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Fetal weight projection model to define growth velocity and validation against pregnancy outcome in a cohort of serially scanned pregnancies

O. HUGH and J. GARDOSI

Perinatal Institute, Birmingham, UK

KEYWORDS: birth weight; estimated fetal weight; fetal growth velocity; large-for-gestational age; small-for-gestational age; stillbirth; ultrasound scan

CONTRIBUTION

What are the novel findings of this work?
We have defined limits for normal, slow and accelerated fetal growth which are specific to the ultrasound measurement interval, have a false-positive rate limited to 10% and are associated with perinatal outcome. Two-thirds of pregnancies at increased risk of stillbirth due to slow growth were not small-for-gestational age at the last scan.

What are the clinical implications of this work?
This method for defining normal and abnormal fetal growth presents an additional, size-independent parameter for antenatal surveillance by serial fetal biometry. Greater emphasis on monitoring growth velocity will help identify pregnancies at risk and prevent adverse perinatal outcome.

ABSTRACT

Objective *Fetal growth assessment is central to good antenatal care, yet there is a lack of definition of normal and abnormal fetal growth rate which can identify pregnancies at risk of adverse outcome. The aim of this study was to develop and test a model for defining normal limits of growth velocity which are specific to the fetal weight measurement interval.*

Methods *The cohort consisted of 102 138 singleton pregnancies which underwent at least two third-trimester measurements of ultrasound estimated fetal weight (EFW), usually carried out because routine early-pregnancy risk assessment had indicated an increased risk of fetal growth restriction. We projected the EFW from the first of each consecutive measurement pair along its own centile rank to the gestational age of the second scan. Normal growth was defined as the second EFW being within a weight range based on limits derived by partial receiver-operating-characteristics-curve (pROC) analyses for small-for-gestational-age (SGA; $< 10^{th}$ centile) and large-for-gestational-age (LGA; $> 90^{th}$ centile) birth weight. The limits were measurement-interval specific and calculated for a fixed false-positive rate (FPR) of 10%. The resultant normal, slow and accelerated growth rates calculated from consecutive EFW pairs were evaluated against the following predefined perinatal outcome measures: stillbirth, neonatal death, SGA and LGA at birth, 5-min Apgar score < 7 and admission to the neonatal intensive care unit. Slow growth based on the last two scans was compared with SGA fetal weight (EFW $< 10^{th}$ centile) at the last scan and association with stillbirth risk was assessed, expressed as relative risk (RR) with 95% CI.*

Results *The optimal cut-off limits for normal growth rate between consecutive scans varied according to the length of the measurement interval, with an average of −8.0% for slow growth and +9.3% for accelerated growth at a fixed FPR of 10%. Slow growth between random consecutive scan pairs was associated significantly with all predefined outcome measures including stillbirth (RR, 2.19; 95% CI, 1.84–2.53) and neonatal death (RR, 2.28; 95% CI, 1.60–3.13). Accelerated growth was associated with LGA at birth (RR, 2.15; 95% CI, 2.10–2.20), while normal growth was protective of all adverse outcome measures. Slow growth between the last two scans (which were performed at a median gestational age of 33 + 1 to 36 + 4 weeks) and SGA at the last scan were each predictors of stillbirth, and stillbirth risk was highest when both were present (RR, 2.65; 95% CI, 1.67–4.20).*

Correspondence to: Prof. J. Gardosi, Perinatal Institute, Birmingham B15 3BU, UK (e-mail: jgardosi@perinatal.org.uk)

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However, 66.2% of pregnancies with slow growth were not SGA at the last scan and these cases also had an increased risk of stillbirth (RR, 2.07; 95% CI, 1.40–3.05).

Conclusion *Fetal growth velocity defined by projected, measurement-interval specific fetal weight limits is associated independently with perinatal outcome and should be used for antenatal surveillance in addition to assessment by fetal size.*

INTRODUCTION

There is substantial evidence of a causal association between fetal growth restriction (FGR) and adverse perinatal outcome[1–3]. As proxy for FGR, a fetus that is small-for-gestational age (SGA) has a 10-fold increased risk of intrauterine death if SGA is not detected antenatally, whereas antenatal detection can reduce the risk by half[4]. Such evidence has led to an increased emphasis on antenatal recognition of FGR through improved methods of surveillance[5–8]. In England, this has included risk assessment in early pregnancy followed by serial fundal height measurement in the third trimester, with clear referral protocols in low-risk pregnancy and serial fetal weight measurements in high-risk pregnancy, supported by Doppler assessment when indicated[9]. Such a program has resulted in increased antenatal detection of the small fetus and has been linked causally with the recent year-on-year reduction in stillbirth rates in England[10,11]. Conversely, high-risk pregnancies that are not monitored by serial scans have a higher risk of stillbirth[12].

Serial third-trimester measurement of estimated fetal weight (EFW) allows assessment of fetal weight gain which is a predictor of perinatal outcome and neonatal nutritional status[13,14]. However, despite increasing awareness of the importance of longitudinal assessment, there is no agreement on the normal limits of growth velocity, which is expressed as growth rate in grams per day[14–16] or a change in centiles or *Z*-scores over lengthy[17,18] or unspecified[19] gestational-age intervals. An additional challenge is the unknown effect that a scan error may have on the accuracy of single or consecutive measurements[20], and the influence of varying examination intervals[21,22]. We therefore set out to define a standard for fetal growth velocity which takes these factors into consideration and is able to identify increased risk of adverse pregnancy outcome.

METHODS

Data origin

Data sources were two routinely collected, fully anonymized databases: (1) the perinatal episode electronic record (PEER), a previously described[4] regional health service register which was in operation in all 19 National Health Service (NHS) maternity hospitals in the West Midlands, UK, from 2009 to 2012 ($n = 161\,936$); and (2) data from the 30 NHS hospitals with maternity information systems that are running the Growth Assessment Protocol (GAP)[11,23], a program for fetal growth surveillance used in most UK maternity units (2018 to 2021; $n = 92\,899$). Ethics committee approval was not required for this study as all data were recorded prospectively as part of routine care and were fully anonymized before being released for analysis.

Datasets

Cases selected were singleton pregnancies that underwent at least two third-trimester scans with recording of EFW which was usually derived by Hadlock formula 3 or 4[24]. In most cases, the indication for third-trimester serial scans was guideline-based[9] routine risk assessment in early pregnancy which had determined that there was an increased risk of FGR. Maternal characteristics recorded included height, weight at first visit, parity and ethnic origin. Expected date of delivery was based on routine dating scan. Outcome data included gestational age at delivery, live birth, stillbirth, and newborn weight and sex. Stillbirth is defined in the UK as delivery of a fetus with no signs of life from 24 + 0 weeks' gestation.

A total of 45 203 cases from the PEER dataset and 56 935 cases from the GAP dataset were included, giving a total study cohort of 102 138 pregnancies with the required data. The regional PEER dataset also included information on Apgar score (< 7 at 5 min), early neonatal death (within 7 days of delivery) and, for the last part of the data collection period, admission to the neonatal intensive care unit (NICU).

Pairing of scans

A total of 307 596 third-trimester scans were performed in this cohort (average of 3.01 scans per pregnancy). Two consecutive scans were selected randomly in each pregnancy by performing a 100-iteration bootstrap with random selection, resulting in 102 138 pairs of scans.

Calculation of expected weight

The method of calculating the expected fetal weight was based on the previously described principle of gestational-age adjusted projection of EFW[25] using a proportionality curve derived from Hadlock's fetal weight standard[26], with gestational age expressed in days. While Hadlock's curve was derived from cross-sectional data, when converted to a proportionality curve (which delineates the trajectory of percentage term weight by gestational age) it is indistinguishable from the curves of the INTERGROWTH-21st[27] and WHO[28] standards which are based on longitudinal data (as illustrated in figure 2 of Gardosi *et al.*[29]).

The EFW from the previous measurement (EFW_1) was projected along its centile rank to the gestational

age of the next measurement (EFW_2), according to the formula:

$$E(EFW_2) = EFW_1 \times \frac{\exp\left(0.578 + 0.332\ GA_2 - 0.00354\ GA_2^2\right)}{\exp\left(0.578 + 0.332\ GA_1 - 0.00354\ GA_1^2\right)}$$

where GA represents gestational age in weeks, and $E(EFW_2)$ is the expected weight in grams.

Deviation from the fetal weight expected at the time of the next scan was calculated as a percent difference between actual (A) and expected (E) EFW, using the formula:

$$\text{Difference (\%)} = \frac{A(EFW_2) - E(EFW_2)}{E(EFW_2)} \times 100$$

Scan interval and growth limits

The intervals between scans were calculated in exact days, then grouped into weeks to calculate growth-rate cut-offs between consecutive third-trimester scans in eight categories: < 2 weeks (1–13 days), 2 to < 3 weeks (14–20 days), 3 to < 4 weeks (21–27 days), 4 to < 5 weeks (28–34 days), 5 to < 6 weeks (35–41 days), 6 to < 7 weeks (42–48 days), 7 to < 8 weeks (49–55 days) and ≥ 8 weeks (≥ 56 days). Subsequently, day-specific interval cut-off limits were derived by linear interpolation between the weekly integer values to define slow and accelerated growth.

For each of these intervals, we calculated Youden's index[30] through receiver-operating-characteristics-curve (ROC) analysis to define optimal cut-offs using sensitivity and false-positive rate (FPR) (1 − specificity) for percent growth deviation, as predictor of SGA and large-for-gestational-age (LGA) weight at birth, respectively. SGA and LGA were used as indicators because their antenatal detection remains a key objective of fetal surveillance to identify pregnancies at risk. Using instead perinatal morbidity, mortality or a composite indicator for the eight different scan-interval groups was not an option because of their relative rareness.

Similarly, we derived partial ROC (pROC) cut-offs by values of percent deviation at a fixed FPR of 10%. The resultant limits defined the range of fetal weight that are expected/predicted to be reached at the end of each measurement interval. To check for confounding effects due to clinical decision-making in response to perceived risk, we also undertook ROC analysis using covariate balancing propensity scores[31] on the PEER dataset which had a comprehensive record of antenatal risk factors.

SGA and LGA were defined, respectively, as birth weight < 10th and > 90th GROW (gestation-related optimal weight) centile, customized for maternal height, early-pregnancy weight, parity and ethnic origin[32,33]. Weights between the 10th and 90th centiles were defined as appropriate-for-gestational age (AGA). Classification metrics, relative risk (RR) with 95% CI, and population attributable fraction (PAF) were also calculated.

Fetal growth and pregnancy outcome

We examined the association between normal, slow and accelerated growth as defined by their respective, interval-specific pROC cut-offs, with outcome categories including SGA and LGA at birth, stillbirth, 5-min Apgar score < 7, admission to the NICU and early neonatal death (up to 7 days). Normal growth was defined as the second EFW falling within the normal limits calculated after adjustment for measurement interval and limited to 10% FPR. Growth was categorized as slow or accelerated when the second EFW fell below or above these predefined limits, respectively. The analysis was performed for random consecutive scan pairs as well as for the last two scans before delivery. To calculate weight-for-gestational age centiles for stillbirths, the gestational age at delivery was adjusted by an average estimated intrauterine death-to-delivery interval of 2 days[3,34,35].

Fetal size *vs* fetal growth

We compared normal, slow and accelerated fetal growth with fetal size at the last scan. Fetal size was categorized as SGA < 10th centile and LGA > 90th centile, using one of four fetal weight standards: GROW[33], Hadlock[26], INTERGROWTH-21st[27] and WHO[28]. Prevalence with RR, 95% CI and PAF were calculated for fetal growth, fetal size and overlapping groups.

Statistical analysis

Analyses were carried out using Excel (2016; Microsoft, Redmond, WA, USA), R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 1 describes the characteristics of the PEER and GAP study cohorts. Each cohort had a median of three third-trimester scans, with a mean of 2.8 scans and 3.2 scans in the PEER and GAP cohorts, respectively. The pregnancy characteristics were broadly similar between the two datasets, but the GAP cohort, which was collected approximately 9 years after the PEER cohort, had higher median maternal weight (70 kg *vs* 68 kg) and body mass index (26.2 kg/m^2 *vs* 25.5 kg/m^2) and a higher rate of nulliparity (39.4% *vs* 33.4%) compared to the PEER dataset. The GAP cohort also had a lower SGA rate (15.5% *vs* 22.2%) and a lower rate of stillbirth (2.21/1000 *vs* 2.65/1000) compared with the PEER cohort. A set of additional variables recorded for the PEER cohort is listed in Table S1.

The reasons for third-trimester scans, recorded in the PEER dataset only, are listed in Table 2. The most common indication was increased risk of growth problems identified at the early-pregnancy assessment visit.

Tables 3 and 4 display results according to scan-interval category from < 2 weeks to ≥ 8 weeks for slow and

Table 1 Characteristics of pregnancies from the perinatal episode electronic record (PEER) dataset (2009–2012) and the Growth Assessment Protocol (GAP) dataset (2018–2021) which contributed to the study cohort ($n = 102\,138$)

Characteristic	*PEER* (n = *45 203*)	*GAP* (n = *56 935*)
Parity		
0	15 076 (33.4)	22 437 (39.4)
1	15 605 (34.5)	19 721 (34.6)
2	8213 (18.2)	8611 (15.1)
≥ 3	6309 (14.0)	6166 (10.8)
Maternal height (cm)	163.4 ± 6.9; 163 (159–168)	164.2 ± 6.7; 164 (160–169)
Maternal weight at first visit (kg)	72.4 ± 19.6; 68 (58–83)	74.4 ± 18.9; 70 (60–85)
BMI (kg/m^2)	27.1 ± 6.9; 25.5 (21.9–31.1)	27.6 ± 6.6; 26.2 (22.7–31.4)
< 18.5	2543 (5.6)	1864 (3.3)
18.5 to < 25	18 751 (41.5)	22 122 (38.9)
25 to < 30	11 048 (24.4)	15 658 (27.5)
30 to < 35	5973 (13.2)	8808 (15.5)
≥ 35	6888 (15.2)	8483 (14.9)
Non-British ethnic origin	13 165 (29.1)	16 979 (29.8)
Third-trimester scans (*n*)	2.8 ± 1.0; 3 (2–3)	3.2 ± 1.1; 3 (2–4)
Infant sex		
Male	22 957 (50.8)	29 240 (51.4)
Female	22 246 (49.2)	27 695 (48.6)
GA at delivery (days)	275.1 ± 12.0; 276 (269–284)	274.0 ± 11.2; 275 (268–281)
< 37 weeks	3227 (7.1)	3921 (6.9)
< 34 weeks	545 (1.2)	589 (1.0)
Birth weight (g)	3235 ± 575; 3240 (2880–3605)	3311 ± 548; 3335 (2980–3680)
SGA (< 10th centile)	10 046 (22.2)	8849 (15.5)
LGA (> 90th centile)	3659 (8.1)	5501 (9.7)
Stillbirths per 1000 births	120 (2.65)	126 (2.21)
SGA at birth	53/120 (44.2)	45/126 (35.7)
LGA at birth	5/120 (4.2)	8/126 (6.3)

Data are given as *n* (%), mean ± SD with median (interquartile range), or *n*/*N* (%). BMI, body mass index; GA, gestational age; LGA, large-for-gestational age; SGA, small-for-gestational age.

accelerated growth, respectively. The most common intervals between EFW measurement pairs were 2 to < 3 weeks (27.6%) and 4 to < 5 weeks (26.9%), with an overall median interval of 28 (interquartile range (IQR), 16–33) days.

The growth deviation cut-offs for slow growth, defined using Youden's index[30], are listed for each scan interval, and ranged from −1.4% to −3.7% with an average of −2.0% (Table 3). This was associated with high FPRs, up to 36.1% (scan interval of 3 to < 4 weeks) and an average of 34.0%. The pROC-derived cut-offs for slow growth, with FPR fixed at 10%, also varied between scan intervals, from −7.0% to −10.1% (average, −8.0%) of the predicted weight at that gestation, and identified an average of 12.0% of the cohort as having had slow growth. Sensitivity (the proportion of SGA births which were detected antenatally by serial scans showing slow growth) was 21.0%, increasing from 18.2% to 32.0% with longer scan intervals. The average positive predictive value (PPV; proportion of slow growth observations that correctly predicted SGA) was 32.3%, ranging from 27.9% to 45.9%.

For accelerated growth, LGA rates ranged from 7.3% to 10.0% and did not have a similar relationship to scan intervals as did SGA rates (Table 4). Youden's index ranged from + 0.6% to + 3.4% (average of + 1.8%), and was associated with even higher FPRs than at the SGA end of the distribution (range of 34.4–44.7% and average of 38.8%). The pROC-derived cut-offs for accelerated growth, when FPR was fixed at 10%, ranged from + 8.6% to + 10.8% (average of + 9.3%). The sensitivity of pROC-based cut-offs for accelerated growth to detect LGA at birth ranged from 11.1% to 37.4%, and the PPV increased with longer interval between the measurements, from 8.1% at 1–13 days to 25.9% at ≥ 56 days.

As shown in Table 3, the SGA rate at birth was highest (31.8%) when consecutive scans were performed less than 2 weeks apart, and lowest (13.4%) in the longest (≥ 8 weeks) interval category. However, ROC analysis using risk factor balancing propensity score showed only minor changes to cut-offs defining normal growth and no

Table 2 Reason for ultrasound scans in the third trimester, recorded in the perinatal episode electronic record (PEER) dataset ($n = 45\,203$)

Parameter	*1st scan* (n = *45 203*)	*2nd scan* (n = *45 203*)	*3rd scan* (n = *23 571*)	*4th scan* (n = *8774*)	*5th scan* (n = *2786*)
Gestational age at scan (days)	200	235	251	257	261
Reason for scan					
Early-pregnancy risk factors	22 651 (50.1)	21 318 (47.2)	10 937 (46.4)	3759 (42.8)	1160 (41.6)
Suspected fetal growth restriction	6253 (13.8)	6979 (15.4)	4008 (17.0)	1831 (20.9)	703 (25.2)
Pregnancy complications	2686 (5.9)	2996 (6.6)	1694 (7.2)	609 (6.9)	126 (4.5)
Placental location	1535 (3.4)	1255 (2.8)	456 (1.9)	101 (1.2)	26 (0.9)
Suspected LGA	1217 (2.7)	990 (2.2)	351 (1.5)	95 (1.1)	21 (0.8)
Late first visit	863 (1.9)	454 (1.0)	75 (0.3)	18 (0.2)	7 (0.3)
Decreased fetal movements	835 (1.8)	853 (1.9)	479 (2.0)	143 (1.6)	41 (1.5)
Fetal presentation	674 (1.5)	1190 (2.6)	612 (2.6)	191 (2.2)	59 (2.1)
Amniotic fluid volume	343 (0.8)	436 (1.0)	231 (1.0)	107 (1.2)	33 (1.2)
Other	2182 (4.8)	2286 (5.1)	1201 (5.1)	483 (5.5)	168 (6.0)
Undocumented	5964 (13.2)	6446 (14.3)	3527 (15.0)	1437 (16.4)	442 (15.9)

Data are given as median or *n* (%). LGA, large-for-gestational age.

difference in trend across the eight measurement intervals (Table S2).

Tables 5, 6 and 7 show the association between, respectively, normal, slow and accelerated growth, as determined from randomly selected consecutive scan pairs performed on average at 31 + 4 and 35 + 4 weeks, and perinatal outcome. Normal growth velocity (Table 5) appeared to be protective of each adverse outcome indicator and, consistent with our calibration of growth velocity limits, also protective of SGA and LGA at birth. Slow growth was also protective of LGA, and associated with increased risk of stillbirth, 5-min Apgar score < 7, admission to the NICU and neonatal death (Table 6). Slow growth was also associated with SGA at birth, more strongly if the weight was below the 3rd centile. Accelerated growth was associated with increased risk of LGA at birth, with stronger association if the weight was > 97th centile, and was protective of SGA at birth (Table 7). Tables S3, S4 and S5 show similar results when the same analysis was undertaken for the last two scans

Table 3 Cut-off limits for estimated fetal weight to define slow growth, grouped by length of interval between two consecutive third-trimester scans, according to Youden's index with variable false-positive rates (FPR) and according to partial receiver-operating-characteristics-curve (pROC) analysis with FPR fixed at 10% ($n = 102\,138$)

Interval between scans	*Pregnancies*		*Average GA (days)*		*SGA at birth*	*Youden's index*		*pROC*	*Centile difference**		*Slow growth*	*SGA at birth after slow growth**			
						Cut-off	*FPR*	*Cut-off*	*Per*	*Over*		*Sens*	*PPV*	*RR*	*PAF*
(weeks (days))	N	%	*Scan 1*	*Scan 2*	*(%)*	*(%)*	*(%)*	*(%)*	*week*	*interval*	*(%)**	*(%)*	*(%)*	*(95% CI)*	*(%)*
< 2 (1–13)	4344	4.3	231	242	31.8	−2.9	26.0	−7.3	−10.4	−20.8	12.6	18.2	45.9	1.54 (1.45–1.64)	6.4
2 to < 3 (14–20)	28 241	27.6	231	247	26.1	−1.4	33.5	−7.0	−7.6	−15.2	11.9	17.2	37.8	1.54 (1.49–1.62)	6.1
3 to < 4 (21–27)	17 683	17.3	223	245	15.5	−1.7	36.1	−7.8	−7.8	−23.4	11.8	21.8	28.6	2.08 (1.98–2.22)	11.3
4 to < 5 (28–34)	27 515	26.9	214	242	14.3	−2.1	34.2	−8.2	−6.4	−25.6	11.9	23.2	27.9	2.24 (2.15–2.34)	12.9
5 to < 6 (35–41)	7154	7.0	211	248	14.4	−2.8	32.0	−8.8	−5.6	−28.0	12.3	25.8	30.2	2.48 (2.36–2.61)	15.4
6 to < 7 (42–48)	9929	9.7	202	245	14.7	−2.5	35.7	−9.3	−4.9	−29.4	12.2	24.9	30.0	2.39 (2.29–2.49)	14.5
7 to < 8 (49–55)	2936	2.9	202	253	13.7	−1.9	36.0	−9.1	−4.1	−28.7	13.1	32.9	34.3	3.24 (3.04–3.45)	22.8
≥ 8 (≥ 56)	4336	4.2	196	260	13.4	−3.7	29.9	−10.1	−3.4	−27.2	12.9	32.0	33.1	3.17 (3.03–3.33)	21.9
Overall	102 138	100.0	221	249	18.5	−2.0	34.0	−8.0	−5.2	−24.4	12.0	21.0	32.3	—	—

*Values based on pROC analysis. GA, gestational age; PAF, population attributable fraction; PPV, positive predictive value; RR, relative risk; Sens, sensitivity; SGA, small-for-gestational age.

Table 4 Cut-off limits for estimated fetal weight to define accelerated (accel.) growth, grouped by length of interval between two consecutive third-trimester scans, according to Youden's index with variable false-positive rates (FPR) and according to partial receiver-operating-characteristics-curve (pROC) analysis with FPR fixed at 10% ($n = 102\,138$)

Interval between scans	*Pregnancies*		*Average GA (days)*		*LGA at birth*	*Youden's index*		*pROC*	*Centile difference**		*Accel. growth*	*LGA at birth after accel. growth**			
						Cut-off	*FPR*	*Cut-off*	*Per*	*Over*		*Sens*	*PPV*	*RR*	*PAF*
(weeks (days))	N	%	*Scan 1*	*Scan 2*	*(%)*	*(%)*	*(%)*	*(%)*	*week*	*interval*	*(%)**	*(%)*	*(%)*	*(95% CI)*	*(%)*
< 2 (1–13)	4344	4.3	231	242	7.3	+3.4	38.0	+10.8	23.2	23.2	10.1	11.1	8.1	1.11 (0.83–1.37)	0.2
2 to < 3 (14–20)	28 241	27.6	231	247	8.1	+2.3	39.6	+9.9	10.7	21.4	10.2	12.9	10.2	1.30 (1.20–1.39)	3.0
3 to < 4 (21–27)	17 683	17.3	223	245	9.8	+0.6	44.7	+8.6	8.4	25.2	11.0	20.5	18.2	2.08 (1.94–2.20)	10.6
4 to < 5 (28–34)	27 515	26.9	214	242	10.0	+2.2	34.4	+8.7	6.6	26.4	11.3	23.5	20.7	2.40 (2.29–2.52)	13.7
5 to < 6 (35–41)	7154	7.0	211	248	9.3	+1.8	37.1	+9.0	5.3	26.5	11.3	24.4	20.0	2.53 (2.39–2.70)	14.8
6 to < 7 (42–48)	9929	9.7	202	245	8.0	+0.6	41.7	+9.2	4.7	28.2	11.4	27.7	19.5	2.96 (2.82–3.12)	18.3
7 to < 8 (49–55)	2936	2.9	202	253	8.3	+1.5	39.6	+9.8	3.9	27.3	11.9	33.2	23.2	3.67 (3.42–3.93)	24.2
≥ 8 (≥ 56)	4336	4.2	196	260	8.5	+2.1	35.4	+10.0	3.2	25.6	12.3	37.4	25.9	4.25 (4.07–4.45)	28.6
Overall	102 138	100.0	221	249	9.0	+1.8	38.8	+9.3	6.3	26.9	11.0	21.1	17.2	—	—

*Values based on pROC analysis. GA, gestational age; LGA, large-for-gestational age; PAF, population attributable fraction; PPV, positive predictive value; RR, relative risk; Sens, sensitivity.

in each pregnancy, with the exception that low Apgar score was not significantly associated with slow growth (Table S4). In this analysis, the scans were performed at an average of 33 + 1 and 36 + 4 weeks, approximately 1 week later than when the scan pairs were chosen randomly.

To compare outcome associated with slow fetal growth *vs* small fetal size, we applied, first, the pROC-based definitions for slow growth between the last two scans in each pregnancy, and second, SGA based on EFW $< 10^{th}$ centile at the last scan, as predictors of stillbirth risk. A total of 21 605 (21.2%) pregnancies had either slow growth ($n = 11\,964$) or an EFW indicating SGA at the last scan ($n = 9641$) (Table 8). In 4043 of these pregnancies, the groups overlapped, in that they had slow growth as well as SGA at the last scan, and these

Table 5 Association of normal fetal growth (based on estimated fetal weight (EFW) on two randomly selected consecutive scans performed at average gestational ages of 31 + 4 and 35 + 4 weeks, with the second EFW within the predicted normal limits) with perinatal outcome

			Normal growth						
Outcome	*Pregnancies* (N)	*Outcome* (n *(%)*)	*%*	*Sens (%)*	*Spec (%)*	*PPV (%)*	*NPV (%)*	*RR (95% CI)*	*PAF (%)*
SGA at birth	102 138	18 895 (18.5)	76.8	72.7	22.2	17.5	78.2	0.80 (0.79–0.82)	−18.0
LGA at birth	102 138	9160 (9.0)	76.8	72.2	22.7	8.4	89.3	0.78 (0.77–0.81)	−19.9
Stillbirth	102 138	246 (0.2)	76.8	67.0	23.2	0.2	99.7	0.61 (0.54–0.71)	−42.3
5-min Apgar score < 7*	44 778	549 (1.2)	72.5	70.2	27.4	1.2	98.7	0.89 (0.81–0.99)	−8.4
NICU admission*	34 139	708 (2.1)	71.9	59.5	27.8	1.7	97.0	0.57 (0.53–0.61)	−44.1
Neonatal death*	45 203	60 (0.1)	72.5	58.1	27.5	0.1	99.8	0.52 (0.36–0.71)	−52.5

*Data collected in perinatal episode electronic record (PEER) dataset only. LGA, large-for-gestational age; NICU, neonatal intensive care unit; NPV, negative predictive value; PAF, population attributable fraction; PPV, positive predictive value; RR, relative risk; Sens, sensitivity; SGA, small-for-gestational age; Spec, specificity.

Table 6 Association of slow fetal growth (based on estimated fetal weight (EFW) on two randomly selected consecutive scans performed at average gestational ages of 31 + 4 and 35 + 4 weeks, with the second EFW being below the predicted limits) with perinatal outcome

			Slow growth						
Outcome	*Pregnancies* (N)	*Outcome* (n *(%)*)	*%*	*Sens (%)*	*Spec (%)*	*PPV (%)*	*NPV (%)*	*RR (95% CI)*	*PAF (%)*
SGA at birth	102 138	18 895 (18.5)	11.9	20.9	90.1	32.4	83.4	1.95 (1.92–1.99)	10.2
3^{rd} to $< 10^{th}$ centile	102 138	11 768 (11.5)	11.9	17.7	88.8	17.1	89.2	1.58 (1.54–1.63)	6.5
$< 3^{rd}$ centile	102 138	7127 (7.0)	11.9	26.3	89.1	15.4	94.2	2.63 (2.55–2.71)	16.3
LGA at birth	102 138	9160 (9.0)	11.9	6.3	87.5	4.8	90.5	0.50 (0.48–0.52)	−6.3
Stillbirth	102 138	246 (0.2)	11.9	22.9	88.1	0.5	99.8	2.19 (1.84–2.53)	12.5
5-min Apgar score < 7*	44 778	549 (1.2)	14.6	16.7	85.4	1.4	98.8	1.18 (1.01–1.32)	2.5
NICU admission*	34 139	708 (2.1)	15.0	28.4	85.3	3.9	98.3	2.25 (2.08–2.43)	15.8
Neonatal death*	45 203	60 (0.1)	14.6	28.1	85.4	0.3	99.9	2.28 (1.60–3.13)	15.7

*Data collected in perinatal episode electronic record (PEER) dataset only. LGA, large-for-gestational age; NICU, neonatal intensive care unit; NPV, negative predictive value; PAF, population attributable fraction; PPV, positive predictive value; RR, relative risk; Sens, sensitivity; SGA, small-for-gestational age; Spec, specificity.

Table 7 Association of accelerated fetal growth (based on estimated fetal weight (EFW) on two randomly selected consecutive scans performed at average gestational ages of 31 + 4 and 35 + 4 weeks, with the second EFW being above the predicted limits) with perinatal outcome

			Accelerated growth						
Outcome	*Pregnancies* (N)	*Outcome* (n *(%)*)	*%*	*Sens (%)*	*Spec (%)*	*PPV (%)*	*NPV (%)*	*RR (95% CI)*	*PAF (%)*
SGA at birth	102 138	18 895 (18.5)	11.2	6.4	87.7	10.6	80.5	0.54 (0.53–0.56)	−5.4
LGA at birth	102 138	9160 (9.0)	11.2	21.4	89.8	17.1	92.1	2.15 (2.10–2.20)	11.5
97^{th} to $> 90^{th}$ centile	102 138	5318 (5.2)	11.2	18.4	89.1	8.5	95.2	1.78 (1.73–1.84)	8.1
$> 97^{th}$ centile	102 138	3842 (3.8)	11.2	25.6	89.3	8.6	96.8	2.71 (2.60–2.81)	16.2
Stillbirth	102 138	246 (0.2)	11.2	10.1	88.8	0.2	99.8	0.88 (0.69–1.09)	−1.3
5-min Apgar score < 7*	44 778	549 (1.2)	12.9	13.0	87.1	1.2	98.8	1.01 (0.89–1.18)	0.2
NICU admission*	34 139	708 (2.1)	13.1	12.1	86.8	1.9	97.9	0.91 (0.83–1.02)	−1.2
Neonatal death*	45 203	60 (0.1)	12.9	13.9	87.1	0.1	99.9	1.09 (0.74–1.54)	1.2

*Data collected in perinatal episode electronic record (PEER) dataset only. LGA, large-for-gestational age; NICU, neonatal intensive care unit; NPV, negative predictive value; PAF, population attributable fraction; PPV, positive predictive value; RR, relative risk; Sens, sensitivity; SGA, small-for-gestational age; Spec, specificity.

pregnancies had the highest risk of stillbirth (RR, 2.65; 95% CI, 1.67–4.20). Cases with slow growth alone (RR, 2.07; 95% CI, 1.40–3.05) and SGA at the last scan alone (RR, 2.20; 95% CI, 1.42–3.40) were also at increased risk of stillbirth compared with pregnancies that had neither. Of the 11 964 cases with slow growth, 7921 (66.2%) were not SGA at the last scan. There were 32 stillbirths in this group, the majority ($n = 19$; 59.4%) of which were also not SGA at delivery, with a median centile of 31.5 (IQR, 19.3–71.5).

The analysis of slow growth *vs* SGA at the last scan was repeated for the Hadlock[26], INTERGROWTH-21st[27] and WHO[28] standards and showed similar findings (Tables S6, S7 and S8). Although the rate of SGA at the last scan, and hence stillbirth risk, varied between standards, slow growth was able to identify in each instance many additional at-risk cases which were not SGA according to the respective fetal weight standard.

Table 8 Risk of stillbirth in cases with slow growth based on the last two scans* and/or small-for-gestational age (SGA) based on estimated fetal weight < 10th centile at the last scan ($n = 102\,138$)

	Slow growth	*SGA*
Cases (*n* (%))	11 964 (11.7)	9641 (9.4)
Stillbirths (*n* (/1000))	53 (4.4)	45 (4.7)

	Slow growth only	*Slow growth and SGA*	*SGA only*
Cases (*n* (%))	7921 (7.8)	4043 (4.0)	5598 (5.5)
Stillbirths (*n* (/1000))	32 (4.0)	21 (5.2)	24 (4.3)
RR (95% CI)	2.07 (1.40–3.05)	2.65 (1.67–4.20)	2.20 (1.42–3.40)
PAF (%)	10.5	9.0	8.8

*Scans performed at average gestational ages of 33 + 1 and 36 + 4 weeks. PAF, population attributable fraction; RR, relative risk.

DISCUSSION

We present a definition of normal and abnormal fetal growth velocity that can be used in serial assessment of fetal weight in the third trimester. The model projects an expected weight based on the centile of the previous EFW measurement, with a normal range which is adjusted for the interval between measurements and limited to a FPR of 10%. Using percentage of predicted weight to express the normal range also allows for the proportionate variation within the upper and lower limits of normal fetal weight.

Our analysis shows that EFW measurements within this predicted range are protective of adverse outcome, while those below or above this range can be designated as slow and accelerated growth, respectively, and are associated with an increased risk of adverse perinatal outcome.

Figure 1 illustrates how normal growth limits are derived, with examples of slow and accelerated growth. Calculation requires software which is freely available from the Perinatal Institute as a web-based application (https://www.perinatal.org.uk/growthrate).

Growth velocity

Fetal growth rate or velocity can be expressed in grams of weight gain per unit of time[14,16], but this cannot be averaged for the whole antenatal period, as the slope of the growth curve varies throughout pregnancy and is specific to gestational age[36,37]. An alternative approach is to

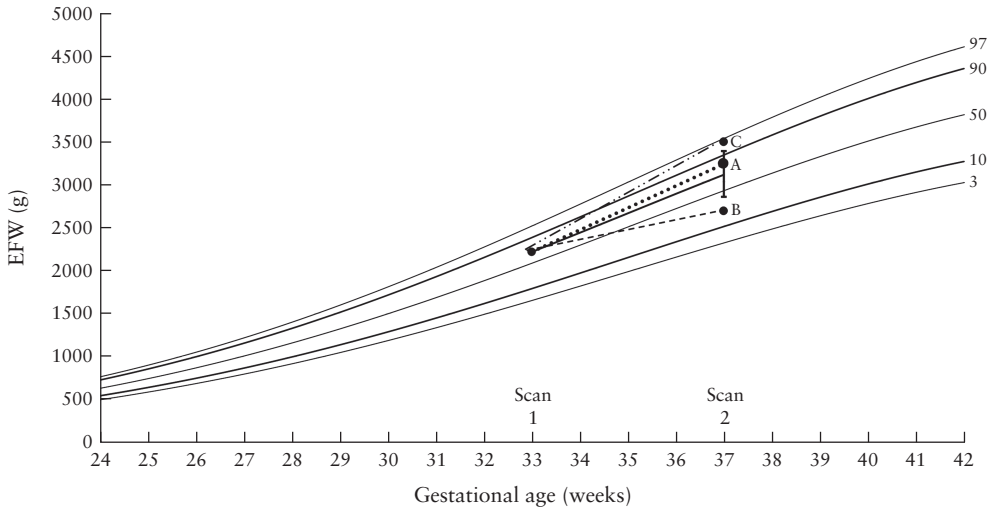

Figure 1 Illustration of fetal growth velocity assessment between two third-trimester scans based on the estimated fetal weight (EFW) projection model, on a fetal growth chart for a mother of average size. Scan 1 was performed at 33 + 0 weeks and the measured EFW was 2200 g (72nd centile). Scan 2 was performed at 37 + 0 weeks. The projected EFW for the 72nd centile at 37 weeks is 3081 g with predicted normal range of 2830–3349 g. In scenario A, the EFW measurement at 37 weeks is 3200 g, which translates to a percentage difference of + 3.9% (83rd centile), indicating normal growth. In scenario B, the EFW measurement at 37 weeks is 2660 g, which translates to a percentage difference of −13.7% (23rd centile), indicating slow growth. In scenario C, the EFW measurement at 37 weeks is 3459 g, which translates to a percentage difference of + 12.3% (96th centile), indicating accelerated growth.

express growth velocity as a change in centiles or *Z*-scores over time, with values often based on biometry data from long measurement intervals of 8 weeks[17,18], 12 weeks or more[38]. In clinical practice, however, pregnancies at risk of growth problems will require more frequent assessment during the third trimester. At the other end of the scan frequency spectrum, error of measurements at short intervals can increase disproportionately and even exceed the actual increment of growth. Scan intervals of less than 2 weeks are therefore not recommended because of high scan error rates[21,22].

Our method addresses these challenges by defining gestational-age and measurement-interval specific limits for growth velocity. The effect of scan error, including the potentially magnifying effect of random errors in serial assessment, is limited by defining the normal EFW range against a 10% FPR. As seen in Tables 3 and 4, the risk of increased scan error inherent to short scan intervals is mitigated by a larger range defining normal growth, meaning that a greater deviation from the expected weight range is required before growth velocity is designated as slow or accelerated. Thereby, the 10% FPR 'cap' acts to limit the potential effect of confounding factors.

Our results show that growth trajectories staying within such projected, gestational-age and measurement-interval specific limits are protective, and demonstrate increased risk of adverse perinatal outcomes outside these limits.

Fetal size *vs* fetal growth

A number of studies have investigated the relative benefits of fetal biometry in a single scan compared to fetal growth rate derived by serial assessment. While the benefit of single 'routine' third-trimester scans in low-risk pregnancy is unproven[39–41] and not recommended[9,42,43], there is nevertheless evidence that later scans are more predictive than those performed at earlier gestations[44,45]. However delayed one-off scans will not help to identify fetuses at risk due to earlier-onset growth problems.

Serial third-trimester biometry in pregnancies identified as being at high risk for FGR are recommended by various professional and health service guidelines[9,43,46] and adherence to such a policy reduces stillbirth risk[12]. Longitudinal assessment can also provide information about fetal growth rate or velocity, although there is evidence that, for the prediction of SGA at birth, reduced growth velocity adds little to a one-off scan[47,48]. However, for identification of risk of adverse outcome, unless there is evidence of normal Doppler[49], fetal growth rate does add benefit to assessment of fetal size alone[17,18,37,50]. In the current study, 66.2% of cases that were at risk of stillbirth due to slow growth rate were not SGA at the last scan (Table 8). This is not surprising when considering that only 39.8% of stillbirths were SGA at birth (Table 1), a proportion similar to previous findings in our population[3]. In fact, stillbirths which had slow growth but were not SGA at the last scan nor at delivery were still relatively small, with an average centile of 31.5. This reflects the known downward skewness of the stillbirth weight distribution[51], with a higher proportion of weights between the 10th and $< 50^{th}$ centile than between the 50th and $< 90^{th}$ centile, suggesting that, in many pregnancies ending in intrauterine death, the fetus had growth deficit without dropping below the SGA limit. The ability for slow growth defined by this method to recognize a substantial number of additional cases at risk of stillbirth extends to other fetal weight curves, as shown in the additional analyses using Hadlock[26], INTERGROWTH-21st[27] and WHO[28] standards (Tables S6–S8).

Strengths and limitations

A strength of this study is its large size, comprising a cohort of over 100 000 pregnancies with at least two third-trimester fetal weight assessments and perinatal outcome indicators including stillbirth and neonatal death. Our cohort had a higher rate of SGA at birth (18.5%; Table 5) than the general population, which is a reflection of the selection criterion of two or more third-trimester scans, most of which were performed for increased risk of growth problems according to early-pregnancy assessment (Table 2). However, apart from the elevated SGA rate, 96.4% of pregnancies had none of the recorded perinatal complications (Table 5), and our analysis was able to define a large normal subgroup with a significantly reduced rate of adverse outcome.

An even larger dataset may allow definition of limits of normal and abnormal growth against perinatal mortality and other adverse outcomes, instead of weight categories at birth as used here. However, SGA and LGA are valid indicators, as their antenatal detection remains a key objective of fetal surveillance to identify pregnancies at risk.

We had no data on second-trimester EFWs, as these were usually calculated or recorded at the routine anomaly scan. We also had no information on Doppler studies, whose role in investigating growth velocity requires further research. The retrospective nature of this study may include confounding when assessing growth *vs* scan interval, as the frequency of repeat scans may have been influenced by clinical concern. However, management and scanning frequency would also be affected in prospective studies, as the results of scans would have to be revealed in real time.

Conclusions

We demonstrate a model for defining normal and abnormal growth velocity which is predictive of pregnancy outcome, specific to gestational age and measurement interval, and restricted to a 10% FPR to limit the effect of scan errors. Comparison with fetal weight at the last scan as predictor of stillbirth risk showed that, in two-thirds of cases at risk because of slow growth, the result of the last EFW was within normal limits.

While growth surveillance programs and audits focusing on antenatal detection of SGA have made significant contributions to the decline in stillbirth rates[11,46], our findings emphasize the need to also improve the identification of slow growing AGA fetuses. Integration into routine growth surveillance will allow this method to be evaluated prospectively.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Additional variables collected in PEER dataset ($n = 45\,203$)

Table S2 Covariate balancing propensity analysis of the effect of risk factors on cut-off limits to define slow growth, in the PEER dataset ($n = 43\,584$)

Table S3 Association of normal growth (based on last two scans, with second scan within predicted limits) with perinatal outcome

Table S4 Association of slow growth (based on last two scans, with second scan below the predicted limits) with perinatal outcome

Table S5 Association of accelerated growth (based on last two scans, with second scan above the predicted limits) with perinatal outcome

Table S6 Risk of stillbirth in cases with slow growth based on the last two scans and/or small-for-gestational age (SGA) at the last scan using the Hadlock standard[26] ($n = 102\,138$)

Table S7 Risk of stillbirth in cases with slow growth based on the last two scans and/or small-for-gestational age (SGA) at the last scan using the INTERGROWTH-21st standard[27] ($n = 102\,138$)

Table S8 Risk of stillbirth in cases with slow growth based on the last two scans and/or small-for-gestational age (SGA) at the last scan using the WHO standard[28] ($n = 102\,138$)