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ORIGINAL ARTICLE *Early pregnancy*

Assessing first trimester growth: the influence of ethnic background and maternal age

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BACKGROUND: First trimester growth restriction may predict miscarriage or adverse outcome later in the pregnancy, but determinants of early growth are not well described. Our objective was to examine factors influencing fetal and gestational sac size in the first trimester.

METHODS: Prospective observational study of 1828 singleton pregnancies before 12 weeks gestation. Maternal characteristics (ethnicity, maternal age, obstetric history, abdominal pain and vaginal bleeding), crown rump length (CRL) and mean gestational sac diameter (MSD) were recorded. A stepwise linear mixed effects analysis was performed to determine factors influencing rate of change in CRL and MSD.

RESULTS: 1063 scans, in 464 women, were included. Rate of increase in CRL was higher in women of black ethnic origin ($P = 0.0261$) compared with white, and increased with advancing maternal age ($P = 0.0046$). Maternal age also influenced MSD: older women had gestational sacs which were 0.118 mm larger for each one year increase in maternal age ($P = 0.0073$). Bleeding, pain and prior obstetric history did not influence CRL or MSD.

CONCLUSIONS: Rate of increase in CRL was greater in fetuses of black versus white women and increased with advancing maternal age. As CRL is used to date pregnancies, and this influences further growth assessment, consideration should be given to the use of individualized growth charts which take account of maternal factors found to influence first trimester growth.

Key words: fetal growth / age / ethnicity / first trimester / ultrasound

Introduction

Early pregnancy dating by crown rump length (CRL), rather than estimation of gestation from last menstrual period (LMP) dates, is commonly performed to date pregnancies up to 14 weeks (NICE recommendation, 2008). Dating at this stage forms the basis for decisions regarding timing of delivery and assessment of growth during the second and third trimesters (Mongelli and Gardosi, 1996; Gardosi, 1997).

Pregnancy dating by transabdominal sonographic measurement of CRL was described by Robinson (1973) and subsequent studies have shown similar growth patterns using high-frequency transvaginal sonography (Hadlock *et al*., 1992; Grisolia *et al*., 1993). These studies assumed uniform embryonic growth regardless of maternal characteristics. They used predominantly white populations and did not take account of either maternal characteristics or symptoms.

It is known that maternal characteristics affect fetal growth in the second and third trimesters, leading to the rationale for customized birthweight centiles. It is also known that a smaller than expected fetal CRL in the first trimester is associated with an increased likelihood of miscarriage (Mantoni and Pederson, 1982; Falco *et al*.,1996; Reljic, 2001; Choong *et al*., 2003; Mukri *et al*., 2008) or adverse later pregnancy outcome such as low birthweight and preterm delivery (Smith *et al*., 1998; Bukowski *et al*., 2007). Vaginal bleeding, which occurs in about 20% of women in the first trimester, is also known to be associated with adverse pregnancy outcomes, including preterm prelabour rupture of membranes and preterm labour (Johns and Jauniaux, 2006).

Nevertheless, neither maternal characteristics nor symptoms have been assessed as potential factors affecting embryonic or early fetal size. Our objective was, therefore, to evaluate the influence of these factors on first trimester growth.

Materials and Methods

St George's Hospital serves a multi-ethnic inner city population. The Early Pregnancy Unit (EPU) is an open access, walk-in centre. Women either self refer, or are referred by another practitioner and there is no minimum gestation or restriction on indication for attendance. All women complete a written questionnaire of their demographic details (including ethnicity and age), obstetric history and pregnancy symptoms (pain or bleeding) immediately prior to consultation. These details are confirmed in person by the examining sonographer (specialist nurse, midwife or gynaecologist). All women undergo transvaginal ultrasound assessment using a 5 MHz transducer for B mode imaging (Aloka SSD 900, 2000, 4000 or GE Voluson 730). Structured detailed assessment includes standardized measurement of CRL and three orthogonal measurements of the gestation sac. All details are recorded contemporaneously onto a computerized database (Viewpoint PIA database, LB systems, Vienna, Austria). Dependent on the outcome of the assessment, women are managed according to standard departmental protocols. All women with viable pregnancies are then offered a routine scan at 11–14 weeks in order to assess viability, gestation and risk of chromosomal abnormality by measurement of fetal nuchal translucency thickness in the hospital's Fetal Medicine Unit (FMU). Gestation sac measurement is not performed at the 11–14-week scan.

In order to achieve our aims of assessing factors influencing first trimester growth, women were included in this study only if they had a certain menstrual history, and for this paper gestational age (GA) is defined as the number of days from LMP. All consecutive women recruited between January and October 2006 were included in the analysis if they met the following criteria: spontaneous conception, certain date of LMP, regular 26–30 day cycles, no recent pregnancy or hormonal contraception, singleton pregnancy, not more than 12 weeks gestation at initial presentation and subsequent confirmed viability at the 11–14 weeks scan with no reported fetal abnormality. Women were only enrolled on their first attendance to the EPU during the index pregnancy, and all CRL measurements taken on subsequent scans (in EPU and FMU) were included for each included pregnancy. Outcomes (viable pregnancy, miscarriage or termination of pregnancy) were obtained at the scheduled time of the routine 11–14-week scan (where these were available on the hospital records) or by contacting the women directly (where prior consent had been obtained). Formal confirmation that ethical approval was not required for this observational (non-interventional) study was obtained.

Statistical analysis

The variables considered were CRL and mean gestation sac diameter (MSD). Measurements were excluded if a CRL was measured at less than 37 days (as this is biologically implausible) or after 98 days (as this is 14 weeks, the upper limit of recommended CRL measurement). Similarly, the GA range for MSD was restricted to 29–85 days (85 days being the upper limit of assessment in the EPU, where MSD is measured). In order to exclude extreme outliers with an LMP that was biologically highly unlikely, data points more than four SDs from the expected CRL or MSD for GA [using Robinson (1973) and Hellman *et al*. (1969), respectively, as well validated reference ranges] were considered as outliers and also excluded (Healy, 1979). Statistical analyses were performed using SAS Version 9.1.3 for Windows (SAS Institute Inc., Cary, NC, USA, 2002–2003).

CRL and MSD measurements were considered as related to GA. A linear mixed-effects model for longitudinal data was built for each of the relationships, with GA as an independent or explanatory variable and expanded with a polynomial term up to the power of two (GA^2) (because of evidence for a non-linear relation between GA and CRL based on scatter plots). Multiple linear mixed-effects models were developed incorporating the fixed effects: maternal age (continuous variable), ethnicity (categorical/qualitative variable), the presence or absence of vaginal bleeding (dichotomous variable) and their interaction with GA (and GA^2) for analysing the interaction with CRL and MSD measurements and GA (Verbeke and Molenberghs, 2000).

For the analysis, ethnicity was simplified to three categories (white, black or Asian) as the numbers in the original nine categories would have been too small for meaningful analysis. Interaction terms between maternal characteristics and GA (or GA^2) were included to verify whether growth in CRL and MSD differed between women with different characteristics (such as different age, ethnicity or bleeding history). The covariance structure for the fixed effects was set to a simple structure with only the variances equal to σ^2 while each covariance was set to zero. An exponential and Gaussian structure did not lead to an improvement in the likelihood. As random effects, an intercept was included to account for within-subject variability as well as GA and GA^2 because growth expressed in terms of CRL is not considered to be linear (Robinson, 1973). For MSD, GA^2 was not considered as a random effect based on the standard linear curve of Hellman *et al*. (1969). An unstructured covariance matrix was chosen for the random effects. The parameters of the model were estimated with the maximum likelihood approach. Starting from the most general model expanded with the variables parity, pain, previous miscarriage and anxiety, a backward elimination method was applied in which fixed effects were removed in order of increasing significance until the reduction in likelihood became significant.

The final model required all model coefficients to be statistically significant at the 0.05 level. For each model, the Akaike Information Criterion (AIC), taking the complexity of the model into account, was calculated as a measure for the goodness of fit of the model.

Results

During the study period, 1828 women attended the EPU of whom 464 met the inclusion criteria, undergoing 1063 scans. This provided 908 CRL measurements and 662 MSD measurements. The first assessment was at a median GA of 50 days (range 29–83 days) from LMP. The mean maternal age was 31.2 (17–44) years. Median parity was 0 (0–6) and the median number of previous pregnancies in non-primigravid women was 2 (1–12). Maternal demographic characteristics and indications for attendance, number of scans for each woman and number of data points for each variable (CRL or MSD) are reported in Table I.

Table I Maternal age, ethnicity, presenting symptoms and number of scans performed for women included in the study ($n = 464$)

Variable	*n* (%)
Age (years)	
Mean (range)	31.2 (17–44)
<20	14 (3.0)
20–24	46 (9.9)
25–29	103 (22.2)
30–34	173 (37.3)
35–39	107 (23.1)
40 and above	21 (4.5)
Ethnic background	
White	287 (61.9)
Black	70 (15.1)
Asian	60 (12.9)
Mixed/Other	12 (2.6)
Missing	35 (7.5)
Presenting symptoms[a]	
Bleeding	197 (42.5)
Pain	239 (51.5)
Previous miscarriage	75 (16.2)
Anxiety	26 (5.6)
Other	65 (14.0)
Previous obstetric history	
Primigravida	126 (27.2)
Nulliparous	248 (53.4)
Previous miscarriage	75 (16.2)
Scans performed	
Total number of scans	1063
Number of scans per woman, Mean (range)	2.29 (1–8)
Total number of crown-rump length measurements	908
Total number of gestational sac size measurements[b]	662

Data are presented as *n* (%) or mean (range) where indicated.
[a]Women could present with more than one symptom.
[b]Gestational sac size was only available from Early Pregnancy Unit scans.

The most common reasons for exclusion of the 1364 pregnancies were miscarriage (40%) or termination (28%) prior to 11–14 weeks. Other reasons included ectopic pregnancy, failed pregnancy of unknown location, multiple pregnancy or loss to follow up. Comparison of the 464 included pregnancies to the 1364 excluded pregnancies showed no significant differences in maternal age. There were more Asian women in the included pregnancies but no other differences in ethnicity were seen. In the included pregnancies, fewer women reported vaginal bleeding, while more reported abdominal pain, anxiety or one or more previous miscarriages.

For the variable CRL, 42 data points were excluded: two data points according to the 4SD-rule, three data points which occurred at a GA of less than 37 days and 37 data points which occurred at a GA of 99 days or later. For the variable MSD, 26 data points were removed according to the 4SD-rule.

Univariate analysis showed that CRL was significantly influenced by maternal ethnicity and age. For MSD, the only significant variable was age. There was no significant influence on CRL or MSD from vaginal bleeding, parity, pain, previous miscarriage or anxiety. In multivariate analysis, the same maternal characteristics remained significant for CRL and MSD. These results are described in more detail later.

Ethnicity

A total of 818 CRL measurements from 420 pregnancies could be used ranging from 37 to 98 days of gestation. The linear mixed-effects curve of CRL as a function of GA and ethnicity was as follows and is

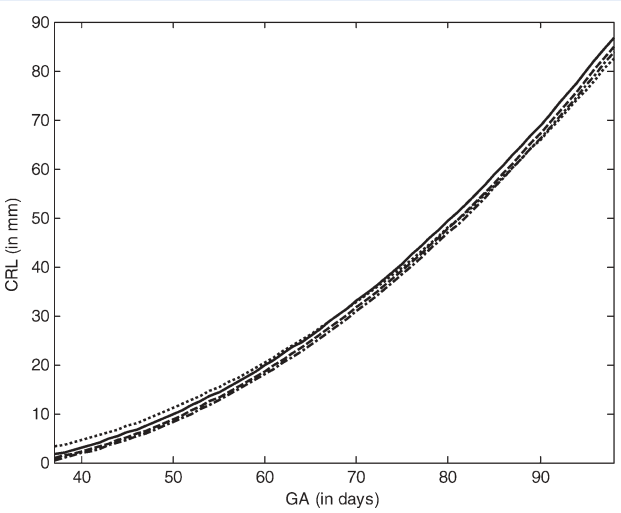

Figure 1 Growth model for CRL versus GA as a function of ethnicity; growth curve for black patients (solid line), growth curve for white patients (dashed line), growth curve for Asian patients (dash-dotted line), Robinson (1973) curve (dotted line). CRL, crown-rump length; GA, gestational age.

shown in Fig. 1:

$$\text{CRL} = 7.845 - 0.788 \times \text{GA} + 0.0114 \times x_W \times \text{GA} + 0.0306 \times x_B \times \text{GA} + 0.016 \times \text{GA}^2$$

with $x_W = 1$ when white, 0 otherwise and $x_B = 1$ when black, 0 otherwise.

The linear slope of CRL versus GA for fetuses with a black ethnic origin was −0.758 (SE = 0.0517), with a white ethnic origin −0.777 (SE = 0.0513) and for an Asian ethnic origin −0.788 (SE = 0.0505). Black ethnic origin was associated with a greater rate of increase in CRL compared with white and Asian ethnic origin ($P = 0.0261$ and 0.0078, respectively), equivalent to an extra increase in CRL in black women of 0.019 and 0.030 mm per day gestation, respectively. White and Asian fetuses however did not differ significantly in growth ($P = 0.222$). The AIC of the model was 4535.1.

Comparing black with white and Asian ethnic origin, ethnicity accounted for 0.81 and 1.28 mm difference in CRL at 6 weeks gestation, 1.61 and 2.57 mm difference at 12 weeks and 1.88 and 2.99 mm difference at 14 weeks, respectively (illustrated in Fig. 1). The difference at 12 weeks between black and Asian ethnic origin was equivalent to approximately 1.5 days gestation.

Maternal age

CRL and maternal age

906 CRL measurements from 465 pregnancies could be used ranging from GA 37 to 98 days. The linear mixed-effects model was as follows, and is shown in Fig. 2:

$$\text{CRL} = 14.405 - 0.968 \times \text{GA} + 0.0164 \times \text{GA}^2 - 0.144 \times \text{age} + 0.0042 \times \text{age} \times \text{GA}$$

Although older women had a slightly smaller fetus at the beginning of pregnancy ($P = 0.0279$) (SE = 0.065), there was a positive association between maternal age and the rate of change of CRL throughout the first trimester such that older women had fetuses with a greater increase in CRL ($P = 0.0046$) (SE = 0.0015). This was equivalent to an extra increase of 0.0042 mm in CRL per day of gestation for each 1 year increase in maternal age. The AIC of the model was 5038.6.

This difference in CRL at 12 weeks gestation between a woman of 20 years and a woman of 40 years was 4.18 mm (equivalent to approximately 2 days gestation).

MSD and maternal age

A total of 662 data points from 465 pregnancies could be used. The linear mixed-effects model was as follows and is shown in Fig. 3:

$$\text{MSD} = -43.93 + 1.435 \times \text{GA} - 0.0039 \times \text{GA}^2 + 0.118 \times \text{age}$$

There was a positive correlation between maternal age and MSD throughout the first trimester such that older women had gestational sacs which were 0.118 mm larger for each 1 year increase in maternal age ($P = 0.0073$) (SE = 0.044). The AIC of the model was 3978.6.

Influence of maternal age and ethnicity: combined models

Only CRL was influenced by both maternal age and ethnicity. 818 CRL measurements from 420 pregnancies could be used ranging from GA 37 to 98 days. The linear mixed-effects model is as follows:

$$\text{CRL} = 12.752 - 0.942 \times \text{GA} + 0.0078 \times x_W \times \text{GA} + 0.0279 \times x_B \times \text{GA} + 0.016 \times \text{GA}^2 - 0.156 \times \text{age} + 0.005 \times \text{age} \times \text{GA}$$

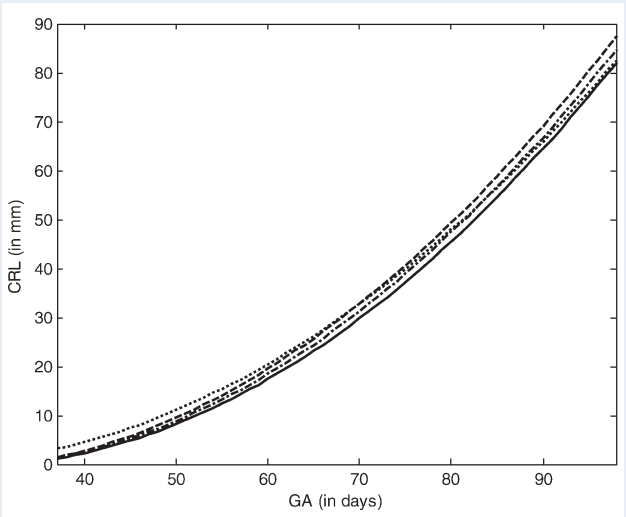

Figure 2 Growth model for CRL versus GA as a function of maternal age; growth curve for patients of age 20 years (solid line), growth curve for patients of age 30 years (dash-dotted line), growth curve for patients of age 40 years (dashed line), Robinson (1973) curve (dotted line). CRL, crown-rump length.

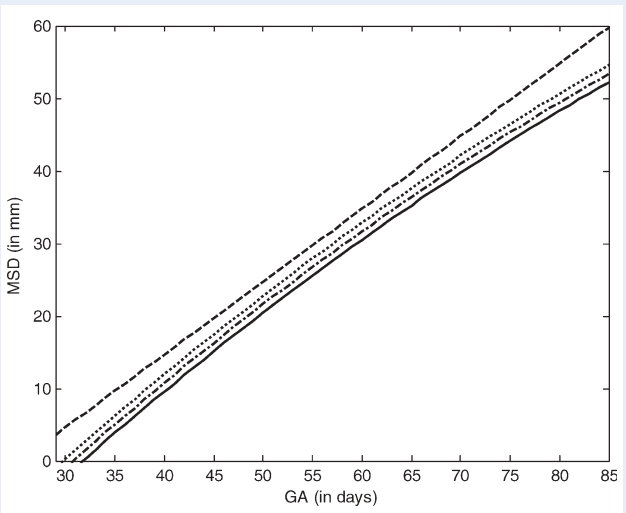

Figure 3 Growth model for MSD versus GA as a function of maternal age; growth curve for patients of age 20 years (solid line), growth curve for patients of age 30 years (dash-dotted line), growth curve for patients of age 40 years (dotted line), Hellman *et al.* (1969) curve (dashed line). MSD, mean gestational sac diameter.

with $x_W = 1$ when white, 0 otherwise and $x_B = 1$ when black, 0 otherwise.

The positive correlation between maternal age or ethnicity and rate of increase in CRL remained after considering both maternal characteristics together. The linear slope of CRL versus GA for fetuses with a mother of black ethnic origin was −0.915 (SE = 0.0705), with a white ethnic origin −0.935 (SE = 0.0702) and for an Asian ethnic origin −0.942 (SE = 0.0696). Black ethnic origin was associated with a greater rate of increase in CRL compared with white and Asian ethnic origin ($P = 0.0196$ and 0.0141, respectively), equivalent to an extra increase in CRL in black women of 0.020 and 0.027 mm, respectively per day of gestation. Older women had fetuses with a greater increase in CRL ($P = 0.0014$) (SE = 0.0015), equivalent to an extra increase of 0.005 mm per day of gestation for each 1 year increase in maternal age. Fetuses of older women were however slightly smaller at the beginning of the pregnancy ($P = 0.0248$) (SE = 0.069). The AIC of the model was 4525.9.

Discussion

This study has shown that maternal factors may affect embryonic and early fetal growth. Prior to 14 weeks gestation, fetuses of black women show a faster increase in CRL than those of white or Asian women and CRL also increases at a greater rate with increasing maternal age. Older women also show a faster increase in MSD. CRL and MSD are not influenced by vaginal bleeding, pain, parity, previous miscarriage or anxiety. This is the first study to suggest a difference in embryonic and fetal growth rate for different maternal characteristics in the first trimester and a validation study in a large independent data set is now planned.

In considering possible explanations for these results we considered whether, despite the menstrual history being taken in detail and validated by the clinician in every case, fetuses of older women or black women have greater CRL because of either inaccurate reporting of menstrual dates or delayed ovulation. This explanation is unlikely because the difference found between CRL in black and white or Asian women and between older and younger women is not a constant factor but increases with GA, showing that the increased CRL in black and older women is likely to be due to a true increased growth rate.

There are well documented birthweight variations between populations of different race or ethnic background (Parker *et al*., 1982; Hadlock *et al*., 1990; Lai and Yeo, 1995; Jacquemyn *et al*., 2000; Alshimmiri *et al*., 2003; Drooger *et al*., 2005; Merialdi *et al*., 2005; Kramer *et* al., 2006). Many studies have shown that the proportion of low birthweight (<2500 g) babies is elevated in blacks (David and Collins, 1997; Hessol *et al*., 1998; MacDorman *et al*., 2002; Harding *et al*., 2006). Birthweight is strongly related to perinatal and infant mortality (Alexander *et al*., 1999) and to morbidity and mortality in later life (Barker, 1995; Curhan *et al*., 1996). Delayed growth in black women might therefore have been expected during the first trimester, but this was not shown in our study.

Previous authors have considered whether the ethnic variation in pregnancy outcome is due to physiology or pathology (Kramer *et al*., 2006). Black women are more likely to experience pregnancy-related disorders, such as pre-eclampsia, which are known to account for diminished fetal growth. Extrapolating back to the early first trimester the question, therefore, is whether the accelerated growth of black fetuses before 11–14 weeks is physiological, related simply to ethnic variation, or whether it may relate to pathology known to occur later in the pregnancy.

One limitation of the study is that ethnicity is difficult to define due to the wide ethnic diversity in developed countries—black women may be African, Caribbean, another origin or have mixed ethnicity. Any influence of maternal ethnicity on fetal growth may also be mitigated by country of birth of the mother. In addition, due to the inability to confirm what is reported, we did not record paternal ethnic background.

Increasing maternal age is associated with increased pregnancy complications including miscarriage, abruption, growth retardation, perinatal loss, pre-eclampsia and gestational diabetes (Jacobsson *et al*., 2004, Bewley *et al*., 2005). Although advanced maternal age is known to increase the risk of miscarriage (Nybo Andersen *et al*., 2000), the relationship between maternal age and first trimester growth in pregnancies that survive has not previously been studied. Increasing numbers of women are having children in later life. The mean age of women included in our study was 31.2 years [with 27.8% (128/465) over 35 years], thus demonstrating that our population is not considerably different in age from the general antenatal population of women in the UK which had a mean age of 29.2 years in 2006 (Office of National Statistics, 2008).

It is of interest that the Hellman curve appears to suggest a considerably higher MSD for GA at all points than the modeled curves from this study. This may be accounted for by the fact that the original work was performed in 25 women (38 measurements) with transabdominal ultrasound imaging (Hellman). The women studied had certain LMP dates, but no cycle length information was reported. It is likely that our study is more accurate in view of the larger number of patients, high frequency transvaginal sonography and the more detailed menstrual history taken.

Of the women excluded from the study analysis, more reported vaginal bleeding. This was expected as the study was designed only to look at women with viable pregnancies at the end of the first trimester, so those with bleeding who subsequently miscarried were excluded. The increased number of women with pain, anxiety and previous miscarriage history in the included group reflects the number of women who attend our unit for reassurance scans.

Although this study aimed to examine a number of maternal factors that may have influenced fetal size, other factors that were not evaluated, such as smoking history or BMI may also be possible confounding variables and further studies should be considered to include these possible influencing factors. The issue of inter-observer and intra-observer variability in early pregnancy ultrasound measurement has not been explored well in the literature but is another possible confounding variable in our study, despite all ultrasound examinations being performed by experienced trained sonographers and doctors. However, such measurement inaccuracies are likely to result in random error rather than systematic error in women of black race or older age.

Fetal growth is an increasingly important area of study and has mainly focused on fetal size assessment from the end of the first trimester, only recently addressing early growth (Smith *et al*., 1998; Bukowski *et al*., 2007). With the development of the placenta occurring with the secondary trophoblastic wave and the placental unit

holding a fundamental role in fetal growth, studies which examine influences on fetal size at this early stage may contribute to further understanding of the pathophysiology of growth-related problems in later pregnancy.

The clinical relevance of the study findings is that they suggest that the traditional early pregnancy growth curves developed by Robinson (1973) and Hadlock *et al*. (1992) may not be optimal, as they do not take into account the ethnic diversity of populations, or the variation in age of the pregnant women. Although the absolute differences demonstrated according to ethnic group or maternal age are small in terms of percentage difference in fetal size between two groups, recent evidence shows that the number of days a pregnancy is re-dated in the first trimester predicts the diagnosis of growth retardation in later pregnancy, confirming the importance of accurate individualized dating for all pregnancies (Thorsell *et al*., 2008).

Conclusions

This study shows that rate of increase in CRL in the first trimester is greater in fetuses of black women compared with those of white and Asian ethnic origin, and that it also increases with advancing maternal age. This study therefore demonstrates that differences in fetal size related to maternal characteristics are evident during the first trimester of pregnancy. Not all potential confounding variables were available to us, and predictors, such as maternal height, BMI, anthropometry or smoking history should also be explored prospectively. The current charts for assessing GA should be improved on the basis of such more detailed individualized information.

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