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

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5 **PREVENTING TERM STILLBIRTH: BENEFITS AND LIMITATIONS**
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7 **OF USING FETAL GROWTH REFERENCE CHARTS**
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4 **Purpose of review**
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6 This review examines the variation in clinical practice with regards to ultrasound
7 estimation of fetal weight, as well as calculation of fetal weight centiles from
8 population/customised fetal growth references or fetal growth standards.
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15 **Recent findings**
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17 Placental dysfunction is associated with fetal smallness from intrauterine malnutrition as
18 well as fetal disability and even stillbirth from hypoxemia. Although estimating fetal weight
19 can be done accurately, the issue of which fetal weight centile chart should be used
20 continues to be a contentious topic. The arguments against local fetal growth charts
21 based on national borders and customization for variables known to be associated with
22 pathology are substantial. As for other human diseases such as hypertension and
23 diabetes, there is a rationale for the use of an international fetal growth reference
24 standard. Irrespective of the choice of fetal growth reference standard, a significant
25 limitation of national SGA detection programs to prevent stillbirth is that the majority of
26 stillborn infants at term were not SGA at the time of demise.
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38 **Summary**
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40 Placental dysfunction can present with SGA from malnutrition and/or stillbirth from
41 hypoxemia depending on the gestational age of onset. Emerging data show that at term,
42 fetal Doppler arterial redistribution is associated more strongly with perinatal death than
43 fetal size. Properly conducted trials of the role for maternal characteristics, fetal size,
44 placental biomarkers and Dopplers assessing fetal wellbeing are required urgently.
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52 **Keywords**
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54 Stillbirth, small for gestational age, fetal growth restriction, estimated fetal weight, fetal
55 weight centile, fetal growth charts, fetal growth references, fetal growth standards
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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 achieved using the Hadlock HC, AC and FL formula [21].

CHARTS TO ESTIMATE FETAL WEIGHT CENTILE

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

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16 These are charts defined by the geography of a particular area (local) or country
17 (national). The charts are typically constructed retrospectively from existing ultrasound
18 biometry and birth weight data from the source population. The developers of such charts
19 rationalise their use on the basis that there is recognised regional variation in child and
20 adult stature, presumably due to ethnicity, social, economic and nutritional factors. These
21 charts describe how babies in a particular geographical cohort 'have grown', but do not
22 tell us what is clinically relevant - which is how a normal baby 'should grow' [23]. The main
23 limitation with retrospectively constructed charts is that the pregnancy cohort contains
24 hidden maternal and fetal morbidity which may have impaired fetal growth. Some charts
25 have used retrospective 'cleaning' of the cohort data to overcome this limitation, but such
26 an approach is typically incomplete and does not eliminate occult health problems.
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37 Another limitation of geographical charts is that, usually preterm births are used to
38 establish normograms despite the finding that median BW for babies born preterm is
39 substantially lower than median EFW [24,25]. This difference is likely to be the
40 consequence of pathological fetal growth in the majority of preterm births. Therefore,
41 reference ranges for BW contains an overrepresentation of pathological pregnancies
42 particularly for gestational ages <37 weeks. Nicolaides and colleagues established a BW
43 chart using fetuses still in utero, thereby overcoming the problem of underestimation of
44 growth restriction in preterm birth [26]. Using the latter chart, the authors demonstrated
45 that for preterm birth, BW was below the 10th centile in a very high proportion of cases
46 (Figure 2) [26], both for iatrogenic causes (52.5%) and spontaneous preterm births
47 (19.8%). The latter charts would seem the appropriate choice for screening for preterm
48 placental dysfunction and FGR.
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4 Despite the apparent limitations, local and national charts are in wide usage across the
5 world, even though it is not clear how multicultural populations are represented in such
6 charts. An unresolved major issue that undermines the justification for the use of such
7 charts is a believable biological explanation for how nationality/national borders influence
8 fetal growth.
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10 **Customized charts**

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14 A potential approach to deal with the limitations of population-based local or national
15 growth charts is customization, where expected fetal growth is modulated according to
16 individual variables that are known to affect fetal growth [27]. Proponents of customized
17 growth charts established the growth potential of each fetus according to physiological
18 variations in maternal characteristics such as height, weight, ethnic origin, parity and fetal
19 sex, but not for pathology such as premature birth, smoking, hypertensive disorders or
20 diabetes [28-32]. It has been suggested customizing expected fetal growth for these
21 variables will result in improved diagnosis of SGA pregnancies at risk of adverse outcome
22 [33]. For instance, it has been suggested that use of customised charts will reduce the
23 number of pregnancies classified as SGA to approximately 10% when used in Asian or
24 low BMI populations. The latter groups typically have much higher rates of SGA when
25 classified using population-based fetal growth charts, which supposedly identify 'normally
26 small' rather than FGR babies as risk of adverse outcome.
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40 Whilst it is certainly true that certain maternal characteristic are associated with altered
41 fetal growth, the very same variables also predispose to increased fetal morbidity and
42 mortality. For example, customization 'normalises' smaller fetuses in Asian and Afro-
43 Caribbean women, when women from these ethnicities are also at increased risk of
44 stillbirth [34]. Similarly, other variable used in customised fetal growth charts such as
45 maternal age, weight and parity have also been shown to be related to risk of stillbirth
46 [35,36]. Apart from the concern that customisation of fetal growth is 'normalising' for
47 variables that predispose to pregnancy pathology, there is also the question of biological
48 rationale for customisation. The well-accepted associations between these variables and
49 fetal weight cannot be causative, as it is inconceivable that the 1-2% of genes that
50 determine maternal skin colour are also coincidentally responsible for controlling fetal
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4 growth. Similarly, the placenta cannot 'know' the age of the mother, her weight or parity,
5 making the latter variables proxy markers for uteroplacental dysfunction rather than
6 directly controlling fetal growth [37].
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10 Regardless of the justification for the use of customisation, it is important to recognise
11 that customisation was proposed as a means of better identifying at-risk pregnancies.
12 However, systematic evaluation of the use of customisation has failed to show increased
13 performance in the detection of adverse pregnancy outcome in several large or
14 prospectively conducted studies [38,39,40]
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19 **International reference standard**

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21 The popularity of local, national or customised fetal growth reference charts is based on
22 the reasoning that approximately 10% of fetuses in any given population should be SGA.
23 This assumption is fundamentally at odds with the known variation in rates of neonatal
24 malnutrition at birth worldwide (Figure 3) ranging from as high as 27% in South Asia to a
25 low of 7% in Europe [41]. This variation in malnutrition at birth is attributed to differences
26 in nutrition, maternal co-morbidity and other socioeconomic factors – and is used as
27 justification by proponents of an international fetal growth reference standard [23,42].
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33 Fetal growth reference standards are prescriptive charts that are constructed
34 prospectively in populations that have been screened before recruitment to ensure
35 minimal bias from detrimental environmental and medical confounders that may affect
36 fetal growth. So as opposed to retrospective local or national charts that describe how
37 fetuses in a certain population have grown, fetal growth reference standards describe
38 how fetuses should grow if they were free of any environmental or clinical constraints.
39 Two consortiums used this approach to define optimal fetal growth reference standards
40 [23, 43]. The Intergrowth-21st consortium adapted the same stringent standards to control
41 for environmental and medical confounders as was used for the well-established WHO
42 Child Growth Standards [44]. Intergrowth-21st showed that human growth in low risk
43 environments is very similar in fetuses regardless of where they live or their ethnic/racial
44 background [23]. These findings would suggest that perinatal health and fetal growth are
45 mainly affected by the environmental, nutritional, socioeconomic factors across
46 populations [23]. In contrast, the NICHD consortium 'standardised' pregnancies by
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4 hospital, which introduced bias as it does not necessarily remove environmental
5 constraints [23]. The NICHD study showed that fetal growth was minimally – but
6 significantly different in four self-reported ethnic groups [43]. Interestingly, the NICHD
7 study also demonstrated that marital status, level of education, annual income and private
8 insurance influenced fetal growth.
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14 Retrospective evaluations of the Intergrowth-21 fetal growth reference standard in two
15 large population studies concluded that there was a reduced identification of SGA fetuses
16 and cases of perinatal death [45, 46]. It should be noted that the poorer performance of
17 the Intergrowth-21 reference standards was for a much lower number of pregnancies
18 classified as SGA. Neither of the studies provided a comparison of screening efficiency
19 for adverse outcome at comparable screen positive rates – which would have provided a
20 better head-to-head comparison of different growth references and standards.
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29 **SHOULD WE ASSESS FETAL GROWTH INSTEAD OF FETAL SIZE?**

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32 Fetal growth - the relative change in fetal size over a time period - is often used as an
33 alternative indicator of fetal wellbeing in screening programs using serial ultrasound
34 assessment. Many clinicians believe that assessment of fetal growth over two or more
35 scans is superior to assessment of fetal size alone, especially with the current uncertainty
36 over which charts to use and whether to customise fetal size assessment by correcting
37 for certain maternal characteristics. Although fetal growth can be objectively assessed by
38 measuring change in fetal weight centile over the interval between scans, how this data
39 should be interpreted is yet to be resolved. There are no evidenced-based guidelines that
40 outline the risk of adverse outcome based on i) change in fetal weight centile, ii) over the
41 interval of fetal growth assessment and iii) whether the same change in growth implies
42 similar risks at different gestations. For example, is a 20% drop in fetal weight centile over
43 a two-week interval clinically significant and is this significance similar at 28, 32 and 36
44 weeks' gestation? Thresholds for intervention on the basis of pathological deviation in
45 fetal growth are likely to depend on gestational age at onset of placental insufficiency, as
46 well as the rate over which that growth deviation occurs and the ability of the fetus to
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4 endure such compromise. It would be churlish to assume that a given fetal growth
5 threshold could serve to identify and prevent stillbirth at any given gestation.
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9 In a large randomised controlled trial of early-onset fetal growth restriction <32 weeks,
10 the TRUFFLE investigators demonstrated that fetal growth velocity did not help predict or
11 prevent adverse outcome [47]. Similarly, in late pregnancy, the POP study in which
12 women were allocated to either routine pregnancy care or serial (clinically blinded)
13 ultrasound scans, fetal growth velocity was significantly associated with adverse
14 outcome, but only in the SGA fetuses and not in appropriate-for-gestational-age births
15 [48]. Several retrospective but larger studies have also shown that growth velocity does
16 not improve prediction of adverse pregnancy outcome due to placental dysfunction [49-
17 51] . The authors also demonstrated that the lack of clinical benefit from assessing fetal
18 growth held true for whether the inter-scan interval was large (from 20 to 36 weeks) or
19 small (from 32 to 36 weeks).
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31 **DOES ASSESSMENT OF FETAL SIZE REDUCE STILLBIRTH AT TERM?**

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33 The prevalent clinical focus on routinely monitoring fetal size is predicated on the
34 association with stillbirth and the desire to deliver the pregnancy before this adverse
35 outcome occurs. However, unlike preterm stillbirth where the majority of stillborn are SGA,
36 intrauterine demise at term occurs in appropriately grown fetuses in 60–70% of cases
37 (Figure 4) [52]. More recently, it has become evident that after a stillbirth, fetuses lose
38 approximately 20% of their bodyweight through intrauterine maceration before birth and
39 dehydration ex-utero before having their weight formally recorded [53]. Therefore, the 30-
40 40% of term stillbirths that are classified as SGA were probably incorrectly classified with
41 a significant proportion being AGA at the time of intrauterine demise. Whilst it is not in
42 doubt that there is an association between SGA and stillbirth, it is clear that a health policy
43 focused entirely on identification of SGA fetuses not prevent the majority of stillbirths at
44 term. The latter is supported by population studies such as by Monier and colleagues [54]
45 in a population-based study of routine third-trimester ultrasound in 14,000 pregnancies
46 detected only 21.7% of SGA infants and resulted in a high false positive rate for SGA
47 diagnosis, six-fold increase in provider-initiated preterm deliveries and unchanged
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4 perinatal mortality. In a follow-up study of over 90,000 pregnancies, the same group
5 reported a disappointing protective effect of SGA/FGR detection than previously reported
6 as over 40% of stillbirths occurred despite detection of SGA [55]. In a prospective study
7 of over 45,000 pregnancies, Akolekar and colleagues demonstrated that although in SGA
8 babies had an increased risk of adverse perinatal outcome, 84% of adverse perinatal
9 events occur in the AGA group – resulting in poor predictive performance of SGA
10 detection for adverse perinatal outcome [56]. Both research groups called into question
11 a focus solely on improving SGA detection without addressing post-detection
12 management taking into account maternal characteristics, gestational age and Doppler
13 assessment.
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25 **EARLY AND LATER FETAL GROWTH RESTRICTICION – TWO DIFFERENT** 26 **DISORDERS?** 27

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29 As well as reaching expert opinion on a definition of placental FGR a Delphi consensus
30 has also been reached for both early and late-onset disease [57]. The underlying
31 commonality between early and late gestation FGR is that they occur as a consequence
32 of placental dysfunction. Both conditions are also associated with increased incidence of
33 poor neurodevelopmental, cardiovascular and metabolic long-term outcomes for the
34 affected fetus. Early FGR is less common and represents approximately 20-30% of all
35 cases of growth restriction. It is associated with severe placental insufficiency and
36 preeclampsia in up to 50% of cases. Late gestation FGR is more common and constitutes
37 approximately 70-80% of all cases of growth restriction. It is associated with mild placental
38 insufficiency and preeclampsia in approximately 10% of cases [58]. There is ongoing
39 debate as to whether the placental dysfunction in late gestation FGR is a consequence
40 of milder disease compared to early onset FGR or as a result of placental dysfunction
41 occurring later in pregnancy.
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54 Our understanding of placental dysfunction is based on the fundamental assumption that
55 the association between fetal size and adverse perinatal outcome is a causative one -
56 that is to say that fetal smallness causes stillbirth. The placenta is responsible for multiple
57 functions such as nutrition, respiration and excretion amongst many other life processes.
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4 As such, placental dysfunction will confer both nutritional as well as respiratory
5 consequences to the developing fetus [59]. It should be noted that failure to meet
6 nutritional demands result in growth deficiency and can usually be tolerated for several
7 few days/weeks, whereas failed respiratory function results in hypoxia which can only be
8 tolerated for minutes/hours. Fetal nutritional needs follow a logarithmic curve (Figure 5)
9 whilst respiratory demands show exponential growth [59, 60]. In early-onset placental
10 dysfunction, fetal nutrition is compromised more severely than respiration, thereby
11 predominantly resulting in growth restriction as the main presenting feature. At this early
12 stage of pregnancy, fetal respiratory demands are low and usually continue to be met by
13 a dysfunctional placenta for several weeks. The latter explains why in early-onset
14 placental dysfunction, SGA develops over several weeks of nutritional insufficiency. In
15 contrast, late onset of placental dysfunction at term will disproportionately affect fetal
16 respiratory demands which are increasing exponentially at this stage of pregnancy, just
17 as nutritional demands begin to plateau. Thus, a 3000g fetus near term that is affected
18 by placental failure is likely to die from hypoxia related to respiratory dysfunction within a
19 few days, long before it can become small from failing to grow over several weeks.
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34 Put simply, placental dysfunction a disorder which may manifest signs of either SGA from
35 malnutrition or stillbirth from respiratory failure. The nutritional and respiratory demands
36 of a fetus vary significantly with advancing gestation, and the consequences of either
37 nutritional or respiratory compromise have different presentations (SGA versus stillbirth)
38 and temporal patterns (protracted versus rapid). Early-onset placental dysfunction
39 presents predominantly with SGA, whereas in late-onset disease, critical fetal hypoxia
40 may occur in a term fetus before SGA has time to develop.
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50 **MANAGEMENT OF LATE-ONSET PLACENTAL DYSFUNCTION**

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

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4 Requires the use of validated EFW formula that can be used in any clinical setting, such
5 as those published by Hadlock *et al.* (1985) and Hammami A *et al.* (2018) using multiple
6 fetal biometric measures.
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9 10 **Establishing fetal weight centile**

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12 In preterm pregnancies, charts established using fetuses still in utero to overcome the
13 problem of underestimation of preterm growth restriction, such as developed by
14 Nicolaides K *et al.* should be used [26]. Near term, irrespective of which charts are used,
15 the majority of adverse pregnancy outcomes will occur in non-SGA pregnancies, hence
16 the choice of fetal growth reference charts is unlikely to have a major clinical impact. This
17 makes the case for use of an international fetal growth reference standard so that
18 meaningful comparisons of SGA rates between countries and before/after birth can be
19 made.
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22 23 **Assessing fetal wellbeing**

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25 In preterm pregnancies should include the use of computerised CTG and DV Doppler up
26 to 32 weeks gestation along with indicated delivery for reversed end-diastolic umbilical
27 artery blood flow from 32 weeks and for absent end-diastolic umbilical artery blood flow
28 from 34 weeks [61]. Near term, even though the risk of stillbirth is increased in SGA
29 pregnancies, the majority of stillbirths occur in normally sized babies. Cerebroplacental
30 ratio (CPR) - the ratio of the middle cerebral artery pulsatility index to the umbilical artery
31 pulsatility index - is emerging as a potentially useful marker of fetal hypoxemia at term
32 [62, 63]. Low CPR is known to be a marker for fetal hypoxemia at term in AGA fetuses
33 [49], and is associated with low abdominal circumference growth velocity and adverse
34 pregnancy outcomes including stillbirth, neonatal unit admission and neonatal morbidity
35 [49]. As the risk of perinatal mortality seems to increase only when EFW is below the 30th
36 centile of birthweight for gestation (Figure 6) [39], the latter population would seem to be
37 a reasonable target for fetal Doppler/CPR evaluation. Unfortunately, it is still not evident
38 whether the use of fetal Doppler evaluation in this sub-population can prevent stillbirth
39 and improve perinatal outcome. It is likely that combined evaluation of maternal
40 characteristics, fetal size, placental biomarkers and Doppler indices in a diagnostic
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4 algorithm may be of value in identifying pregnancies that justify earlier scheduled birth
5 because of an increased risk of adverse outcome and [64, 65].
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10 **CONCLUSION**

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13 Placental dysfunction is associated with fetal smallness due to intrauterine malnutrition
14 as well as fetal disability and even death from respiratory hypoxemia. Fetal size is
15 universally used as a common clinical proxy for placental dysfunction. The issue of which
16 fetal weight centile assessment should be used continues to be a contentious topic. The
17 arguments against local fetal growth charts based on national borders and customization
18 for maternal variables associated with pregnancy pathology are considerable. As for other
19 human diseases such as hypertension and diabetes, the rationale for the use of an
20 international fetal growth reference standard makes a lot of sense. Variation in national
21 rates of SGA is perceived as a limitation of these charts, but not when one considers that
22 these variations are aligned to the rates of neonatal malnutrition seen in these countries.
23
24 Irrespective of the choice of fetal growth reference standard, a significant limitation of
25 national SGA detection programs to prevent stillbirth is that the majority of stillborn infants
26 at term were not SGA at the time of demise. That placental dysfunction may present either
27 with signs of SGA from malnutrition or stillbirth from hypoxemia is explained when one
28 understands the varying fetal nutritional and respiratory demands with advancing
29 gestation. Emerging data show consistently that fetal Doppler arterial redistribution is
30 associated more strongly than fetal size with perinatal death at term. Properly conducted
31 and powered trials of the role for maternal characteristics, fetal size, placental biomarkers
32 and Doppler indices for assessing fetal wellbeing at term are now urgently required.
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4 **KEY POINTS:**
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- 6 • Accurately estimating fetal weight can be achieved by using validated
7 multiparameter fetal biometry formulae
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- 9 • Establishing fetal weight centile can be undertaken using population/customised
10 fetal growth references or international fetal growth standards
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- 12 • Population charts are limited by the lack of a believable biological explanation for
13 how nationality or national borders influence fetal growth
14
- 15 • Whilst certain maternal characteristics are associated with altered fetal growth, the
16 very same variables also predispose to increased fetal mortality questioning the
17 rationale for customisation.
18
- 19 • Stillbirth prevention policies based identifying SGA fetuses are significantly limited
20 by the finding that at term, the majority of antenatal stillbirths are appropriately
21 grown at the time of intrauterine demise
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- 23 • Fetal Doppler arterial redistribution is more strongly associated with perinatal death
24 at term than fetal size
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53 **CONFLICTS OF INTEREST**
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55 No conflicts of interest to declare
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4 **FIGURE LEGENDS**
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9 **Figure 1** Association between birth weight and estimated fetal weight derived from model
10 of Hadlock *et al.*²¹ using measurements of head circumference, abdominal circumference
11 and femur length in the study population ($r=0.959$, $p<0.0001$). Reproduced with
12 permission from Hammami A *et al.*²⁰
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19 **Figure 2** Percentage of cases in a cohort of 95,579 pregnancies with birth weight below
20 3rd (clear bars), 5th (grey bars) and 10th (dark bars) percentiles of reference range of
21 birth weight according to gestational age. Reproduced with permission from Nicolaides K
22 *et al.*²⁶
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29 **Figure 3** Low birth weight prevalence by UNICEF regions. Taken from UNICEF-WHO low
30 birth weight estimates 2019.⁴¹
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36 **Figure 4** Birth weight according to gestational age at delivery in 436 pregnancies
37 complicated by stillbirth, plotted against 10th, 50th and 90th percentiles of 112582 live births
38 (solid lines) and those of the Intergrowth 21st standard (dotted lines). Reproduced with
39 permission from Poon L *et al.*⁵²
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46 **Figure 5** Increase in fetal nutrition (green line) and respiratory (red line) demands with
47 advancing gestation. Early onset placental dysfunction (vertical gray solid line) will impact
48 at a time when fetal nutritional demands (green arrows) rise exponentially and therefore
49 will have a disproportionate effect on fetal growth compared with development of fetal
50 hypoxemia and demise. Placental dysfunction at term (vertical gray dotted line) will impact
51 at a time when fetal respiratory needs (red arrows) rise exponentially and therefore likely
52 to compromise fetal wellbeing before fetal growth is impaired. Reproduced with
53 permission from Thilaganathan B.⁵⁹
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Figure 6 Infant mortality and stillbirth according to birthweight centiles. Reproduced with permission from Iliodromiti S *et al.*³⁹

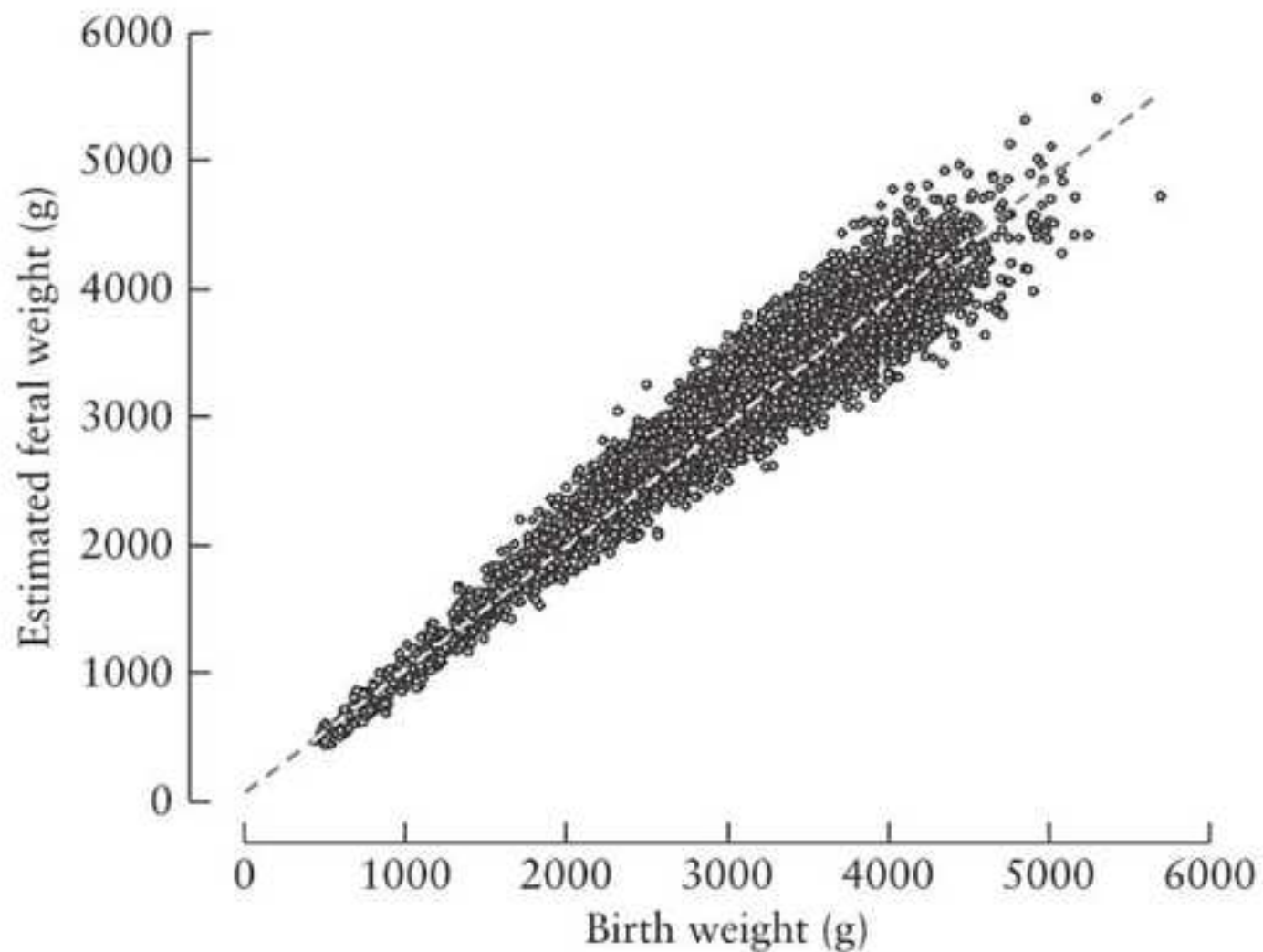


Figure 2 Association between birth weight and estimated fetal weight derived from model of Hadlock *et al.*¹⁵ using measurements of head circumference, abdominal circumference and femur length in study population ($r = 0.959$; $P < 0.0001$).

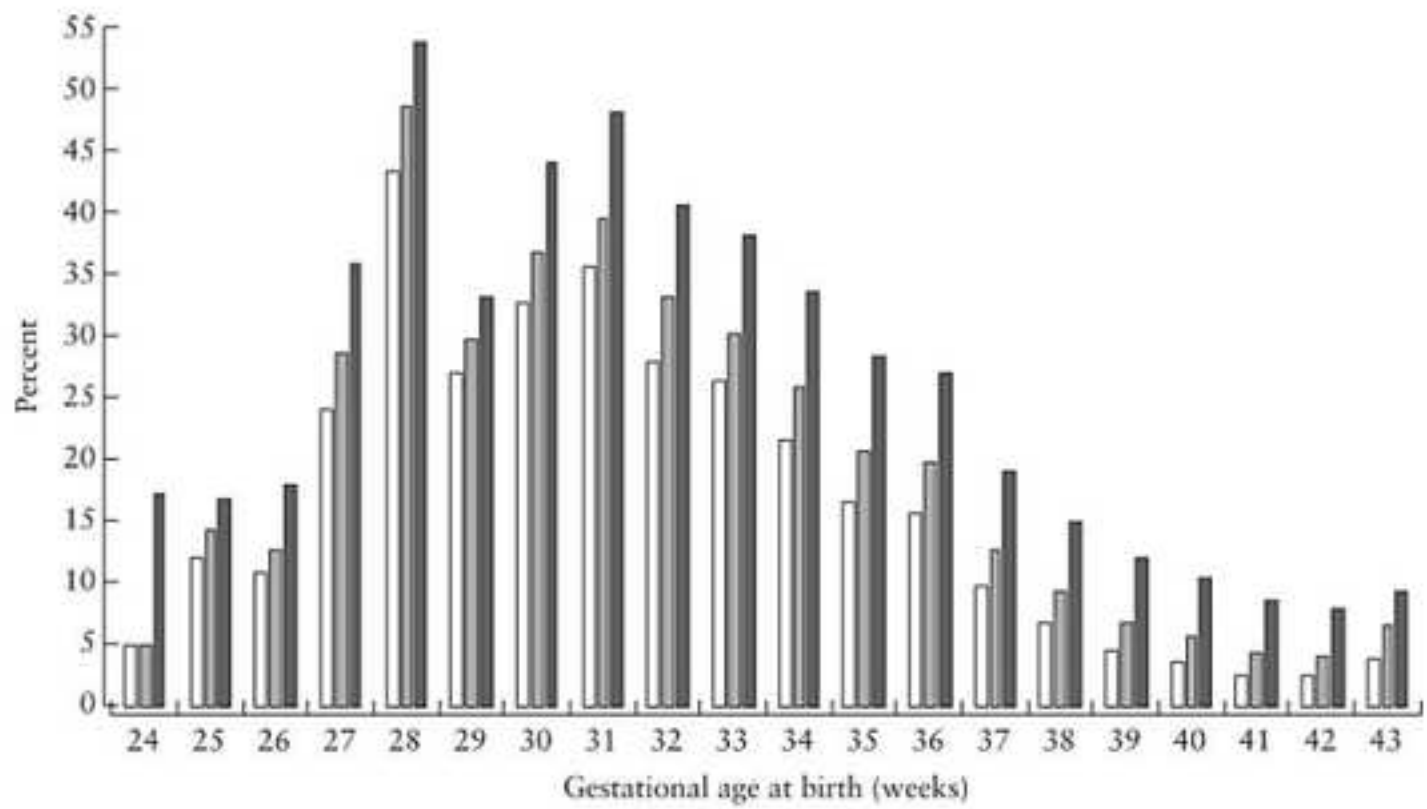
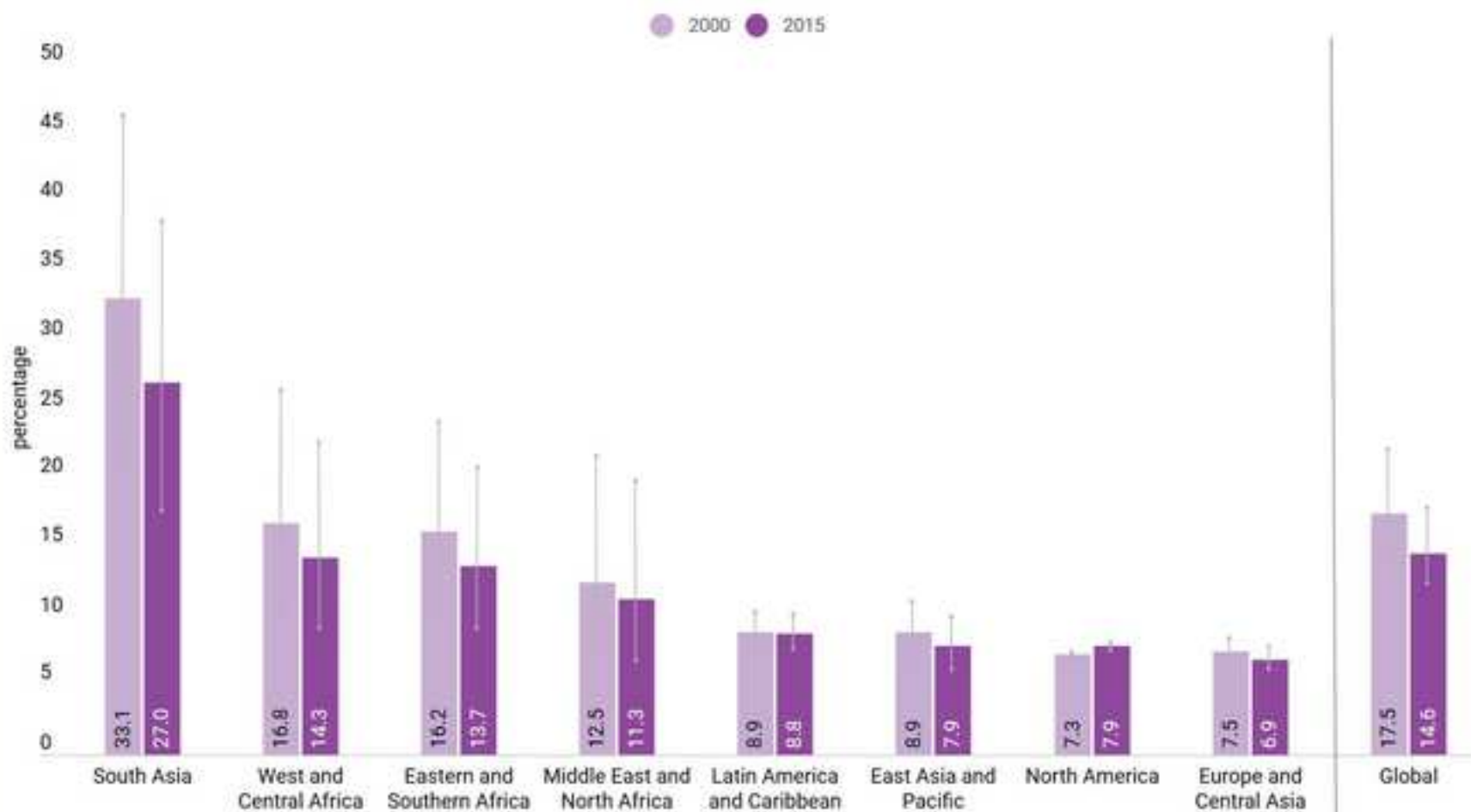


Figure 4 Percentage of cases in Dataset 2 with birth weight below 3rd (□), 5th (▒) and 10th (■) percentiles of reference range of birth weight according to gestational age.



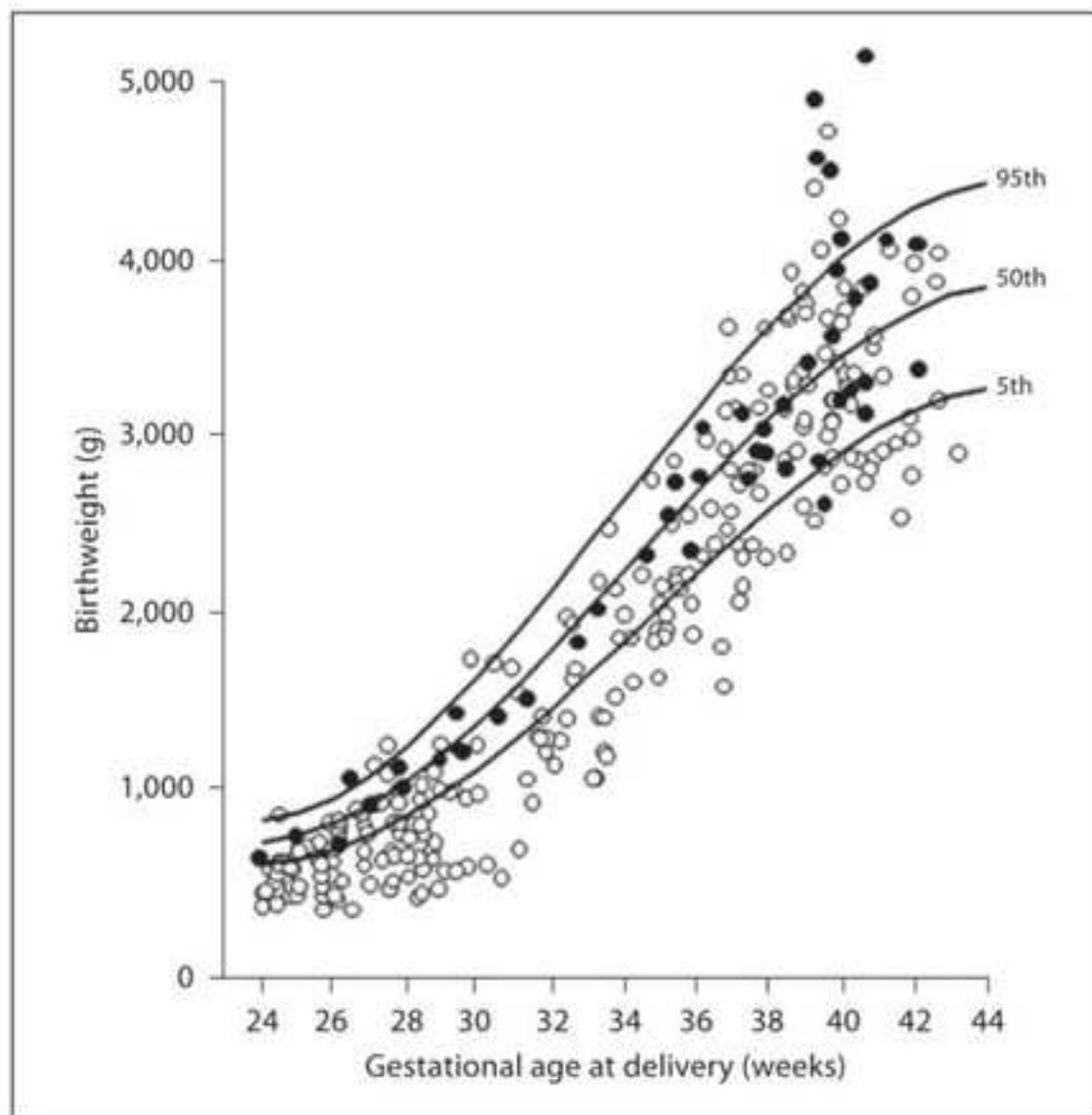
Progress on reducing low birthweight has been stagnant in all regions since 2000



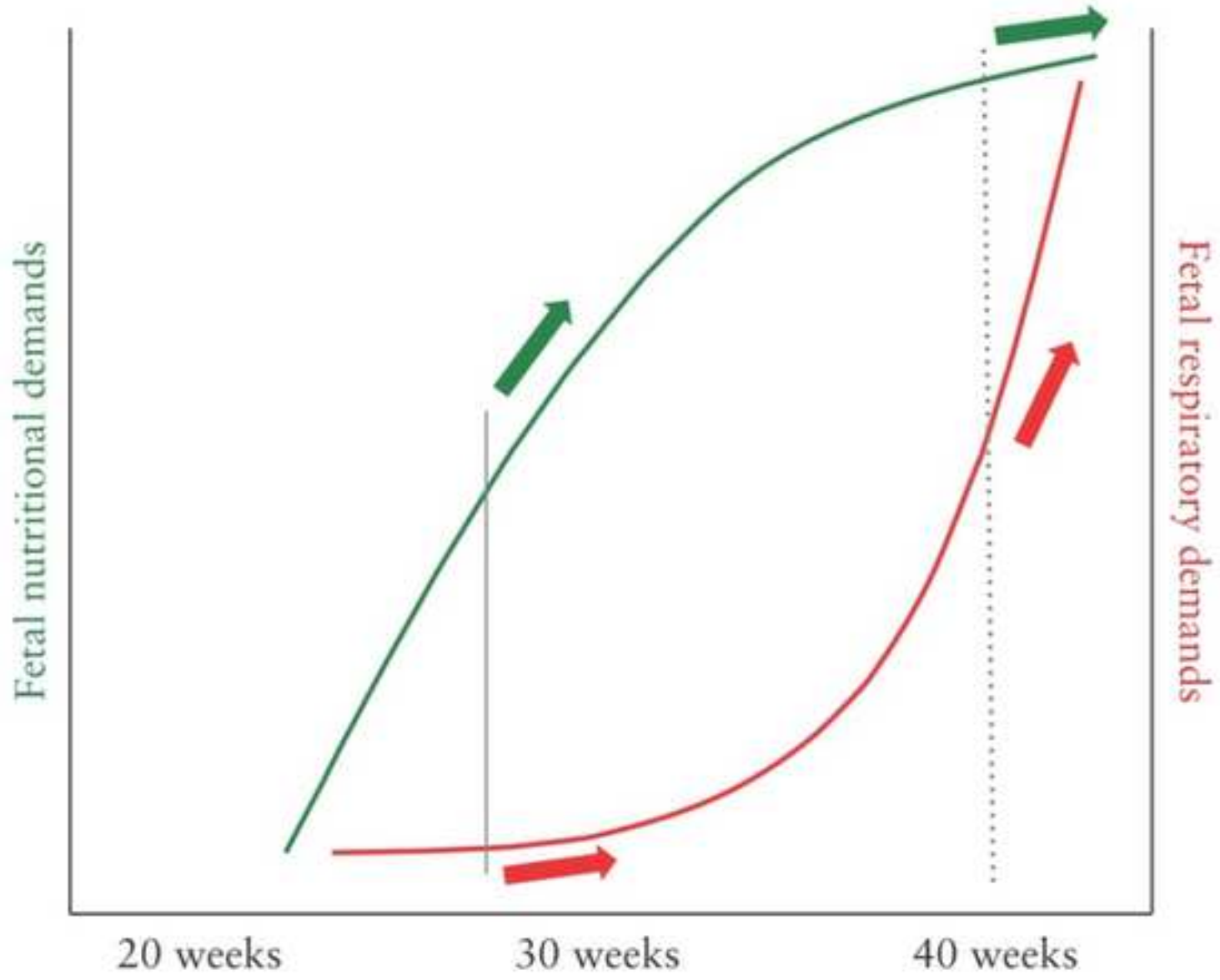
Low birthweight prevalence, by UNICEF regions and global, 2000 and 2015

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

Figure



Figure



Infant and stillbirth mortality

