percentile and <2 standard deviations.[4] We identified 37,257 preterm births before 37 weeks of GA. There were 26,891 once we had excluded births <24 weeks, multiple births, missing birthweights or GA and discordant birthweights for GA (<300g or Z-score <6 or >4 standard deviations).

Our literature review identified the eight growth charts most commonly used to examine intrauterine growth and health: two intrauterine standards (World Health Organization, Intergrowth intrauterine), two intrauterine references (Maršál, Hadlock), one birthweight standard (Intergrowth birthweight), two birthweight references (Sankilampi, Fenton) and the customised GROW chart (Table S1). Most are sex-specific, except Intergrowth intrauterine and Hadlock; Sankilampi has separate charts for primiparous and multiparous births. We used each chart to calculate the percentage of preterm SGA infants by GA, grouped in two week categories.

The proportions of preterm SGA births were: Fenton (7.6%), Intergrowth birthweight (9.3%), Intergrowth intrauterine (11.8%), customised (17.2%), Hadlock (20.3%), Sankilampi (21.8%), World Health Organization (22.3%) and Maršál (22.6%). SGA births varied between charts and across gestations (Figure 1) with most variation at 28-29 weeks: 9.1%-29.8% for the birthweight charts, 31.3%-47.7% for the intrauterine charts and 33.9% for the customised chart. The absolute differences between the fetal and birthweight charts were highest at these GA, then declined. The proportions after 34 weeks ranged from 13.8%- 20.9%, except for the Fenton (7.3%), Intergrowth intrauterine (8.5%) and Intergrowth birthweight (8.6%) charts. The Fenton and Intergrowth birthweight charts systematically provided lower SGA proportions across GA than the other charts. Patterns were similar using the threshold of -2SD, with a range of 1.9%-11.2% (Figure S1).

There were large differences in how the eight charts classified SGA, particularly for the intrauterine and birthweight charts at 28-32 weeks of GA. This may reflect more induced

deliveries for early onset FGR at these gestations. We also observed differences between national and international charts, as Fenton and the intergrowth charts provided lower SGA proportions than the Nordic charts. This suggests that the international charts may not accurately describe Finnish birthweight distributions. Other studies have also shown that Intergrowth charts underestimated SGA in Nordic countries.[5]

These results highlight the importance of choosing the right chart when quantifying FGR in preterm births, and suggest that using the 10th percentile threshold with international or birthweight charts may underestimate how many children risk adverse outcomes due to growth impairment, in particular those born at 28-32 weeks of GA. Using different charts also makes it difficult to compare research findings. The charts used in FGR research should be detailed in papers, so that meta-analyses can assess any impact on their findings. More prospective studies on neonatal and long-term outcomes are needed to provide evidence on the best charts to use. These should include the threshold for monitoring FGR in children born preterm.

ABBREVIATIONS

FGR, fetal growth restriction; SGA, small for gestational age; GA, gestational age

CONFLICTS OF INTEREST

No conflict of interest to declare.

FUNDING

This research was supported by the RECAP Preterm project, EU Horizon 2020 (N°7733280), Academy of Finland, Sigrid Juselius Foundation, Signe and Ane Gyllenberg Foundation, Foundation for Pediatric Research and Novo Nordisk Foundation. A Hocquette was supported by an EHESP grant (N°2019/353/DRH/EHESP).

DATA AVAILABILITY STATEMENT

Individual participant data are not available. Growth chart data are available in referenced publications.

REFERENCES

1. Saenger P, Czernichow P, Hughes I, Reiter EO. Small for gestational age: short stature and beyond. *Endocr Rev*. 2007;28(2):219-251

2. Pels A, Beune IM, van Wassenaer-Leemhuis AG, Limpens J, Ganzevoort W. Early-onset fetal growth restriction: A systematic review on mortality and morbidity. *Acta Obstet Gynecol Scand*. 2020;99(2):153-166

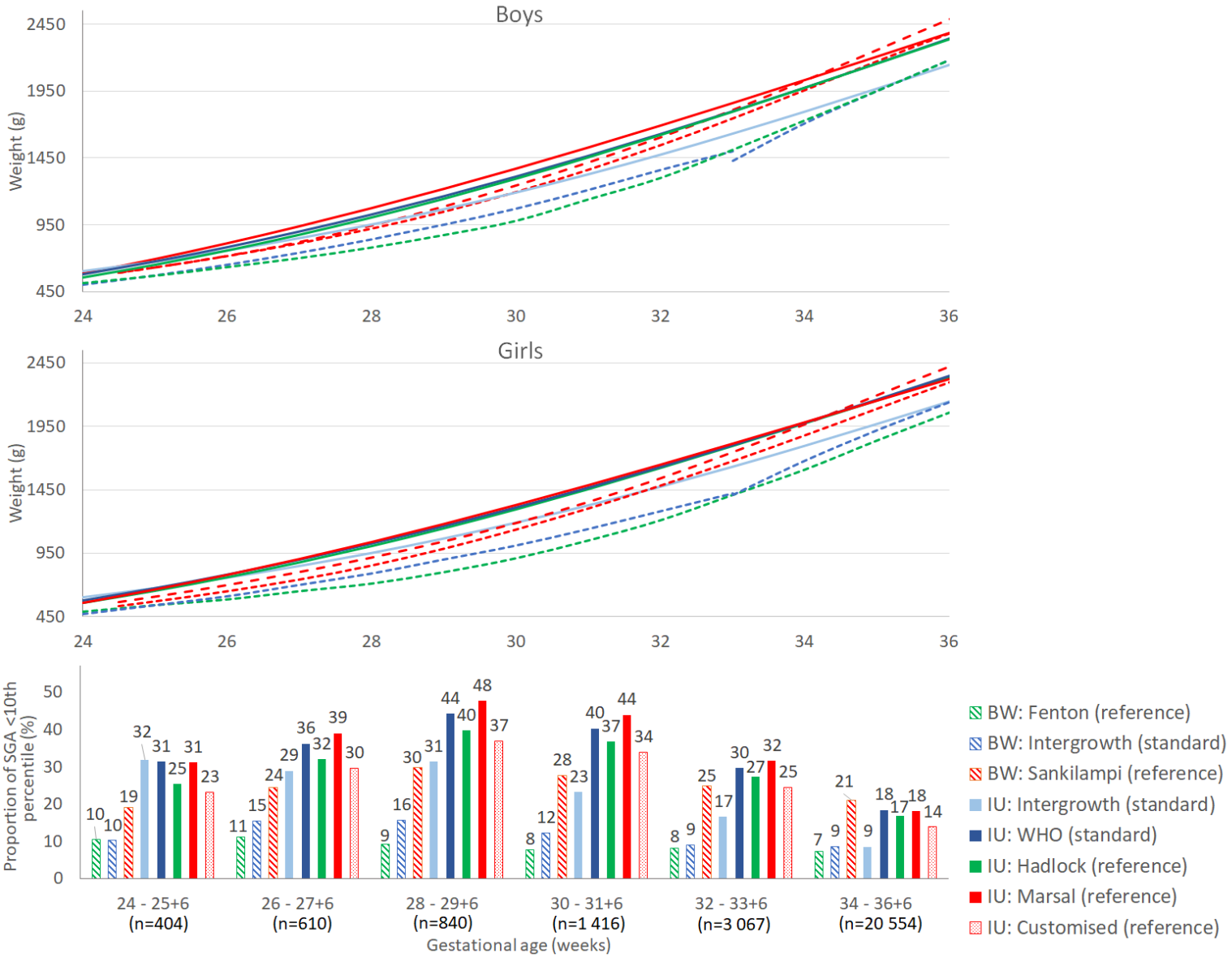
3. Boghossian NS, Geraci M, Edwards EM, Horbar JD. Neonatal and fetal growth charts to identify preterm infants <30 weeks gestation at risk of adverse outcomes. *Am J Obstet Gynecol*. 2018;219(2):195.e1-195.e14

4. Lees CC, Stampalija T, Baschat AA, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol*. 2020;56(2):298-312

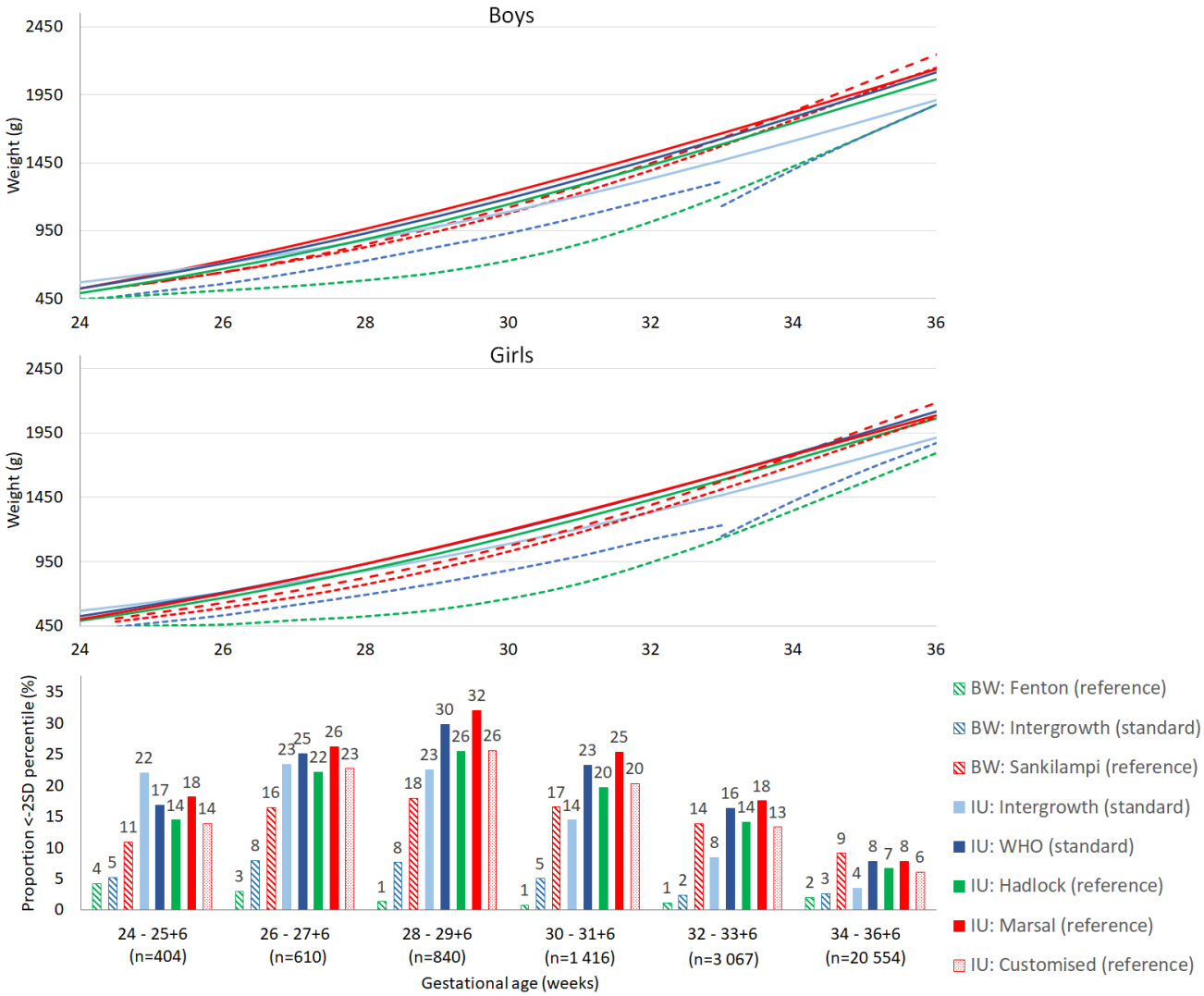
5. Hocquette A, Durox M, Wood R, et al. International versus national growth charts for identifying small and large-for-gestational age newborns: A population-based study in 15 European countries. *Lancet Reg Health Eur*. 2021;8:100167

Supplementary Table 1 : Publications used to construct each chart

Charts	Publications
Fenton	Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013 Apr 20;13:59.
Intergrowth birthweight	Villar J, Ismail LC, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. The Lancet. 2014 Sep 6;384(9946):857–68. Villar J, Giuliani F, Fenton TR, Ohuma EO, Ismail LC, Kennedy SH. INTERGROWTH-21st very preterm size at birth reference charts. The Lancet. 2016 Feb 27;387(10021):844–5.
Sankilampi	Sankilampi U, Hannila M-L, Saari A, Gissler M, Dunkel L. New population-based references for birth weight, length, and head circumference in singletons and twins from 23 to 43 gestation weeks. Ann Med. 2013 Sep;45(5–6):446–54.
Intergrowth intrauterine	Stirnemann J, Villar J, Salomon LJ, Ohuma E, Ruyan P, Altman DG, et al. International estimated fetal weight standards of the INTERGROWTH-21st Project. Ultrasound Obstet Gynecol. 2017 Apr;49(4):478–86.
WHO	Kiserud T, Piaggio G, Carroli G, Widmer M, Carvalho J, Neerup Jensen L, et al. The World Health Organization Fetal Growth Charts: A Multinational Longitudinal Study of Ultrasound Biometric Measurements and Estimated Fetal Weight. PLoS Med. 2017 Jan 24;14(1).
Hadlock	Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth a sonographic weight standard. Radiology. 1991 Oct;181(1):129–33.
Maršál	Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr Oslo Nor 1992. 1996 Jul;85(7):843–8.
Customised	Gardosi J, Mongelli M, Wilcox M, Chang A. An adjustable fetal weight standard. Ultrasound Obstet Gynecol. 1995Sep;6(3):168–74.


Boys
Weight (g)
2450
1950
1450
950
450
24
26
28
30
32
34
36
Girls
Weight (g)
2450
1950
1450
950
450
24
26
28
30
32
34
36
Proportion of SGA <10th percentile (%)
50
40
30
20
10
0
10 10 19 32 31 25 31 23
11 15 24 29 36 32 39 30
9 16 30 31 44 40 48 37
8 12 28 23 40 37 44 34
8 9 25 17 30 27 32 25
7 9 21 9 18 17 18 14
24 - 25+6 (n=404)
26 - 27+6 (n=610)
28 - 29+6 (n=840)
30 - 31+6 (n=1 416)
32 - 33+6 (n=3 067)
34 - 36+6 (n=20 554)
Gestational age (weeks)
BW: Fenton (reference)
BW: Intergrowth (standard)
BW: Sankilampi (reference)
IU: Intergrowth (standard)
IU: WHO (standard)
IU: Hadlock (reference)
IU: Marsal (reference)
IU: Customised (reference)

Supplementary Figure 1: Values for the -2SD threshold and proportions of infants with a birthweight under -2SD by gestational age according to eight growth charts



NOTE: The threshold of -1.96 SD is represented for WHO
Intergrowth birthweight charts were obtained from two different publications: one for births before 33+0 weeks of gestation and one after