Fetal Growth and the Risk of Spontaneous Preterm Birth in a Prospective Cohort Study of Nulliparous Women

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ABBREVIATIONS

AC	Abdominal circumference
EFW	Estimated fetal weight
FGR	Fetal growth restriction
FL	Femur length
HC	Head circumference
iPTB	Iatrogenic preterm birth
POP study	Pregnancy Outcome Prediction study
PTB	Preterm birth
sPTB	Spontaneous preterm birth

ABSTRACT

Previous studies have suggested an association between fetal growth restriction and the risk of spontaneous preterm birth (sPTB). However, addressing this association is methodologically challenging. We conducted a prospective cohort study of nulliparous women with a singleton pregnancy in Cambridge, UK, 2008-2012. Ultrasonic fetal biometry was performed at 20 weeks of gestation as per routine clinical care. Participants also had blinded research ultrasonography at ~28 weeks. Biometric measurements were expressed as gestational age-adjusted z-scores. Fetal growth velocity was quantified by change in z-score between 20 and 28 weeks. Risk of sPTB, defined as delivery ≥28 and <37 weeks associated with labor in the absence of induction, was analysed using cause-specific Cox regression. 98 (2.5%) of 3,892 women had sPTB. When compared to the rest, the lowest decile of growth velocity of fetal femur between 20 and 28 weeks was associated with increased risk of sPTB (hazard ratio 2.37; 95% confidence interval: 1.43, 3.93; P<0.001). Adjustment for maternal characteristics was without material effect (hazard ratio: 2.50; 95% confidence interval: 1.50, 4.14; P<0.001). There were no significant associations between other fetal measurements and risk of sPTB. To conclude, slow growth velocity of fetal femur is associated with an increased risk of sPTB.

KEYWORDS

Fetal biometry, fetal growth, growth velocity, spontaneous preterm birth.

In the attempt to achieve the Millennium Development Goals, a global effort has been made to address the preventable causes of maternal and child mortality and to improve maternal and child health (1-4). As notable gains are being made, poorly understood causes, such as preterm birth (PTB), are contributing to an increasingly large proportion of maternal and child morbidity and mortality (5). The World Health Organization estimates that approximately 15 million babies are born preterm each year, out of which 1 million die, making prematurity the leading cause of neonatal death and the second leading cause of under-5 mortality worldwide (5, 6). Importantly, this figure is on the rise, with increases noted both in the number of iatrogenic and spontaneous PTBs (iPTB and sPTB, respectively)(5-8). The pathophysiology of sPTB is poorly understood (5, 7, 9, 10). Better understanding of the mechanisms might allow screening and intervention.

Previous studies have shown associations between placental biomarkers and sPTB, including pregnancy-associated plasma protein A, alpha-fetoprotein, and corticotropin releasing hormone (11-17). However, the mechanistic link with the risk of sPTB is unclear. A number of studies have described relationships between fetal growth restriction (FGR) and the risk of sPTB. As FGR is associated with some of the same biomarkers (11-18), it could be on the causal pathway linking biomarker levels to sPTB. Growth restricted fetuses are often iPTBs, but less is known about the direct relationship between specific aspects of fetal growth patterns and the timing of sPTB (19-21).

A handful of studies have directly explored the relationship between fetal growth and sPTB. Some lack a clear definition of abnormal fetal growth, using birth weight or birth weight for gestational age as a proxy, which does not fully capture the process of growth in utero (22-25). Others have used ultrasound measures of fetal biometry at one time point, which provides a snapshot of fetal size but not the process of growth (26-30). In some cases, gestational age was measured by the last menstrual period (LMP), which decreases reliability of classification of prematurity (26, 28, 31). Importantly, many of the studies based on fetal growth as measured by ultrasonography have not explicitly mentioned blinding of measurements of fetal growth (13, 22-33), and some have also not specifically distinguished between iPTB and sPTB (34). Some studies have not reported individual biometric measurements but only the estimated fetal weight. Varying reference standards have been used and different cut-offs have been applied to define FGR. The studies vary in their design, and analytic methods e.g. logistic regression (13-16, 22-25, 28, 30, 33), linear regression (13, 31) or time-to-event analysis (35).

In the present study, we used data from the Pregnancy Outcome Prediction (POP) study, a prospective cohort study of nulliparous women with a viable singleton pregnancy in Cambridge, UK, where women had serial blinded ultrasonography through pregnancy (36). Previous analyses of the POP study data have addressed the utility of universal ultrasonography as a screening test for FGR (37). In the present analysis, we investigate the association between early fetal growth and the subsequent risk of sPTB.

METHODS

Study Population

The Pregnancy Outcome Prediction study was a prospective cohort study of nulliparous women with a viable singleton pregnancy, based at the Rosie Hospital in Cambridge, UK. The study was approved by the Cambridge Local Research Ethics Committee (reference number 07/H0308/163). A full study protocol and the study cohort have been described elsewhere (36, 37).

Briefly, women attending the Rosie Hospital meeting the study criteria (nulliparous, viable singleton pregnancy) were invited to enrol from 14 January 2008 to 31 July 2012. Written informed consent was obtained by research midwives. In addition to the routine ultrasound scans at approximately 12-14 (for dating) and 20 weeks (for anomaly) weeks of gestational age, women underwent ultrasonography for the purposes of research at 28 and 36 weeks of gestational age. Participants and their care providers were blinded to the results of these scans, unless a major incidental finding was observed (major congenital anomaly, placenta previa, severe oligohydramnios, or non-cephalic presentation at 36 weeks).

Gestational age was defined by ultrasound at the time of the dating scan. Maternal age was recorded at recruitment, maternal weight was measured at the dating scan appointment and maternal height was measured at the 20-week appointment. Body mass index (BMI) was calculated from weight and height. Information on maternal characteristics were collected either through a computer assisted questionnaire at the 20-week scan, from examination of the clinical case record, or through linkage to

the hospital's electronic databases (marital status, previous spontaneous and therapeutic abortion, ethnicity, smoking status, age at leaving full time education and Index of Multiple Deprivation (IMD) 2007 score based on residential area (37)).

Participants who withdrew or delivered elsewhere were excluded from the study. Additional exclusion criteria for the purposes of this analysis were stillbirths, pregnancies ending before 28 weeks of gestational age, defaults from any scans and history of essential hypertension or pre-existing diabetes mellitus.

Statistical analysis

Wilcoxon's rank sum test was used to compare continuous variables and Pearson's Chi-squared test or Fisher's exact test were used to compare binary outcomes. Fetal growth was assessed by (a) z-scores of ultrasound measures of fetal biometry at 20 and 28 weeks of gestational age, and (b) fetal growth velocity, defined as change in z-score of fetal biometry between 20 and 28 weeks of gestational age. Z-scores were adjusted for gestational age, estimated within the POP study using the method outlined by Altman & Chitty (1994) (38). Measures of fetal biometry included head circumference (HC), abdominal circumference (AC), femur length (FL), estimated fetal weight (EFW, calculated using the Hadlock equation (39)), HC:AC ratio, and AC:FL ratio (37). Additionally, z-scores were calculated with respect to the recently-published INTERGROWTH-21st references for fetal growth (40) where the given measurement was reported (EFW, and HC:AC and AC:FL ratios were not reported). sPTB was defined as birth before 37 weeks of gestational age in the absence of induction of labor or elective caesarean section. Preliminary analyses included logistic regression on sPTB, excluding iPTBs. Linearity of associations and

interactions between fetal biometry and maternal characteristics on sPTB were tested using the likelihood ratio test.

Cause-specific Cox regression was used to estimate the risk of sPTB with respect to each of the measures of fetal biometry or fetal growth velocity. The at-risk period for sPTB was defined as 28 +0/7 – 36+6/7 weeks of gestational age. The number of deliveries <28 weeks was very small and these pre-dated the 28 week scan. Clinically indicated preterm deliveries were treated as censored at the time of delivery. The analysis on sPTB was repeated using competing risks regression (Fine and Gray model) treating indicated preterm deliveries as competing events. Each growth measure was analysed (1) on its own in relation to sPTB and (2) adjusted for maternal characteristics. Records with missing values were excluded from the regression analysis.

We further examined the relationship between fetal biometry and the risk of sPTB by dichotomising biometric and growth velocity measures into the extreme decile of change associated with slowest growth versus the other 9 deciles. In most cases the lowest decile was clearly the extreme decile associated with poor growth. However, elevated HC:AC ratio is associated with poor fetal growth and analysis of this measure compared the highest decile with the other nine. In addition to regression analyses, cumulative incidence curves were produced using the competing risks method for each group and the population attributable fraction (PAF) related to the extreme decile was calculated using the cause-specific method. All analyses were performed using Stata version 14.0 (StataCorp, Texas).

RESULTS

Out of 4,512 women enrolled in the study, a total of 620 were excluded due to one or more of the following reasons: formally withdrawn (n=67), delivered elsewhere (n=255), stillbirths (n=12), pregnancies ending prior to 28 weeks of gestational age (n=42), defaulted from any scan (n=184), reported prior primary hypertension (n=73) or diabetes mellitus (n=15). A total of 3892 women were included in the analyses.

The characteristics of the study population are described by the birth type (Table 1). 98 (2.5%) births were sPTB and 59 (1.5%) were iPTB (including 3 women with ruptured membranes whose labor was induced only after 3 days of rupture), and data on the nature of 9 (0.2%) births was missing. Women who had term deliveries were taller, but were similar regarding age, BMI, the number of previous spontaneous and therapeutic abortions, ethnicity and indicators of socio-economic status.

When the results of fetal biometry at 20 weeks were analysed as continuous variables, the risk of sPTB was directly associated with EFW (Table 2). A one SD increase in EFW was associated with 26% increase in the risk of sPTB after adjustment for maternal characteristics. At 28 weeks, the risk of sPTB was inversely associated with the FL and was directly associated with the ratio of AC:FL (Table 2). A one SD increase in these measures was associated with a 19% decrease and a 23% increase in the risk of sPTB, respectively. However, both associations were attenuated by adjustment for maternal characteristics, and were no longer statistically significant. We next assessed the relationship between growth velocity

between the 20 and 28 week scan and the risk of sPTB (i.e. the change in the z-score of paired measurements between the two scans, with lower values representing smaller relative measurements at the time of the second scan). When analysed as continuous variables, higher growth velocity of the FL and EFW were associated with a decreased risk of sPTB (Table 2). A one SD increase in these measures was associated with a 27% decrease and a 21% decrease in the risk of sPTB, respectively. Neither association was affected by adjustment for maternal characteristics. All associations were very similar between the cause-specific and competing risks regression and when the INTERGROWTH-21st reference standard was employed (Table 3).

When biometric measurements were analysed comparing the extreme decile associated with poor growth, there was no association between any measurement at 28 weeks and the risk of sPTB. When the growth velocity was assessed, babies in the lowest decile of FL growth velocity between 20 and 28 weeks of gestational age had a 2 to 3 fold risk of sPTB (Table 4, Figure 1). Adjustment for maternal characteristics was without material effect, and 12% (95% confidence interval [CI]: 3%, 21%) of the sPTBs were estimated to be attributable to fetuses in the lowest decile of FL growth velocity. None of the other extreme deciles of fetal growth velocity were associated with the risk of sPTB (Table 4). There were no interactions between the lowest decile of FL growth velocity and any of the maternal characteristics on sPTB (likelihood ratio test *P* value >0.05 in all tests). None of the infants in the lowest decile of FL growth velocity who delivered preterm had a skeletal dysplasia. Eight babies who had sPTB were delivered by caesarean section. Our main findings persisted when they were excluded: babies in the lowest decile of

FL growth velocity had a 2.88 fold (95% CI: 1.73 to 4.81) risk of sPTB in the cause-specific regression adjusted for maternal characteristics.

DISCUSSION

The key finding of the present study is that reduced growth velocity of the fetal femur between 20 and 28 weeks gestational age was associated with an increased risk of sPTB. The association was evident when FL growth velocity was treated as a continuous variable, and when it was dichotomised as the lowest decile of growth velocity. In the latter case, the risk of sPTB was increased by two to three fold. There was also a weak inverse association between an increase in EFW between 20 and 28 weeks and sPTB. However, as EFW incorporates FL, this may simply be due to the same association, as there were no independent relations between the other biometric measures used to calculate the EFW and the risk of PTB. These data imply that the factors which lead to reduced growth of the fetal femur between 20 and 28 weeks gestational age are also associated with the risk of sPTB.

A number of previous studies have addressed the relationship between first and second trimester fetal growth and the risk of sPTB. The study that is most directly comparable with the present analysis is the Generation R cohort, which also performed serial ultrasonic fetal biometry (33). These authors reported a number of associations, some of which were also observed in the present study and some of which were not. Consistent with our study, they found that a decrease in the relative size of the fetal femur between 20 and 30 weeks gestational age was associated with an increased risk of sPTB. The observation and the magnitude of the

association were very similar to our findings. They also observed that higher values of fetal biometry at 20 weeks gestational age were associated with an increased risk of sPTB. In our study, associations of a similar magnitude were observed but they were statistically significant only in multivariate analysis. Moreover, they observed that reduced growth velocity (between ~20 and ~30 weeks) of both the HC and the AC were also associated with increased risks of sPTB, whereas we did not. There are multiple potential explanations for the discrepant results. The estimates for the association between AC growth velocity and sPTB were similar but since Generation R was a larger cohort, the statistical power to identify associations of this magnitude was higher. However, the estimated association between HC growth velocity and sPTB was clearly different. Some of the key differences in the Generation R cohort were that it included women of mixed parity, that 43% of the cohort was of non-European ethnic origin, and that gestational age in that study was based on either the menstrual history or early ultrasound, depending on the availability of a reliable menstrual record. Further studies, or further analysis of the Generation R study, may help to explain the differences. However, the consistency of the findings with FL in both studies indicates that this association is very likely to be true and to be generalizable.

When we analysed the association between biometry and the risk of sPTB, we studied the measurements both as continuous variables and by dichotomising them into the extreme decile associated with FGR. We used this approach because there may be different etiological associations between factors which cause variation across the whole range of the population, and the factors which lead to a small number of pregnancies having very low values. For example, if we assume that there

is some underlying pathological process that impairs growth of the fetal femur, it is most likely that only a small proportion of pregnancies would be so affected. It would also be expected that the 10% of pregnancies with the lowest value of FL growth velocity would include a much higher proportion of these pathological cases than the other 9 deciles. Hence, it might be expected that analysis of measures as continuous variables addresses primarily the effect of physiological variation in the parameter whereas analysis of measures by the most extreme decile addresses primarily pathological variation of the parameter. Interestingly, when we analysed fetal biometry using the most extreme decile, the only association we identified was between reduced FL growth velocity and sPTB.

The observations described above suggest that there is a strong association between pathological determinants of an isolated short femur in the second trimester and the risk of sPTB. Interestingly, a series of papers have highlighted the association between isolated short femur and the risk of severe early onset fetal growth restriction (34, 41-43). Collectively, these observations suggest that poor growth of the femur in the second trimester may be a marker of an important underlying determinant of adverse pregnancy outcome. Previous studies have found an association between levels of blood biomarkers during pregnancy, such as pregnancy associated plasma protein A and alpha-fetoprotein, and both fetal growth restriction and sPTB (11-18). Both the biochemical and ultrasonic data indicate that the factors which lead to FGR may also lead to sPTB. There is a potentially plausible biological link. Growth restricted fetuses have activation of the stress pathway of the hypothalamopituitary adrenal (HPA) axis (44), and there is extensive evidence linking the HPA axis to the physiological control of the timing of parturition (45).

Studies of growth restriction distinguish between asymmetric growth restriction, where there is an increase in the size of the head to the size of the body and symmetric growth restriction, i.e. where the baby is small but the HC and AC are in proportion. A recent study reported symmetrically growth restricted babies having the greatest deviation from normal height and weight at aged 4 (46) and the authors speculated that symmetric growth restriction leading to PTB is due to early onset placental dysfunction. We have previously reported an association between low first trimester levels of pregnancy associated plasma protein A and PTB (12). Early onset placental dysfunction might explain the observed association between reduced FL growth velocity and sPTB and we are planning to test this hypothesis in the future.

A key strength of the POP study design is its prospective investigation of serial fetal biometric measures at consistent time points. Moreover, gestational age was measured using early pregnancy ultrasound. Spontaneous versus iatrogenic PTB was clearly defined and ascertained by trained midwives. To better capture the growth process, we assessed fetal growth velocity, defined as the change in fetal biometric measure z-score, between 20 and 28 weeks of gestational age. Most importantly, patients and care providers were blinded to the results of the 28 week scan. Hence, the associations between growth velocity and sPTB cannot be explained by biases related to knowledge of the scan result.

We analysed the data using both cause-specific and competing risks approach. The former is preferred for answering etiologic questions (estimation of hazard ratios)

whereas the latter is preferred for prognostic questions (calculation of cumulative incidence). The focus of the present paper is on etiology but we present both approaches as recommended (47, 48). The number of competing events was small (n=59) and the two approaches gave very similar results. The proportion of missing values in the regression analyses varied between 5.7% and 11.7%, and we considered that imputation was not necessary as the bias resulting from missing values was probably small (49-51). Furthermore, we did not make adjustments to statistical significance levels, although we tested multiple hypotheses. This approach was adopted since our exposure measures of fetal biometry were correlated and our approach was hypothesis-driven. Moreover, the *P* value for the association between lowest decile of FL growth and sPTB was <0.001 and it is very unlikely that this could be a chance finding due to multiple comparisons.

The cohort included the first pregnancies of predominantly healthy women from a relatively affluent area in the UK, which may partly explain the relatively low risk of sPTB. It is well recognised that rates of sPTB are much higher in the USA than the majority of high income countries and the reasons for this are incompletely understood. However, the association between fetal growth and sPTB will not necessarily be influenced by the overall prevalence of PTB. Slow growth in FL is unlikely to be simply a marker of maternal characteristics such as maternal height or ethnicity. Although maternal height was associated with both FL growth velocity and sPTB, adjustment for it had very little impact. We did not observe ethnic differences between the sPTB group and babies born at term. The proportion of non-white women was low in the population and we had inadequate statistical power to detect ethnic differences. The recent INTERGROWTH-21st project has indicated that

ethnicity per se has a relatively modest effect on variation in fetal growth (40). Therefore, it is unlikely to be a strong confounder even in ethnically heterogeneous populations. Maternal BMI and socio-economic status were not associated with sPTB in our study and this may be due to insufficient statistical power.

Two main recognized subsets of sPTB include sPTB with intact membranes and preterm premature rupture of membranes. It has been recognized that the pathophysiologies of these are distinct (52, 53). While it might further be hypothesised that fetal growth may play a different role in each, we did not make a distinction between the two and nor have most other studies in this field. Given the low number of PTBs observed in the present study, additional splitting of the study population birth outcomes would have compromised power. This may be a useful avenue for future studies.

In conclusion, we show that reduced growth velocity of the fetal femur between 20 and 28 weeks of gestational is associated with an increased risk of sPTB. These data add to a body of evidence indicating that an isolated short femur could be a marker of early onset FGR, and that FGR may be an important determinant of apparently unexplained sPTB.

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Table 1. Characteristics of Study Participants by Birth Outcome in the Pregnancy Outcome Prediction (POP) Study, Cambridge, UK, 2008-2012.

	Overall[a]			Term[a]			Spontaneous preterm[a]			*P*[b]
	No.	**%**	**Median (IQR)**	**No.**	**%**	**Median (IQR)**	**No.**	**%**	**Median (IQR)**	
Outcome										
Total births	3,892	100		3,726	96		98	2.5		
Gestational age at birth (weeks)			40.3 (39.3- 41.1)			40.4 (39.4-41.1)			35.9 (34.7-36.4)	
Characteristics										
Age (years)			30.3 (26.8-33.3)			30.3 (26.8-33.3)			30.8 (27.3-33.7)	0.23
Height (cm)			165 (161-169)			165 (161-170)			164 (159-167)	0.005
BMI[c]			24.0 (21.8-27.2)			24.0 (21.8-27.2)			24.3 (22.5-26.4)	0.75
Previous spontaneous abortion										
Yes	396	10		375	10		9	9.2		
No	3,496	90		3,351	90		89	91		0.78
Previous therapeutic abortion										
Yes	35	0.9		35	0.9		0	0		
No	3,857	99		3,691	99		98	100		>0.99
White ethnicity										
Yes	3,620	93		3,469	93		89	91		
No	210	5.4		201	5.4		7	7.1		0.44
Missing	62	1.6		56	1.5		2	2		
Smoker										
Yes	183	4.7		174	4.7		6	6.1		
No	3,709	95		3,552	95		92	94		0.5
Married										
Yes	2,670	69		2,547	68		68	69		
No	1,220	31		1,179	32		30	31		0.83
Age discontinued full-time education (years)			21 (18-23)			21 (18-23)			21 (18-23)	0.81
Index of Multiple Deprivation			8.9 (5.7-14.2)			8.9 (5.7-14.2)			8.9 (5.6-12.2)	0.71

[a] Overall characteristics include all birth types in the study population: term, spontaneous preterm, iatrogenic preterm and unknown. Out of the total, 59 (1.5%) preterm births were iatrogenic, and data were missing on the nature of 9 (0.2%) births.

[b] Continuous variables were compared between term births and spontaneous preterm births using the Wilcoxon rank-sum test, and binary variables using Pearson's chi-squared test (apart from previous therapeutic abortion which was compared with Fisher's exact test due to small cell counts). With the exception of Pearson's chi-squared test, all tests for significance were two-sided,

[c] BMI given as kg/m^2.

Table 2. Fetal Growth and the Risk of Spontaneous Preterm Birth in the Pregnancy Outcome Prediction (POP) Study, Cambridge, UK, 2008-2012.

		Cause-specific regression						Competing risks regression					
		Unadjusted			Adjusted[a]			Unadjusted			Adjusted[a]		
Measure	**n**	**HR**	**95% CI**	***P*[b]**	**HR**	**95% CI**	***P*[b]**	**sHR**	**95% CI**	***P*[b]**	**sHR**	**95% CI**	***P*[b]**
Fetal biometry at 20 weeks[c]													
Head circumference	3,619	1.19	0.97, 1.46	0.10	1.22	0.99, 1.49	0.06	1.19	0.98, 1.44	0.08	1.22	1.01, 1.47	0.04
Abdominal circumference	3,660	1.18	0.96, 1.45	0.12	1.20	0.98, 1.48	0.08	1.18	0.96, 1.44	0.12	1.21	0.98, 1.48	0.07
Femur length	3,667	1.12	0.92, 1.36	0.28	1.18	0.96, 1.44	0.12	1.12	0.91, 1.38	0.28	1.18	0.96, 1.46	0.13
Estimated fetal weight	3,658	1.20	0.99, 1.47	0.06	1.26	1.03, 1.54	0.02	1.21	0.99, 1.47	0.06	1.27	1.04, 1.54	0.02
HC:AC ratio	3,609	0.95	0.77, 1.18	0.66	0.95	0.77, 1.18	0.66	0.95	0.76, 1.20	0.68	0.95	0.75, 1.20	0.68
AC:FL ratio	3,658	1.03	0.84, 1.26	0.80	1.00	0.82, 1.23	0.98	1.03	0.84, 1.25	0.80	1.00	0.82, 1.22	0.98
Fetal growth velocity from 20 to 28 weeks[c]													
Δ Head circumference	3,445	0.85	0.67, 1.06	0.15	0.86	0.68, 1.09	0.21	0.85	0.68, 1.08	0.18	0.87	0.68, 1.11	0.21
Δ Abdominal circumference	3,656	0.91	0.74, 1.10	0.33	0.90	0.74, 1.10	0.32	0.91	0.75, 1.11	0.34	0.91	0.74, 1.11	0.34
Δ Femur length	3,662	0.73	0.60, 0.89	0.002	0.73	0.59, 0.89	0.002	0.74	0.60, 0.90	0.004	0.73	0.58, 0.92	0.007
Δ Estimated fetal weight	3,654	0.79	0.64, 0.99	0.04	0.79	0.63, 0.99	0.04	0.80	0.64, 0.99	0.04	0.79	0.63, 0.99	0.05
Δ HC:AC ratio	3,433	0.98	0.81, 1.17	0.80	0.98	0.81, 1.18	0.83	0.98	0.80, 1.19	0.83	0.98	0.80, 1.20	0.84
Δ AC:FL ratio	3,651	1.16	0.97, 1.38	0.11	1.16	0.97, 1.40	0.11	1.16	0.96, 1.40	0.13	1.16	0.96, 1.42	0.13
Fetal biometry at 28 weeks[c]													
Head circumference[d]	3,490	1.02	0.82, 1.27	0.85	1.07	0.86, 1.33	0.57	1.03	0.81, 1.31	0.83	1.07	0.84, 1.37	0.58
Abdominal circumference	3,670	1.06	0.86, 1.29	0.60	1.08	0.88, 1.33	0.47	1.06	0.87, 1.30	0.58	1.09	0.88, 1.34	0.44
Femur length	3,669	0.81	0.66, 0.99	0.04	0.85	0.68, 1.05	0.12	0.81	0.65, 1.02	0.08	0.85	0.67, 1.09	0.20
Estimated fetal weight	3,670	0.99	0.81, 1.22	0.96	1.04	0.85, 1.28	0.70	1.00	0.81, 1.23	0.96	1.05	0.84, 1.30	0.67
HC:AC ratio	3,488	0.99	0.80, 1.23	0.96	0.99	0.80, 1.22	0.93	1.00	0.79, 1.25	0.97	0.99	0.79, 1.24	0.93
AC:FL ratio	3,667	1.23	1.01, 1.51	0.04	1.21	0.99, 1.49	0.06	1.23	0.99, 1.54	0.06	1.21	0.97, 1.52	0.09

Abbreviations: AC, abdominal circumference; CI, confidence interval; FL, femur length; HC, head circumference; HR, hazard ratio; sHR, ratio of the subdistribution hazards.
[a] Adjusted for maternal height, age, BMI, marital status, previous spontaneous abortion, ethnicity, smoking status, age at leaving full time education and Index of Multiple Deprivation (IMD).
[b] *P* values are from the z test specific to each method, i.e. cause-specific or competing risks regression. All tests for significance were two-sided.
[c] Fetal biometry and growth velocity measures are expressed in z-scores estimated in the POP study and therefore hazard ratios are given per one standard deviation increase in fetal biometry or growth velocity measure.
[d] Departure from proportionality for week 28 head circumference was detected in the unadjusted cause-specific regression (Schoenfeld test *P*=0.01) and competing risks regression (z test for interaction with follow-up time *P*=0.008).

Table 3. Fetal Growth and the Risk of Spontaneous Preterm Birth, Using an International Reference Standard in the Pregnancy Outcome Prediction (POP) Study, Cambridge, UK, 2008-2012.

		Cause-specific regression						Competing risks regression					
		Unadjusted			Adjusted[a]			Unadjusted			Adjusted[a]		
Measure	**n**	**HR**	**95% CI**	***P*[b]**	**HR**	**95% CI**	***P*[b]**	**sHR**	**95% CI**	***P*[b]**	**sHR**	**95% CI**	***P*[b]**
Fetal biometry at 20 weeks[c]													
Head circumference	3,619	1.24	0.95, 1.62	0.12	1.28	0.98, 1.67	0.07	1.24	0.97, 1.59	0.09	1.28	1.00, 1.64	0.05
Abdominal circumference	3,660	1.22	0.94, 1.57	0.13	1.25	0.97, 1.62	0.09	1.22	0.95, 1.57	0.12	1.26	0.98, 1.61	0.08
Femur length	3,667	1.14	0.89, 1.45	0.29	1.21	0.95, 1.55	0.12	1.14	0.89, 1.46	0.30	1.22	0.94, 1.57	0.13
Fetal growth velocity from 20 to 28 weeks[c]													
Δ Head circumference	3,445	0.87	0.67, 1.11	0.26	0.89	0.69, 1.15	0.38	0.87	0.67, 1.15	0.33	0.90	0.68, 1.19	0.46
Δ Abdominal circumference	3,656	0.92	0.75, 1.14	0.47	0.93	0.75, 1.15	0.49	0.93	0.75, 1.15	0.49	0.93	0.74, 1.16	0.52
Δ Femur length	3,662	0.72	0.58, 0.89	0.002	0.72	0.58, 0.90	0.003	0.72	0.58, 0.91	0.006	0.73	0.57, 0.93	0.01
Fetal biometry at 28 weeks[c]													
Head circumference[d]	3,490	1.02	0.82, 1.26	0.86	1.06	0.86, 1.32	0.57	1.03	0.81, 1.30	0.83	1.07	0.84, 1.36	0.59
Abdominal circumference	3,670	1.05	0.86, 1.28	0.62	1.08	0.88, 1.32	0.48	1.06	0.87, 1.29	0.59	1.08	0.88, 1.33	0.46
Femur length	3,669	0.82	0.67, 1.00	0.05	0.86	0.70, 1.05	0.13	0.83	0.67, 1.02	0.08	0.86	0.69, 1.08	0.20

Abbreviations: AC, abdominal circumference; CI, confidence interval; FL, femur length; HC, head circumference; HR, hazard ratio; sHR, ratio of the subdistribution hazards.
[a] Adjusted for maternal height, age, BMI, marital status, previous spontaneous abortion, ethnicity, smoking status, age at leaving time education and Index of Multiple Deprivation (IMD).
[b] *P* values are from the z test specific to each method, i.e. cause-specific or competing risks regression. All tests for significance were two-sided.
[c] Fetal biometry and growth velocity measures are expressed in z-scores with respect to the INTERGROWTH-21st Project reference. Hazard ratios are given per one standard deviation increase in fetal biometry or growth velocity measure according to the international reference. Median percentiles (interquartile range) in the POP Study at 20 weeks were HC: 52.8 (32.8 to 71.7), AC: 66.6 (44.4 to 83.0), FL: 48.0 (30.7 to 73.3) and at 28 weeks were HC: 73.4 (46.9 to 90.2), AC: 66.1 (40.3 to 86.7)), FL: 53.2 (27.4 to 79.1). Median percentiles (interquartile range) of changes from 20 to 28 weeks were ΔHC: 70.8 (50.0 to 86.1), ΔAC: 51.9 (27.1 to 74.3) and ΔFL: 53.8 (27.6 to 76.4).
[d] Departure from proportionality for week 28 head circumference was detected in the unadjusted cause-specific regression (Schoenfeld test *P*=0.01) and competing risks regression (z test for interaction with follow-up time *P*=0.008).

Table 4. Fetal Growth and the Risk of Spontaneous Preterm Birth, with Growth Expressed as Extreme Decile Indicative of Impaired Growth in the Pregnancy Outcome Prediction (POP) Study, Cambridge, UK, 2008-2012.

		Cause-specific regression						Competing risks regression					
		Unadjusted			Adjusted[a]			Unadjusted			Adjusted[a]		
Measure	**n**	**HR**	**95% CI**	***P*[b]**	**HR**	**95% CI**	***P*[b]**	**sHR**	**95% CI**	***P*[b]**	**sHR**	**95% CI**	***P*[b]**
Fetal biometry at 20 weeks[c]													
Head circumference	3,619	0.45	0.17, 1.23	0.12	0.41	0.15, 1.13	0.09	0.45	0.17, 1.23	0.12	0.41	0.15, 1.15	0.09
Abdominal circumference	3,660	0.79	0.36, 1.70	0.54	0.75	0.34, 1.62	0.46	0.77	0.36, 1.67	0.52	0.74	0.34, 1.58	0.43
Femur length	3,667	0.79	0.37, 1.72	0.56	0.72	0.33, 1.55	0.40	0.79	0.37, 1.71	0.55	0.71	0.33, 1.54	0.39
Estimated fetal weight	3,658	0.89	0.43, 1.83	0.74	0.84	0.41, 1.74	0.64	0.88	0.42, 1.81	0.72	0.83	0.40, 1.71	0.62
HC:AC ratio	3,609	1.19	0.62, 2.30	0.60	1.22	0.63, 2.35	0.56	1.19	0.62, 2.30	0.60	1.22	0.63, 2.36	0.56
AC:FL ratio	3,658	1.01	0.51, 2.00	0.98	1.05	0.53, 2.10	0.89	1.01	0.51, 2.00	0.99	1.05	0.53, 2.10	0.89
Fetal growth velocity from 20 to 28 weeks[c]													
Δ Head circumference	3,445	1.30	0.67, 2.53	0.43	1.26	0.65, 2.45	0.49	1.27	0.66, 2.47	0.48	1.24	0.64, 2.42	0.53
Δ Abdominal circumference	3,656	1.12	0.58, 2.16	0.74	1.12	0.58, 2.17	0.73	1.12	0.58, 2.16	0.74	1.13	0.58, 2.18	0.73
Δ Femur length	3,662	2.37	1.43, 3.93	<0.001	2.50	1.50, 4.14	<0.001	2.36	1.42, 3.91	0.001	2.48	1.48, 4.17	0.001
Δ Estimated fetal weight	3,654	1.24	0.66, 2.33	0.50	1.26	0.67, 2.37	0.47	1.23	0.65, 2.31	0.53	1.25	0.66, 2.35	0.49
Δ HC:AC ratio	3,433	0.85	0.39, 1.85	0.69	0.87	0.40, 1.89	0.73	0.86	0.39, 1.86	0.69	0.87	0.40, 1.91	0.73
Δ AC:FL ratio	3,651	0.85	0.41, 1.75	0.65	0.86	0.42, 1.78	0.69	0.85	0.41, 1.75	0.66	0.87	0.42, 1.81	0.70
Fetal biometry at 28 weeks[c]													
Head circumference	3,490	1.13	0.56, 2.25	0.73	1.04	0.52, 2.08	0.92	1.11	0.55, 2.21	0.77	1.02	0.51, 2.06	0.95
Abdominal circumference	3,670	0.66	0.29, 1.51	0.32	0.62	0.27, 1.43	0.27	0.64	0.28, 1.48	0.30	0.61	0.27, 1.40	0.24
Femur length	3,669	1.55	0.88, 2.73	0.13	1.41	0.79, 2.51	0.24	1.53	0.87, 2.70	0.14	1.39	0.78, 2.49	0.26
Estimated fetal weight	3,670	1.02	0.51, 2.02	0.96	0.93	0.46, 1.86	0.83	0.99	0.50, 1.98	0.99	0.91	0.44, 1.85	0.79
HC:AC ratio	3,488	0.98	0.48, 2.04	0.97	0.97	0.47, 2.02	0.95	0.98	0.47, 2.04	0.96	0.97	0.47, 2.02	0.93
AC:FL ratio	3,667	0.89	0.43, 1.83	0.75	0.93	0.45, 1.93	0.84	0.89	0.43, 1.83	0.75	0.93	0.45, 1.92	0.85

Abbreviations: AC, abdominal circumference; CI, confidence interval; FL, femur length; HC, head circumference; HR, hazard ratio; sHR, ratio of the subdistribution hazards.

[a] Adjusted for maternal height, age, BMI, marital status, previous spontaneous abortion, ethnicity, smoking status, age at leaving full time education and Index of Multiple Deprivation (IMD).

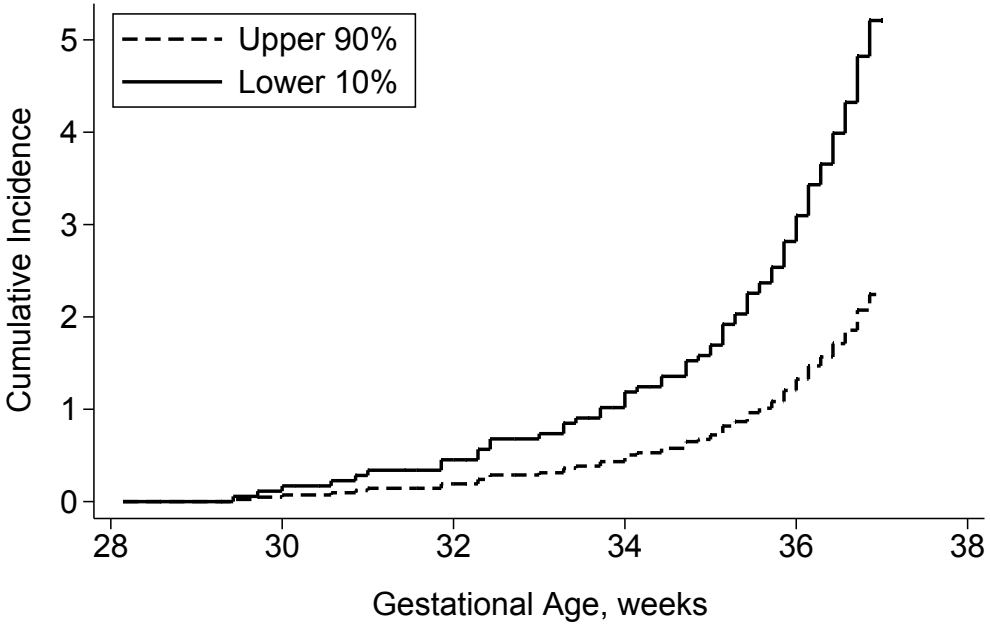
[b] *P* values are from the z test specific to each method, i.e. cause-specific or competing risks regression. All tests for significance were two-sided.

[c] Fetal biometry and growth velocity measures were expressed in z-scores estimated in the POP study and dichotomized to the clinically-relevant extreme decile versus the rest.

[d] Extreme decile cut-off points of z-scores at 20 weeks were HC -1.2835, AC -1.2807, FL: -1.2136, EFW: -1.2640, HC:AC ratio: 1.3296, AC:FL ratio: -1.3030 and at 28 weeks were HC -1.2588, AC -1.2780, FL: -1.2517, EFW: -1.2378, HC:AC ratio: 1.2717, AC:FL ratio: -1.2638. Extreme decile cut-off points of z-score changes from 20 to 28 weeks were ΔHC: -1.1949, ΔAC:-1.3289, ΔFL: -1.3020, ΔEFW: -1.1640, ΔHC:AC ratio: 1.4960, ΔAC:FL ratio: -1.4823.

[d] Hazard ratio associated with being in the lowest decile of each measurement versus the rest was calculated for all measures except for HC:AC ratio and Δ HC:AC ratio, where the highest decile was compared with the rest.

Fig 1. Cumulative incidence (births/100 women) of spontaneous preterm birth between 28+0/7 and 36+6/7 weeks of gestational age in the Pregnancy Outcome Prediction (POP) Study, Cambridge, UK, 2008-2012, comparing fetuses with the lowest decile of femur length growth velocity between 20 and 28 weeks (solid line) and all other fetuses (dashed line) using the competing risks method (*P*=0.001).


Upper 90%
Lower 10%
Cumulative Incidence
0
1
2
3
4
5
28
30
32
34
36
38
Gestational Age, weeks