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PREVENTING TERM STILLBIRTH: BENEFITS AND LIMITATIONS OF USING FETAL GROWTH REFERENCE CHARTS

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Purpose of review

This review examines the variation in clinical practice with regards to ultrasound estimation of fetal weight, as well as calculation of fetal weight centiles from population/customised fetal growth references or fetal growth standards.

Recent findings

Placental dysfunction is associated with fetal smallness from intrauterine malnutrition as well as fetal disability and even stillbirth from hypoxemia. Although estimating fetal weight can be done accurately, the issue of which fetal weight centile chart should be used continues to be a contentious topic. The arguments against local fetal growth charts based on national borders and customization for variables known to be associated with pathology are substantial. As for other human diseases such as hypertension and diabetes, there is a rationale for the use of an international fetal growth reference standard. Irrespective of the choice of fetal growth reference standard, a significant limitation of national SGA detection programs to prevent stillbirth is that the majority of stillborn infants at term were not SGA at the time of demise.

Summary

Placental dysfunction can present with SGA from malnutrition and/or stillbirth from hypoxemia depending on the gestational age of onset. Emerging data show that at term, fetal Doppler arterial redistribution is associated more strongly with perinatal death than fetal size. Properly conducted trials of the role for maternal characteristics, fetal size, placental biomarkers and Dopplers assessing fetal wellbeing are required urgently.

Keywords

Stillbirth, small for gestational age, fetal growth restriction, estimated fetal weight, fetal weight centile, fetal growth charts, fetal growth references, fetal growth standards

INTRODUCTION

Stillbirth is a tragic event that has major psychological, social and economic effects on mothers, families and society in general [1]. The UK still has one of the highest rates of stillbirth in industrialized countries at 3.87 stillbirths per 1000 births – with two-thirds of stillbirths occurring near term at gestations beyond 34 weeks [2]. There is a long-established association between fetal size and stillbirth, with the risk of stillbirth increasing for smaller relative fetal size or poor growth [3]. This observation has lent support to the argument that majority of stillbirth occurs as a consequence of placental dysfunction and therefore, they are potentially avoidable if delivery is effected before fetal demise. Therefore, most strategies for stillbirth prevention rely on ultrasound or serial fundal height measurement to screen for disturbances in fetal growth [4].

Fetal growth restriction (FGR) is defined as the failure of the fetus to reach its growth potential and is considered the commonest major complications of pregnancy [5]. It is a major risk factor for fetal stillbirth as well as other fetal comorbidities such as hypoxic ischemic encephalopathy and cerebral palsy [6-9]. However, as fetal growth potential is difficult to define, small for gestational age (SGA), defined as estimated fetal weight (EFW) below the 10th percentile, is commonly used as a proxy for FGR secondary to placental dysfunction. There is some retrospective evidence to suggest that antenatal detection of small for gestational age (SGA) fetuses could potentially halve the risk of stillbirths through appropriate antenatal surveillance and timely delivery [10, 11].

A policy of SGA detection first requires ultrasound estimation of fetal weight followed by calculation of the fetal weight centile by the use of a fetal weight reference chart or standard [12-14]. Currently, countless fetal weight calculators and fetal weight references exist which add to the clinical complexity and variability in outcomes. To add to the confusion, some academics have suggested customisation of fetal weight charts for certain maternal characteristics and others have challenged the effectiveness and unexpected negative outcomes related to a policy of screening for SGA fetuses [15-19]. This review outlines the background, benefits and limitations of health policies and programmes targeted at SGA detection to prevent stillbirth.

FORMULAE TO ESTIMATE FETAL WEIGHT

Ultrasound estimation of fetal weight is an essential prerequisite to calculating fetal weight centile for the identification of pregnancies at risk of SGA or large-for-gestational-age (LGA) birth. EFW may be derived from various fetal measurements or combinations of measurements of fetal head circumference (HC), biparietal diameter (BPD), femur length (FL) and abdominal circumference (AC) – with more than 50 publications providing formulae for clinical use. However, the majority of these formulae were derived from relatively small studies and most remain clinically unvalidated. Furthermore, there is no clinical consensus regarding the most appropriate formula to be used to calculate fetal weight.

A recent prospective study utilised data from a cohort of 5163 pregnancies between 22–43 weeks' gestation, where a live birth occurred within two days of the ultrasound examination to evaluate the accuracy of existing formulae for estimating fetal weight [20]. The authors evaluated 70 different formulae – some using single fetal measurements and others utilising a composite of between two and four fetal biometric measures. The mean percentage error and absolute mean error was used to compare the accuracy of the various EFW formulae to predict actual birth weight (Figure 1) [21]. They demonstrated that the formula reported in 1985 by Hadlock *et al.*, from measurements of HC, AC and FL, provides the most accurate prediction of birth weight and can be used for assessment of all babies, including those suspected to be either SGA or LGA [21].

A similar evaluation was carried out in twin pregnancy where the risk of SGA, FGR and adverse perinatal outcomes are higher [22]. This was a retrospective cohort study including 4280 singleton and 586 twin fetuses where routine ultrasound biometry was undertaken within 2 days of livebirth. Ultrasound estimation of fetal weight is less accurate in twin than in singleton pregnancies. Furthermore, formulae that include a combination of head, abdomen and femur measurements perform best in both singleton and twin pregnancies. As for singleton pregnancy, the best prediction of intertwin birth-weight discordance was achived using the Hadlock HC, AC and FL formula [21].

CHARTS TO ESTIMATE FETAL WEIGHT CENTILE

Only once fetal weight has been accurately calculated, can we use fetal weight or 'growth' charts to estimate the weight centile for a given gestation. There are several published charts that purport to correctly evaluate EFW centile varying by geographical location, clinical scenario (such as ethnicity, maternal stature, parity etc) or purporting to be an international reference standard.

Local and national charts

These are charts defined by the geography of a particular area (local) or country (national). The charts are typically constructed retrospectively from existing ultrasound biometry and birth weight data from the source population. The developers of such charts rationalise their use on the basis that there is recognised regional variation in child and adult stature, presumably due to ethnicity, social, economic and nutritional factors. These charts describe how babies in a particular geographical cohort 'have grown', but do not tell us what is clinically relevant - which is how a normal baby 'should grow' [23]. The main limitation with retrospectively constructed charts is that the pregnancy cohort contains hidden maternal and fetal morbidity which may have impaired fetal growth. Some charts have used retrospective 'cleaning' of the cohort data to overcome this limitation, but such an approach is typically incomplete and does not eliminate occult health problems.

Another limitation of geographical charts is that, usually preterm births are used to establish normograms despite the finding that median BW for babies born preterm is substantially lower than median EFW [24,25]. This difference is likely to be the consequence of pathological fetal growth in the majority of preterm births. Therefore, reference ranges for BW contains an overrepresentation of pathological pregnancies particularly for gestational ages <37 weeks. Nicolaides and colleagues established a BW chart using fetuses still in utero, thereby overcoming the problem of underestimation of growth restriction in preterm birth [26]. Using the latter chart, the authors demonstrated that for preterm birth, BW was below the 10th centile in a very high proportion of cases (Figure 2) [26], both for iatrogenic causes (52.5%) and spontaneous preterm births (19.8%). The latter charts would seem the appropriate choice for screening for preterm placental dysfunction and FGR.

Despite the apparent limitations, local and national charts are in wide usage across the world, even though it is not clear how multicultural populations are represented in such charts. An unresolved major issue that undermines the justification for the use of such charts is a believable biological explanation for how nationality/national borders influence fetal growth.

Customized charts

A potential approach to deal with the limitations of population-based local or national growth charts is customization, where expected fetal growth is modulated according to individual variables that are known to affect fetal growth [27]. Proponents of customized growth charts established the growth potential of each fetus according to physiological variations in maternal characteristics such as height, weight, ethnic origin, parity and fetal sex, but not for pathology such as premature birth, smoking, hypertensive disorders or diabetes [28-32]. It has been suggested customizing expected fetal growth for these variables will result in improved diagnosis of SGA pregnancies at risk of adverse outcome [33]. For instance, it has been suggested that use of customised charts will reduce the number of pregnancies classified as SGA to approximately 10% when used in Asian or low BMI populations. The latter groups typically have much higher rates of SGA when classified using population-based fetal growth charts, which supposedly identify 'normally small' rather than FGR babies as risk of adverse outcome.

Whilst it is certainly true that certain maternal characteristic are associated with altered fetal growth, the very same variables also predispose to increased fetal morbidity and mortality. For example, customization 'normalises' smaller fetuses in Asian and Afro-Caribbean women, when women from these ethnicities are also at increased risk of stillbirth [34]. Similarly, other variable used in customised fetal growth charts such as maternal age, weight and parity have also been shown to be related to risk of stillbirth [35,36]. Apart from the concern that customisation of fetal growth is 'normalising' for variables that predispose to pregnancy pathology, there is also the question of biological rationale for customisation. The well-accepted associations between these variables and fetal weight cannot be causative, as it is inconceivable that the 1-2% of genes that determine maternal skin colour are also coincidentally responsible for controlling fetal

growth. Similarly, the placenta cannot 'know' the age of the mother, her weight or parity, making the latter variables proxy markers for uteroplacental dysfunction rather than directly controlling fetal growth [37].

Regardless of the justification for the use of customisation, it is important to recognise that customisation was proposed as a means of better identifying at-risk pregnancies. However, systematic evaluation of the use of customisation has failed to show increased performance in the detection of adverse pregnancy outcome in several large or prospectively conducted studies [38,39,40]

International reference standard

The popularity of local, national or customised fetal growth reference charts is based on the reasoning that approximately 10% of fetuses in any given population should be SGA. This assumption is fundamentally at odds with the known variation in rates of neonatal malnutrition at birth worldwide (Figure 3) ranging from as high as 27% in South Asia to a low of 7% in Europe [41]. This variation in malnutrition at birth is attributed to differences in nutrition, maternal co-morbidity and other socioeconomic factors – and is used as justification by proponents of an international fetal growth reference standard [23,42].

Fetal growth reference standards are prescriptive charts that are constructed prospectively in populations that have been screened before recruitment to ensure minimal bias from detrimental environmental and medical confounders that may affect fetal growth. So as opposed to retrospective local or national charts that describe how fetuses in a certain population have grown, fetal growth reference standards describe how fetuses should grow if they were free of any environmental or clinical constraints. Two consortiums used this approach to define optimal fetal growth reference standards [23, 43]. The Intergrowth-21st consortium adapted the same stringent standards to control for environmental and medical confounders as was used for the well-established WHO Child Growth Standards [44]. Intergrowth-21st showed that human growth in low risk environments is very similar in fetuses regardless of where they live or their ethnic/racial background [23]. These findings would suggest that perinatal health and fetal growth are mainly affected by the environmental, nutritional, socioeconomic factors across populations [23]. In contrast, the NICHD consortium 'standardised' pregnancies by

hospital, which introduced bias as it does not necessarily remove environmental constraints [23]. The NICHD study showed that fetal growth was minimally – but significantly different in four self-reported ethnic groups [43]. Interestingly, the NICHD study also demonstrated that marital status, level of education, annual income and private insurance influenced fetal growth.

Retrospective evaluations of the Intergrowth-21 fetal growth reference standard in two large population studies concluded that there was a reduced identification of SGA fetuses and cases of perinatal death [45, 46]. It should be noted that the poorer performance of the Intergrowth-21 reference standards was for a much lower number of pregnancies classified as SGA. Neither of the studies provided a comparison of screening efficiency for adverse outcome at comparable screen positive rates – which would have provided a better head-to-head comparison of different growth references and standards.

SHOULD WE ASSESS FETAL GROWTH INSTEAD OF FETAL SIZE?

Fetal growth - the relative change in fetal size over a time period - is often used as an alternative indicator of fetal wellbeing in screening programs using serial ultrasound assessment. Many clinicians believe that assessment of fetal growth over two or more scans is superior to assessment of fetal size alone, especially with the current uncertainty over which charts to use and whether to customise fetal size assessment by correcting for certain maternal characteristics. Although fetal growth can be objectively assessed by measuring change in fetal weight centile over the interval between scans, how this data should be interpreted is yet to be resolved. There are no evidenced-based guidelines that outline the risk of adverse outcome based on i) change in fetal weight centile, ii) over the interval of fetal growth assessment and iii) whether the same change in growth implies similar risks at different gestations. For example, is a 20% drop in fetal weight centile over a two-week interval clinically significant and is this significance similar at 28, 32 and 36 weeks' gestation? Thresholds for intervention on the basis of pathological deviation in fetal growth are likely to depend on gestational age at onset of placental insufficiency, as well as the rate over which that growth deviation occurs and the ability of the fetus to

endure such compromise. It would be churlish to assume that a given fetal growth threshold could serve to identify and prevent stillbirth at any given gestation.

In a large randomised controlled trial of early-onset fetal growth restriction <32 weeks, the TRUFFLE investigators demonstrated that fetal growth velocity did not help predict or prevent adverse outcome [47]. Similarly, in late pregnancy, the POP study in which women were allocated to either routine pregnancy care or serial (clinically blinded) ultrasound scans, fetal growth velocity was significantly associated with adverse outcome, but only in the SGA fetuses and not in appropriate-for-gestational-age births [48]. Several retrospective but larger studies have also shown that growth velocity does not improve prediction of adverse pregnancy outcome due to placental dysfunction [49-51] . The authors also demonstrated that the lack of clinical benefit from assessing fetal growth held true for whether the inter-scan interval was large (from 20 to 36 weeks) or small (from 32 to 36 weeks).

DOES ASSESSMENT OF FETAL SIZE REDUCE STILLBIRTH AT TERM?

The prevalent clinical focus on routinely monitoring fetal size is predicated on the association with stillbirth and the desire to deliver the pregnancy before this adverse outcome occurs. However, unlike preterm stillbirth where the majority of stillborn are SGA, intrauterine demise at term occurs in appropriately grown fetuses in 60–70% of cases (Figure 4) [52]. More recently, it has become evident that after a stillbirth, fetuses lose approximately 20% of their bodyweight through intrauterine maceration before birth and dehydration ex-utero before having their weight formally recorded [53]. Therefore, the 30-40% of term stillbirths that are classified as SGA were probably incorrectly classified with a significant proportion being AGA at the time of intrauterine demise. Whilst it is not in doubt that there is an association between SGA and stillbirth, it is clear that a health policy focused entirely on identification of SGA fetuses not prevent the majority of stillbirths at term. The latter is supported by population studies such as by Monier and colleagues [54] in a population-based study of routine third-trimester ultrasound in 14,000 pregnancies detected only 21.7% of SGA infants and resulted in a high false positive rate for SGA diagnosis, six-fold increase in provider-initiated preterm deliveries and unchanged

perinatal mortality. In a follow-up study of over 90,000 pregnancies, the same group reported a disappointing protective effect of SGA/FGR detection than previously reported as over 40% of stillbirths occurred despite detection of SGA [55]. In a prospective study of over 45,000 pregnancies, Akolekar and colleagues demonstrated that although in SGA babies had an increased risk of adverse perinatal outcome, 84% of adverse perinatal events occur in the AGA group – resulting in poor predictive performance of SGA detection for adverse perinatal outcome [56]. Both research groups called into question a focus solely on improving SGA detection without addressing post-detection management taking into account maternal characteristics, gestational age and Doppler assessment.

EARLY AND LATER FETAL GROWTH RESTRICITON – TWO DIFFERENT DISORDERS?

As well as reaching expert opinion on a definition of placental FGR a Delphi consensus has also been reached for both early and late-onset disease [57]. The underlying commonality between early and late gestation FGR is that they occur as a consequence of placental dysfunction. Both conditions are also associated with increased incidence of poor neurodevelopmental, cardiovascular and metabolic long-term outcomes for the affected fetus. Early FGR is less common and represents approximately 20-30% of all cases of growth restriction. It is associated with severe placental insufficiency and preeclampsia in up to 50% of cases. Late gestation FGR is more common and constitutes approximately 70-80% of all cases of growth restriction. It is associated with mild placental insufficiency and preeclampsia in approximately 10% of cases [58]. There is ongoing debate as to whether the placental dysfunction in late gestation FGR is a consequence of milder disease compared to early onset FGR or as a result of placental dysfunction occurring later in pregnancy.

Our understanding of placental dysfunction is based on the fundamental assumption that the association between fetal size and adverse perinatal outcome is a causative one - that is to say that fetal smallness causes stillbirth. The placenta is responsible for multiple functions such as nutrition, respiration and excretion amongst many other life processes.

As such, placental dysfunction will confer both nutritional as well as respiratory consequences to the developing fetus [59]. It should be noted that failure to meet nutritional demands result in growth deficiency and can usually be tolerated for several few days/weeks, whereas failed respiratory function results in hypoxia which can only be tolerated for minutes/hours. Fetal nutritional needs follow a logarithmic curve (Figure 5) whilst respiratory demands show exponential growth [59, 60]. In early-onset placental dysfunction, fetal nutrition is compromised more severely than respiration, thereby predominantly resulting in growth restriction as the main presenting feature. At this early stage of pregnancy, fetal respiratory demands are low and usually continue to be met by a dysfunctional placenta for several weeks. The latter explains why in early-onset placental dysfunction, SGA develops over several weeks of nutritional insufficiency. In contrast, late onset of placental dysfunction at term will disproportionately affect fetal respiratory demands which are increasing exponentially at this stage of pregnancy, just as nutritional demands begin to plateau. Thus, a 3000g fetus near term that is affected by placental failure is likely to die from hypoxia related to respiratory dysfunction within a few days, long before it can become small from failing to grow over several weeks.

Put simply, placental dysfunction a disorder which may manifest signs of either SGA from malnutrition or stillbirth from respiratory failure. The nutritional and respiratory demands of a fetus vary significantly with advancing gestation, and the consequences of either nutritional or respiratory compromise have different presentations (SGA versus stillbirth) and temporal patterns (protracted versus rapid). Early-onset placental dysfunction presents predominantly with SGA, whereas in late-onset disease, critical fetal hypoxia may occur in a term fetus before SGA has time to develop.

MANAGEMENT OF LATE-ONSET PLACENTAL DYSFUNCTION

It is not unsurprising given the issues surrounding fetal growth assessment, that there is real controversy and considerable variation in practice for the clinical management of late-onset FGR/placental dysfunction. In spite of these concerns, a number of definitive management decisions can be justified.

Establishing fetal size

Requires the use of validated EFW formula that can be used in any clinical setting, such as those published by Hadlock *et al.* (1985) and Hammami A *et al.* (2018) using multiple fetal biometric measures.

Establishing fetal weight centile

In preterm pregnancies, charts established using fetuses still in utero to overcome the problem of underestimation of preterm growth restriction, such as developed by Nicolaides K *et al.* should be used [26]. Near term, irrespective of which charts are used, the majority of adverse pregnancy outcomes will occur in non-SGA pregnancies, hence the choice of fetal growth reference charts is unlikely to have a major clinical impact. This makes the case for use of an international fetal growth reference standard so that meaningful comparisons of SGA rates between countries and before/after birth can be made.

Assessing fetal wellbeing

In preterm pregnancies should include the use of computerised CTG and DV Doppler up to 32 weeks gestation along with indicated delivery for reversed end-diastolic umbilical artery blood flow from 32 weeks and for absent end-diastolic umbilical artery blood flow from 34 weeks [61]. Near term, even though the risk of stillbirth is increased in SGA pregnancies, the majority of stillbirths occur in normally sized babies. Cerebroplacental ratio (CPR) - the ratio of the middle cerebral artery pulsatility index to the umbilical artery pulsatility index - is emerging as a potentially useful marker of fetal hypoxemia at term [62, 63]. Low CPR is known to be a marker for fetal hypoxemia at term in AGA fetuses [49], and is associated with low abdominal circumference growth velocity and adverse pregnancy outcomes including stillbirth, neonatal unit admission and neonatal morbidity [49]. As the risk of perinatal mortality seems to increase only when EFW is below the 30th centile of birthweight for gestation (Figure 6) [39], the latter population would seem to be a reasonable target for fetal Doppler/CPR evaluation. Unfortunately, it is still not evident whether the use of fetal Doppler evaluation in this sub-population can prevent stillbirth and improve perinatal outcome. It is likely that combined evaluation of maternal characteristics, fetal size, placental biomarkers and Doppler indices in a diagnostic

algorithm may be of value in identifying pregnancies that justify earlier scheduled birth because of an increased risk of adverse outcome and [64, 65].

CONCLUSION

Placental dysfunction is associated with fetal smallness due to intrauterine malnutrition as well as fetal disability and even death from respiratory hypoxemia. Fetal size is universally used as a common clinical proxy for placental dysfunction. The issue of which fetal weight centile assessment should be used continues to be a contentious topic. The arguments against local fetal growth charts based on national borders and customization for maternal variables associated with pregnancy pathology are considerable. As for other human diseases such as hypertension and diabetes, the rationale for the use of an international fetal growth reference standard makes a lot of sense. Variation in national rates of SGA is perceived as a limitation of these charts, but not when one considers that these variations are aligned to the rates of neonatal malnutrition seen in these countries. Irrespective of the choice of fetal growth reference standard, a significant limitation of national SGA detection programs to prevent stillbirth is that the majority of stillborn infants at term were not SGA at the time of demise. That placental dysfunction may present either with signs of SGA from malnutrition or stillbirth from hypoxemia is explained when one understands the varying fetal nutritional and respiratory demands with advancing gestation. Emerging data show consistently that fetal Doppler arterial redistribution is associated more strongly than fetal size with perinatal death at term. Properly conducted and powered trials of the role for maternal characteristics, fetal size, placental biomarkers and Doppler indices for assessing fetal wellbeing at term are now urgently required.

KEY POINTS:

- Accurately estimating fetal weight can be achieved by using validated multiparameter fetal biometry formulae
- Establishing fetal weight centile can be undertaken using population/customised fetal growth references or international fetal growth standards
- Population charts are limited by the lack of a believable biological explanation for how nationality or national borders influence fetal growth
- Whilst certain maternal characteristics are associated with altered fetal growth, the very same variables also predispose to increased fetal mortality questioning the rationale for customisation.
- Stillbirth prevention policies based identifying SGA fetuses are significantly limited by the finding that at term, the majority of antenatal stillbirths are appropriately grown at the time of intrauterine demise
- Fetal Doppler arterial redistribution is more strongly associated with perinatal death at term than fetal size

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CONFLICTS OF INTEREST

No conflicts of interest to declare

REFERENCES

[1] Murphy S, Cacciatore J. The psychological, social, and economic impact of stillbirth on families. Seminars in Fetal and Neonatal Medicine. 2017;22(3):129-134.

[2] Flenady V, Middleton P, Smith G, Duke W, Erwich J, Khong T et al. Stillbirths: the way forward in high-income countries. The Lancet. 2011;377(9778):1703-1717.

[3] Bukowski R, Hansen N, Willinger M, Reddy U, Parker C, Pinar H et al. Fetal Growth and Risk of Stillbirth: A Population-Based Case–Control Study. PLoS Medicine. 2014;11(4):e1001633.

[4] Papageorghiou A, Ohuma E, Altman D, Todros T, Ismail L, Lambert A et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. The Lancet. 2014;384(9946):869-879.

[5] Carberry A, Gordon A, Bond D, Hyett J, Raynes-Greenow C, Jeffery H. Customised versus population-based growth charts as a screening tool for detecting small for gestational age infants in low-risk pregnant women. Cochrane Database of Systematic Reviews. 2014;.

[6] Pilliod R, Cheng Y, Snowden J, Doss A, Caughey A. The risk of intrauterine fetal death in the small-for-gestational-age fetus. American Journal of Obstetrics and Gynecology. 2012;207(4):318.e1-318.e6.

[7] Pasupathy D. Rates of and Factors Associated With Delivery-Related Perinatal Death Among Term Infants in Scotland. JAMA. 2009;302(6):660.

[8] Bukowski R, Burgett A, Gei A, Saade G, Hankins G. Impairment of fetal growth potential and neonatal encephalopathy. American Journal of Obstetrics and Gynecology. 2003;188(4):1011-1015.

[9] McIntyre S, Blair E, Badawi N, Keogh J, Nelson K. Antecedents of Cerebral Palsy and Perinatal Death in Term and Late Preterm Singletons. Obstetrics & Gynecology. 2013;122(4):869-877.

[10] Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and Fetal Risk Factors for Stillbirth. Obstetrical & Gynecological Survey. 2013;68(5):329-331.

[11] Lindqvist P, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome?. Ultrasound in Obstetrics and Gynecology. 2005;25(3):258-264.

[12] Mayer C, Joseph K. Fetal growth: a review of terms, concepts and issues relevant to obstetrics. Ultrasound in Obstetrics & Gynecology. 2013;41(2):136-145.

[13] Willness C. The Oxford handbook of organizational climate and cultureByBenjaminSchneider & Karen M.Barbera (Eds.) New York, NY: Oxford University Press, 2014. $240.00. ISBN 9780199860715. British Journal of Psychology. 2016;107(1):201-202.

[14] McIntire D, Bloom S, Casey B, Leveno K. Birth Weight in Relation to Morbidity and Mortality among Newborn Infants. New England Journal of Medicine. 1999;340(16):1234-1238.

[15] Alexander G, Kogan M, Himes J. Maternal and Child Health Journal. 1999;3(4):225-231.

[16] Alexander G, Himes J, Kaufman R, Mor J, Kogan M. A united states national reference for fetal growth. Obstetrics & Gynecology. 1996;87(2):163-168.

[17] Hadlock F, Harrist R, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology. 1991;181(1):129-133.

[18] Reeves S, Bernstein I. Optimal Growth Modeling. Seminars in Perinatology. 2008;32(3):148-153.

[19] Gardosi J. Customized fetal growth standards: rationale and clinical application. Seminars in Perinatology. 2004;28(1):33-40.

** [20] Hammami A, Mazer Zumaeta A, Syngelaki A, Akolekar R, Nicolaides KH. Ultrasonographic estimation of fetal weight: development of new model and assessment of performance of previous models. Ultrasound Obstet Gynecol. 2018;52:35-43

A comprehensive and well-conducted study which evaluates several fetal weight ultrasound formulae in a large population. The authors validate the accuracy of multiple formulae and make recommendations for the most accurate formulae.

[21] [figure 1] Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements - a prospective study. Am J Obstet Gynecol 1985;151:333–337.

[22] Khalil A1, D'Antonio F, Dias T, Cooper D, Thilaganathan B; Southwest Thames Obstetric Research Collaborative (STORK). Ultrasound estimation of birth weight in twin pregnancy: comparison of biometry algorithms in the STORK multiple pregnancy cohort. Ultrasound Obstet Gynecol. 2014;44:210-20.

* [23] Papageorghiou A, Kennedy S, Salomon L, Altman D, Ohuma E, Stones W et al. The INTERGROWTH-21 fetal growth standards: toward the global integration of pregnancy and pediatric care. American Journal of Obstetrics and Gynecology. 2018;218(2):S630-S640.

A comprehensive article which reviews the biological and scientific rationale for the use of an international fetal growth reference standard.

[24] Maršál K, Persson P, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatrica. 1996;85(7):843-848.

[25] Salomon L, Bernard J, Ville Y. Estimation of fetal weight: reference range at 20–36 weeks' gestation and comparison with actual birth-weight reference range. Ultrasound in Obstetrics and Gynecology. 2007;29(5):550-555.

* [26] Nicolaides K, Wright D, Syngelaki A, Wright A, Akolekar R. Fetal Medicine Foundation fetal and neonatal population weight charts. .Ultrasound Obstet Gynecol 2018; 52: 44–51

Study demonstrating that fetal weight charts developed on preterm births (the majority) severely underestimate fetal weight as these preterm births are derived from pathological pregnancies. The authors present and validate a population fetal growth reference based on intrauterine fetal weight estimation.

[27] Chiossi G, Pedroza C, Costantine M, Truong V, Gargano G, Saade G. Customized vs population-based growth charts to identify neonates at risk of adverse outcome:

systematic review and Bayesian meta-analysis of observational studies. Ultrasound in Obstetrics & Gynecology. 2017;50(2):156-166.

[28] Gardosi J, Chang A, Kalyan B, Sahota D, Symonds E. Customised antenatal growth charts. The Lancet. 1992;339(8788):283-287.

[29] Gardosi J, Mongelli M, Wilcox M, Chang A. An adjustable fetal weight standard. Ultrasound in Obstetrics and Gynecology. 1995;6(3):168-174.

[30] Tamura R, Sabbagha R, Depp R, Vaisrub N, Dooley S, Socol M. Diminished growth in fetuses born preterm after spontaneous labor or rupture of membranes. American Journal of Obstetrics and Gynecology. 1984;148(8):1105-1110.

[31] Ott W. Intrauterine growth retardation and preterm delivery. American Journal of Obstetrics and Gynecology. 1993;168(6):1710-1717

[32] Gardosi J. Prematurity and fetal growth restriction. Early Human Development. 2005;81(1):43-49.

[33] Gardosi J. Intrauterine growth restriction: new standards for assessing adverse outcome. Best Practice & Research Clinical Obstetrics & Gynaecology. 2009;23(6):741-749.

[34] Muglu J, Rather H, Arroyo-Manzano D, Bhattacharya S, Balchin I, Khalil A et al. Risks of stillbirth and neonatal death with advancing gestation at term: A systematic review and meta-analysis of cohort studies of 15 million pregnancies. PLOS Medicine. 2019;16(7):e1002838.

[35] Flenady V, Koopmans L, Middleton P, Frøen J, Smith G, Gibbons K et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. The Lancet. 2011;377(9774):1331-1340.

[36] Morales-Roselló J, Dias T, Khalil A, Fornes-Ferrer V, Ciammella R, Gimenez-Roca L et al. Birth-weight differences at term are explained by placental dysfunction and not by maternal ethnicity. Ultrasound in Obstetrics & Gynecology. 2018;52(4):488-493.

[37] de Onis M, Branca F. Childhood stunting: a global perspective. Maternal & Child Nutrition. 2016;12:12-26

[38] Sovio U, Smith G. The effect of customization and use of a fetal growth standard on the association between birthweight percentile and adverse perinatal outcome. American Journal of Obstetrics and Gynecology. 2018;218(2):S738-S744.

** [39] Iliodromiti S, Mackay D, Smith G, Pell J, Sattar N, Lawlor D et al. Customised and Noncustomised Birth Weight Centiles and Prediction of Stillbirth and Infant Mortality and Morbidity: A Cohort Study of 979,912 Term Singleton Pregnancies in Scotland. PLOS Medicine. 2017;14(1):e1002228.

An evaluation fetal growth references in a large population demonstrating that fetal weight customisation for maternal demographic variables does not improve prediction of stillbirth and adverse outcome.

[40] Odibo A, Nwabuobi C, Odibo L, Leavitt K, Obican S, Tuuli M. Customized fetal growth standard compared with the INTERGROWTH-21st century standard at predicting small-for-gestational-age neonates. Acta Obstetricia et Gynecologica Scandinavica. 2018;97(11):1381-1387.

[41] Low birthweight - UNICEF DATA [Internet]. UNICEF DATA. 2019 [cited 17 August 2019]. Available from: https://data.unicef.org/topic/nutrition/low-birthweight/

[42] 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 Medicine. 2017;14(1):e1002220.

[43] Louis G, Grewal J, Albert P, Sciscione A, Nageotte M, Grobman W et al. 52: Racial/Ethnic differences in fetal growth, the NICHD fetal growth studies. American Journal of Obstetrics and Gynecology. 2015;212(1):S36.

[44] WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr 2006;450:76-85

[45] Anderson N, Sadler L, McKinlay C, McCowan L. INTERGROWTH-21st vs customized birthweight standards for identification of perinatal mortality and morbidity. American Journal of Obstetrics and Gynecology. 2016;214(4):509.e1-509.e7.

[46] Francis A, Hugh O, Gardosi J. Customized vs INTERGROWTH-21 st standards for the assessment of birthweight and stillbirth risk at term. American Journal of Obstetrics and Gynecology. 2018;218(2):S692-S699.

[47] Lees C, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo C, Brezinka C et al. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. The Lancet. 2015;385(9983):2162-2172.

[48] Sovio U, White I, Dacey A, Pasupathy D, Smith G. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. The Lancet. 2015;386(10008):2089-2097.

[49] Khalil A, Morales-Rosello J, Khan N, Nath M, Agarwal P, Bhide A et al. Is cerebroplacental ratio a marker of impaired fetal growth velocity and adverse pregnancy outcome?. American Journal of Obstetrics and Gynecology. 2017;216(6):606.e1-606.e10.

[50] Ciobanu A, Formuso C, Syngelaki A, Akolekar R, Nicolaides K. Prediction of small-for-gestational-age neonates at 35–37 weeks' gestation: contribution of maternal factors and growth velocity between 20 and 36 weeks. Ultrasound in Obstetrics & Gynecology. 2019;53(4):488-495.

[51] Ciobanu A, Anthoulakis C, Syngelaki A, Akolekar R, Nicolaides K. Prediction of small-for-gestational-age neonates at 35–37 weeks' gestation: contribution of maternal factors and growth velocity between 32 and 36 weeks. Ultrasound in Obstetrics & Gynecology. 2019;53(5):630-637.

[52] Poon L, Volpe N, Muto B, Syngelaki A, Nicolaides K. Birthweight with Gestation and Maternal Characteristics in Live Births and Stillbirths. Fetal Diagnosis and Therapy. 2012;32(3):156-165

** [53] Man J, Hutchinson J, Ashworth M, Heazell A, Levine S, Sebire N. Effects of intrauterine retention and postmortem interval on body weight following intrauterine death:

implications for assessment of fetal growth restriction at autopsy. Ultrasound in Obstetrics & Gynecology. 2016;48(5):574-578.

Large post-mortem study demonstrating that following stillbirth, fetuses lose approximately 20% of their body weight by the time that they are weighed after birth.

* [54] Monier I, Blondel B, Ego A, Kaminiski M, Goffinet F, Zeitlin J. Poor effectiveness of antenatal detection of fetal growth restriction and consequences for obstetric management and neonatal outcomes: a French national study. BJOG: An International Journal of Obstetrics & Gynaecology. 2014;122(4):518-527.

Large population study showing that a policy of SGA identification has the potential to significantly increase the risk of iatrogenic preterm birth and associated perinatal morbidity without significantly lowering stillbirth rate.

[55] Ego A, Monier I, Skaare K, Zeitlin J. Antenatal detection of fetal growth restriction and stillbirth risk: a population-based case–control study. Ultrasound in Obstetrics & Gynecology. 2019.

[56] Akolekar R, Panaitescu A, Ciobanu A, Syngelaki A, Nicolaides K. Two-stage approach for prediction of small for gestational age neonates and adverse perinatal outcome by routine ultrasound examination at 35-37 weeks' gestation. Ultrasound in Obstetrics & Gynecology. 2019;.

[57] Gordijn S, Beune I, Thilaganathan B, Papageorghiou A, Baschat A, Baker P et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound in Obstetrics & Gynecology. 2016;48(3):333-339.

[58] Figueras F, Gratacós E. Update on the Diagnosis and Classification of Fetal Growth Restriction and Proposal of a Stage-Based Management Protocol. Fetal Diagnosis and Therapy. 2014;36(2):86-98.

** [59] Thilaganathan B. Ultrasound fetal weight estimation at term may do more harm than good. Ultrasound in Obstetrics & Gynecology. 2018;52(1):5-8.

Opinion piece highlighting the importance of distinguishing the disorder of placental dysfunction from the signs of the disorder SGA (from malnutrition) and stillbirth (from

hypoxia). The author explains how the signs of placental dysfuction vary with the gestational age of disease onset.

[60] Dunsworth H, Warrener A, Deacon T, Ellison P, Pontzer H. Metabolic hypothesis for human altriciality. Proceedings of the National Academy of Sciences. 2012;109(38):15212-15216.

[61] Bilardo C, Hecher K, Visser G, Papageorghiou A, Marlow N, Thilaganathan B et al. Severe fetal growth restriction at 26-32 weeks: key messages from the TRUFFLE study. Ultrasound in Obstetrics & Gynecology. 2017;50(3):285-290.

[62] Vollgraff Heidweiller-Schreurs C, De Boer M, Heymans M, Schoonmade L, Bossuyt P, Mol B et al. Prognostic accuracy of cerebroplacental ratio and middle cerebral artery Doppler for adverse perinatal outcome: systematic review and meta-analysis. Ultrasound in Obstetrics & Gynecology. 2018;51(3):313-322.

[63] Conde-Agudelo A, Villar J, Kennedy S, Papageorghiou A. Predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction: systematic review and meta-analysis. Ultrasound in Obstetrics & Gynecology. 2018;52(4):430-441.

[64] Kalafat E, Morales-Rosello J, Thilaganathan B, Tahera F, Khalil A. Risk of operative delivery for intrapartum fetal compromise in small-for-gestational-age fetuses at term: an internally validated prediction model. American Journal of Obstetrics and Gynecology. 2018;218(1):134.e1-134.e8.

[65] Kalafat E, Morales-Rosello J, Scarinci E, Thilaganathan B, Khalil A. Risk of operative delivery for intrapartum fetal compromise in small-for-gestational-age fetuses at term: external validation of the IRIS algorithm. The Journal of Maternal-Fetal & Neonatal Medicine. 2019;:1-10.

FIGURE LEGENDS

Figure 1 Association between birth weight and estimated fetal weight derived from model of Hadlock *et al.*[21] using measurements of head circumference, abdominal circumference and femur length in the study population (r=0.959, p<0.0001). Reproduced with permission from Hammami A *et al*.[20]

Figure 2 Percentage of cases in a cohort of 95,579 pregnancies with birth weight below 3rd (clear bars), 5th (grey bars) and 10th (dark bars) percentiles of reference range of birth weight according to gestational age. Reproduced with permission from Nicolaides K *et al*.[26]

Figure 3 Low birth weight prevalence by UNICEF regions. Taken from UNICEF-WHO low birth weight estimates 2019.[41]

Figure 4 Birth weight according to gestational age at delivery in 436 pregnancies complicated by stillbirth, plotted against 10th, 50th and 90th percentiles of 112582 live births (solid lines) and those of the Intergrowth 21st standard (dotted lines). Reproduced with permission from Poon L *et al*. [52]

Figure 5 Increase in fetal nutrition (green line) and respiratory (red line) demands with advancing gestation. Early onset placental dysfunction (vertical gray solid line) will impact at a time when fetal nutritional demands (green arrows) rise exponentially and therefore will have a disproportionate effect on fetal growth compared with development of fetal hypoxemia and demise. Placental dysfunction at term (vertical gray dotted line) will impact at a time when fetal respiratory needs (red arrows) rise exponentially and therefore likely to compromise fetal wellbeing before fetal growth is impaired. Reproduced with permission from Thilaganathan B.[59]

Figure 6 Infant mortality and stillbirth according to birthweight centiles. Reproduced with permission from Iliodromiti S *et al.* [39]

Figure

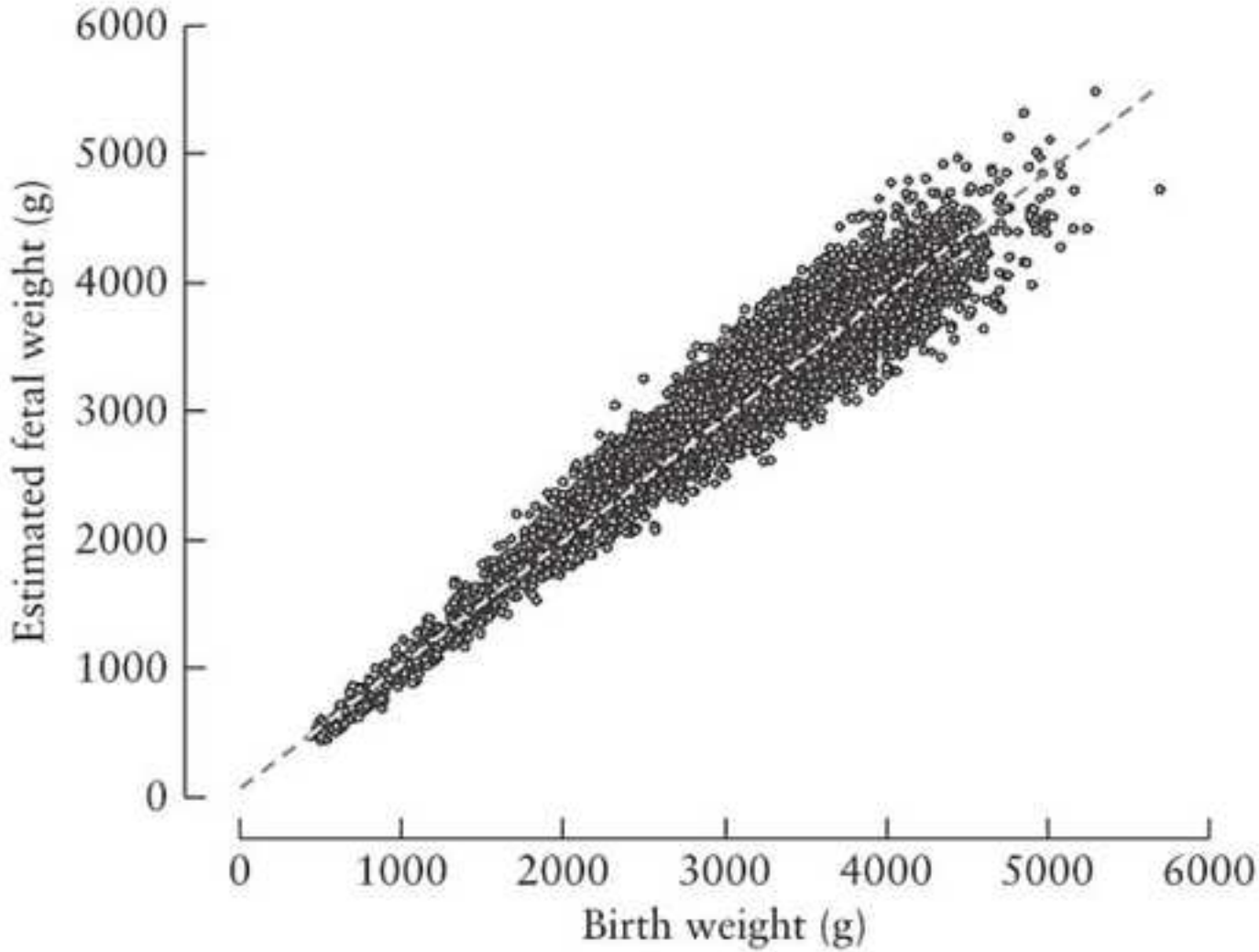


Figure 2 Association between birth weight and estimated fetal weight derived from model of Hadlock *et al.*[15] using measurements of head circumference, abdominal circumference and femur length in study population ($r = 0.959$; $P < 0.0001$).

Figure

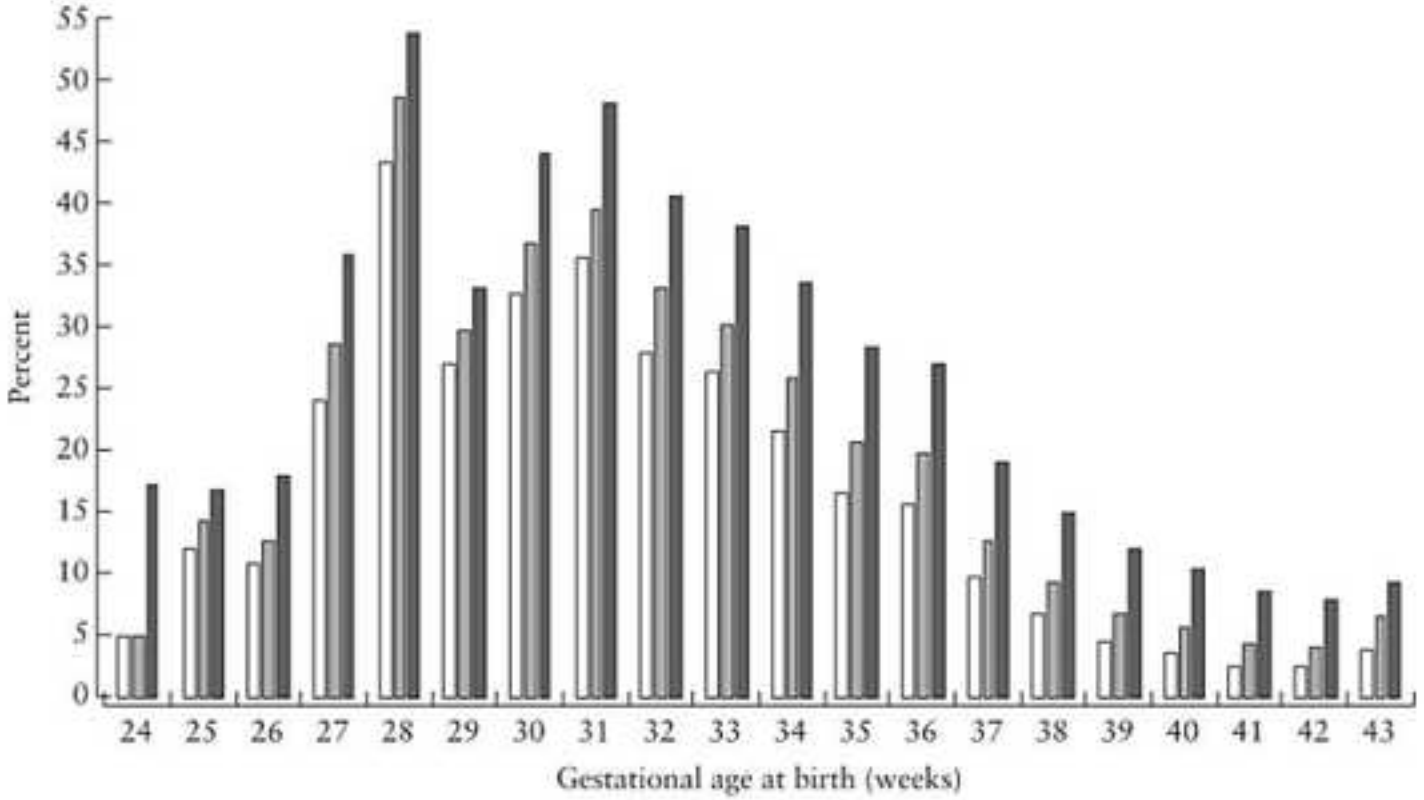
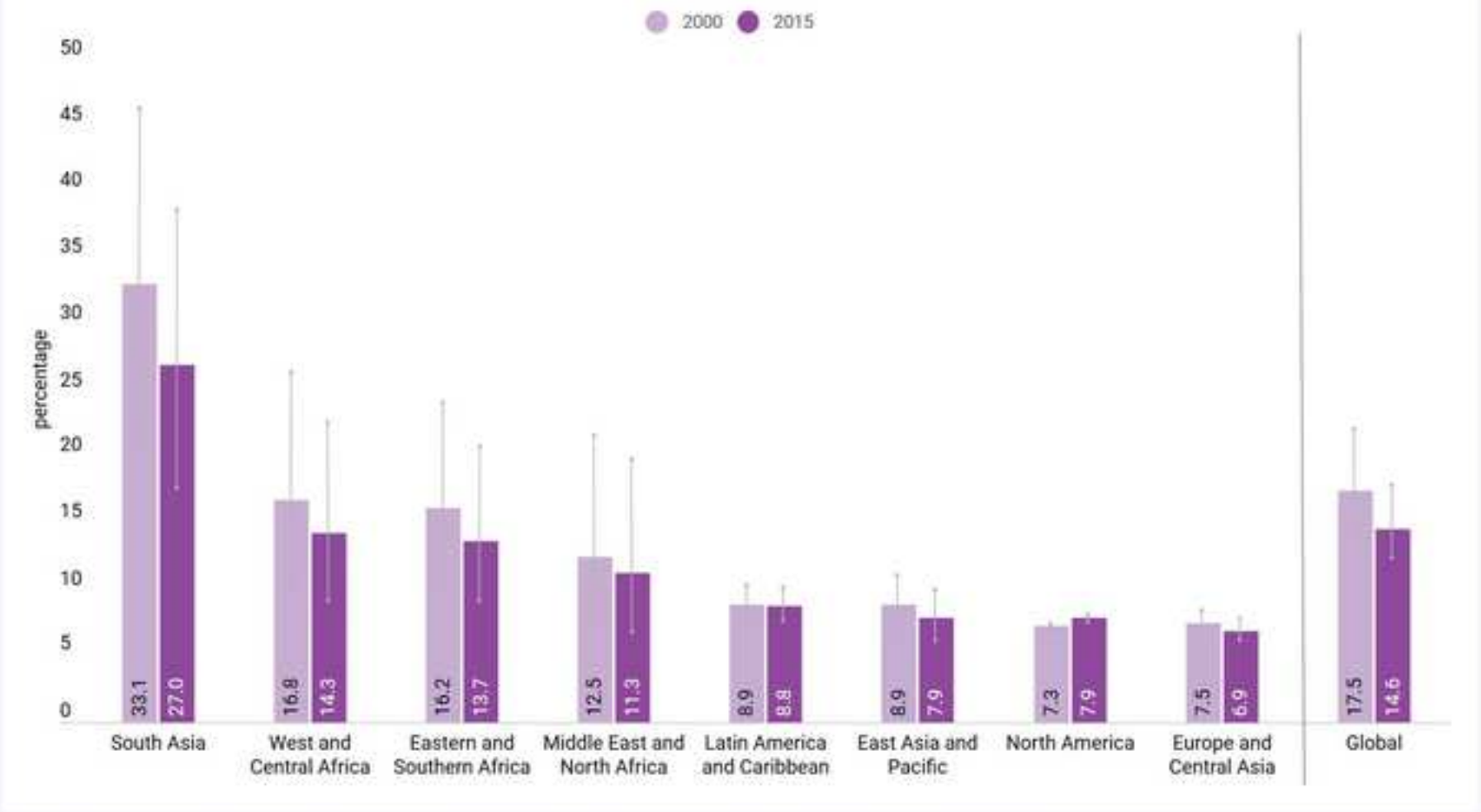


Figure 4 Percentage of cases in Dataset 2 with birth weight below 3rd (□), 5th (▤) and 10th (■) percentiles of reference range of birth weight according to gestational age.

Figure

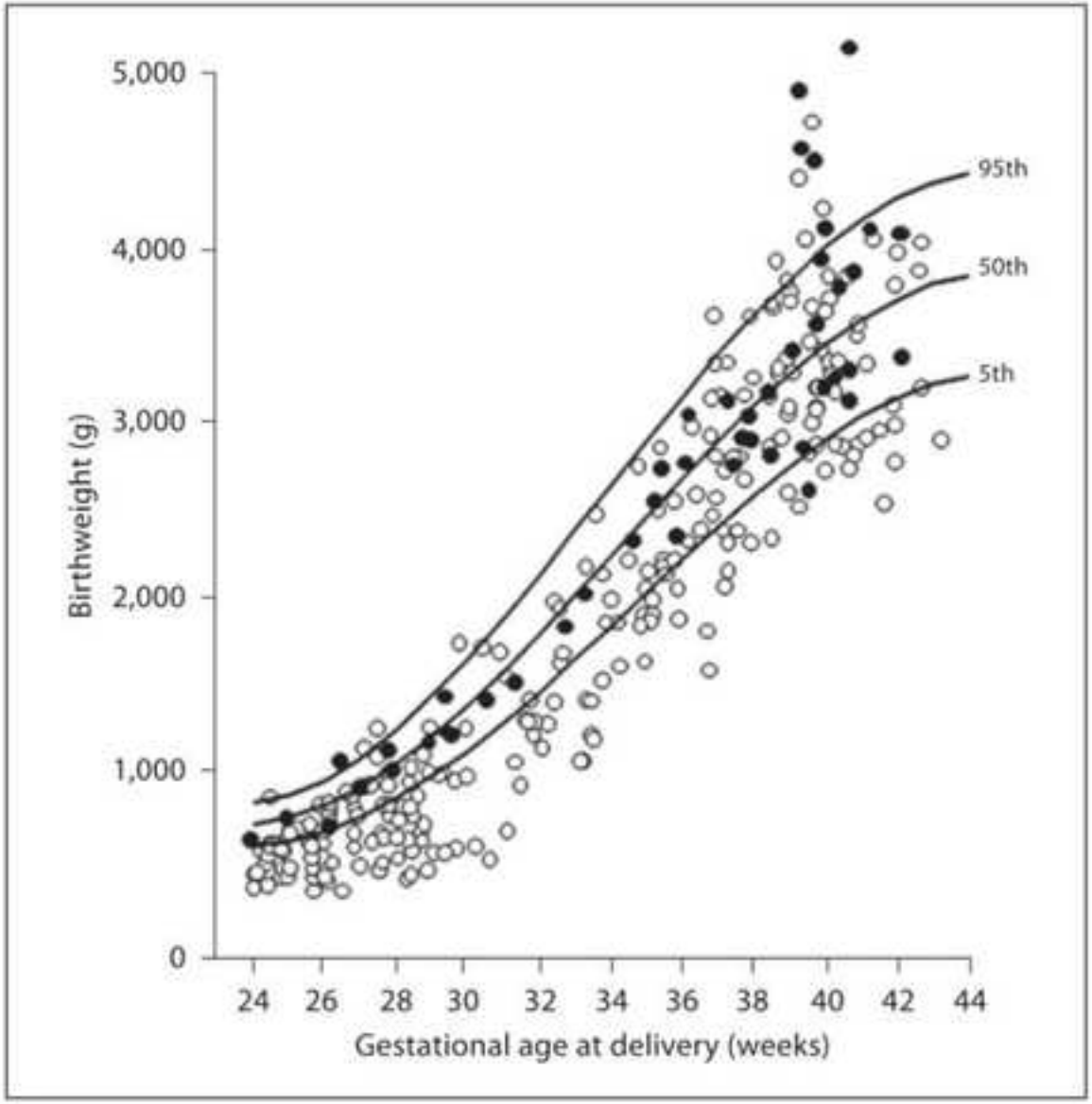
Progress on reducing low birthweight has been stagnant in all regions since 2000



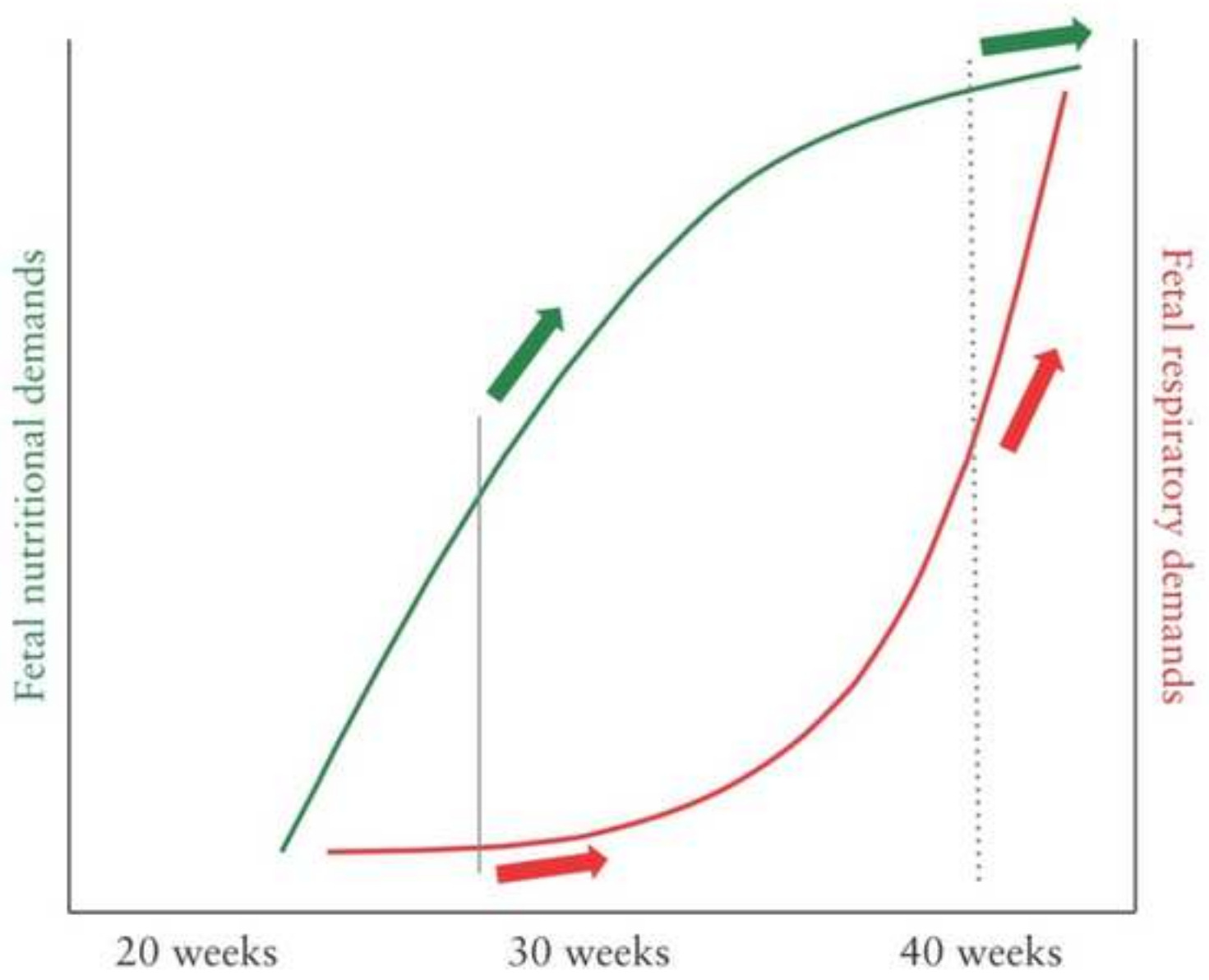
Low birthweight prevalence, by UNICEF regions and global, 2000 and 2015

Source: UNICEF-WHO Low birthweight estimates, 2019. NOTE: None of the changes between 2000 and 2015 were statistically significant for any region.

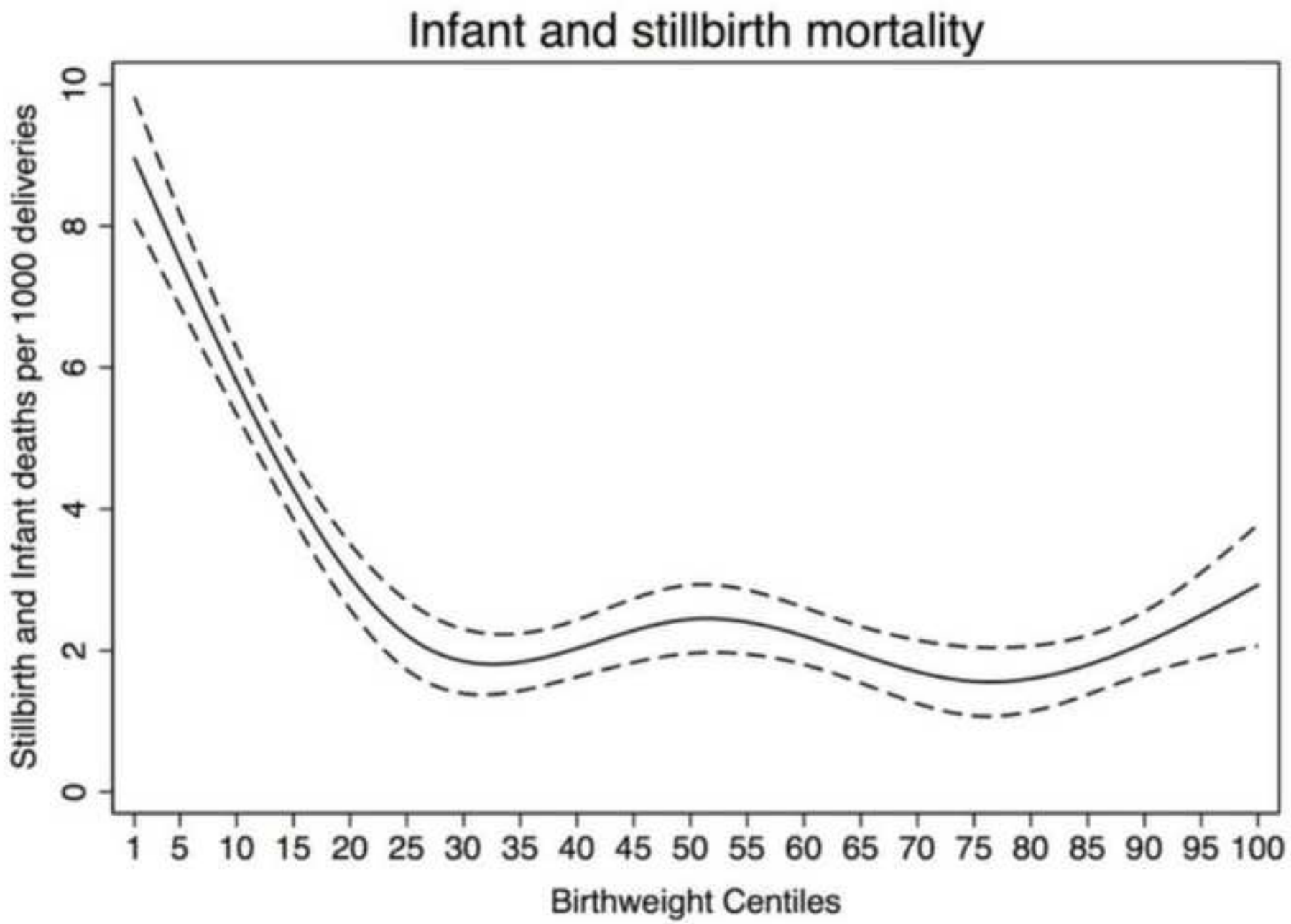
Figure


5,000
4,000
3,000
2,000
1,000
0
Birthweight (g)
95th
50th
5th
24
26
28
30
32
34
36
38
40
42
44
Gestational age at delivery (weeks)

Figure


Fetal nutritional demands
Fetal respiratory demands
20 weeks
30 weeks
40 weeks

Figure


Infant and stillbirth mortality
Stillbirth and Infant deaths per 1000 deliveries
0
2
4
6
8
10
1 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
Birthweight Centiles