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ORIGINAL ARTICLE *Early pregnancy*

# No influence of body mass index on first trimester fetal growth

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**BACKGROUND:** Our objective was to determine what effect maternal BMI has on fetal growth rate in the early first trimester.

**METHODS:** This was a prospective observational study of singleton pregnancies with certain dates, initially presenting for a transvaginal scan (TVS) before 12 weeks of gestation. Maternal characteristics (BMI, ethnicity, maternal age, obstetric history, abdominal pain and vaginal bleeding) were recorded. Fetal crown-rump length (CRL) was measured at the initial scan, and at subsequent ultrasound assessments. In order to assess the fetal growth rates, women with at least two CRL measurements were included in the analysis. A mixed-linear effects model analysis was performed to determine whether BMI influences the rate of change in CRL.

**RESULTS:** A total of 264 pregnancies were analysed. The median BMI was 23.55 (range 16–45), median age was 32 (17–44) and the proportion of white, black and Asian women was 61.0, 15.5 and 5.3%, respectively. Mean gestational age (GA) at first TVS was 56 (range 33–84) days. Studying CRL as a function of GA with a mixed-linear effects model showed that this relationship was neither significantly influenced by BMI when modelling BMI as a continuous variable ($P = 0.7529$), nor when modelling it as a categorical variable using the WHO criteria ($P = 0.8904$).

**CONCLUSIONS:** Dating by CRL influences subsequent growth assessment and previous studies have suggested that first trimester fetal growth rates may be influenced by ethnicity and age. Our data however suggest that maternal BMI does not significantly influence early fetal growth.

**Key words:** first trimester / crown-rump length / body mass index / fetal growth

## Introduction

Measurement of crown-rump length (CRL) is commonly performed to date pregnancies and this may influence decisions regarding timing of delivery and growth assessment during the subsequent trimesters (Mongelli and Gardosi, 1996; Gardosi, 1997). Such dating by measurement of CRL using transabdominal ultrasound was described by Robinson in 1973 and subsequent studies using transvaginal ultrasound have documented similar growth patterns (Hadlock *et al.*, 1992; Grisolia *et al.*, 1993; Pexsters *et al.*, in press).

Maternal characteristics can affect fetal size in the second and third trimesters, and this has led to the construction of customized biometric centiles (Leung *et al.*, 2008; Salpou *et al.*, 2008). Conversely, studies assessing embryonic size in early pregnancy have assumed uniform growth irrespective of maternal characteristics. Variation in first trimester growth may, however, occur due to different maternal characteristics, symptoms or fetal factors. For example, chromosomal abnormalities are associated with first trimester growth restriction (Bahado-Singh *et al.*, 1997; Schemmer *et al.*, 1997), and a smaller than expected CRL in the first trimester is associated with an increased likelihood of miscarriage (Mantoni and Pedersen, 1982; Falco *et al.*, 1996; Reljic, 2001; Choong *et al.*, 2003; Mukri *et al.*, 2008; Bora *et al.*, 2009). Such a lag in early growth may also be associated with adverse pregnancy outcomes such as low birthweight and preterm delivery (Smith *et al.*, 1998; Bukowski *et al.*, 2007a). However, not all deviations in first trimester growth are due to pathological causes: for example, in pregnancies that are considered to be normal, there are observed fetal growth variations in the first trimester. Male fetuses are larger than female fetuses (Bukowski *et al.*, 2007b) and, as we have previously shown, the 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; an increase is also observed with advancing maternal age (Bottomley *et al.*, 2009). This demonstrates that

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differences in fetal size related to maternal characteristics are evident during the first trimester of pregnancy.

Maternal body mass index (BMI) has been reported to affect second and third trimester growth (Jolly et al., 2003; Ehrenberg et al., 2004). In addition, women with high BMI have a higher risk of developing gestational diabetes, pre-eclampsia or eclampsia, having a Cesarean section or delivering a macrosomic infant (Sebire et al., 2001; Weiss et al., 2004; Yu et al., 2006). Our objective was to evaluate the influence of BMI on first trimester growth.

# Methods

This study was part of a prospective longitudinal study whose aim was to identify factors that predict first trimester outcome (Bottomley et al., 2009). It included consecutive unselected women attending the early pregnancy unit (EPU) at St George's Hospital, St George's University of London, from January to October 2006. This analysis was carried out retrospectively using the entire anonymized study database. Patient data were included in the analysis if the woman had certain dates (defined as having a known last menstrual period (LMP) date, a regular cycle length of 26–30 days and no previous pregnancy or hormonal contraception in the 3 months preceding the pregnancy), a spontaneous singleton intrauterine pregnancy, at least two ultrasound examinations demonstrating a live fetus (heart pulsation seen) on separate occasions, no fetal chromosomal or structural abnormalities, and known first trimester outcome as assessed at the routine 11–14 weeks dating and nuchal translucency scan in the hospital's fetal medicine unit (FMU).

All women included had at least one transvaginal scan (TVS) in the EPU and one transabdominal scan (TAS) at 11–14 weeks in the FMU. Additional scans in between were performed when indications for repeat EPU assessment existed such as bleeding, pain or maternal anxiety. Women were included regardless of indication for assessment. All scans were performed by either doctors or sonographers who were experienced in both TVS and TAS. Ultrasound assessment was performed using a 5 (for TVS) and a 2–5 (for TAS) MHz transducer for B mode imaging (Aloka SSD 900, 2000, 4000 or GE Voluson 730). Standardized measurements of CRL were taken from gestational age (GA) of 35–98 days. The measurement of CRL for included pregnancies was obtained during each attendance to the EPU and FMU. In the EPU, women were managed according to standard departmental protocols depending on the outcome of the assessment. Women were excluded from the analysis if they underwent a miscarriage prior to 14 weeks or had a termination of pregnancy (TOP). GA is defined as the number of days from the LMP.

All details of the ultrasound examination were recorded contemporaneously onto a computerized database (Viewpoint PIA database, LB systems, Vienna, Austria). Demographic details (including ethnicity and age), obstetric history and pregnancy symptoms (pain or bleeding) were recorded during the first attendance to the EPU. First trimester pregnancy outcome (viable pregnancy, miscarriage, termination of pregnancy) was ascertained during the routine 11–14 assessment in the FMU. We have previously reported on the effect of maternal age and ethnicity on fetal growth in 464 women (1063 scans) (Bottomley et al., 2009). As the maternal body mass index (BMI) was not available to us at that time, we later obtained it by cross referencing this cohort to the fetal medicine database in order to allow an evaluation of the influence of BMI on first trimester growth.

## Statistical analysis

The GA range for CRL measurements was restricted to between 37 days (anything earlier than this was considered biologically implausible) and 98 days (CRL measurements are taken in our department at the latest at 14 weeks). In order to exclude extreme outliers with an LMP that was biologically highly unlikely, data points more than four SDs from the expected CRL for GA using a well-validated reference range (Robinson, 1973) were considered as outliers and therefore excluded (Healy, 1979). Statistical analyses were performed using SAS version 9.1.3 for Windows (SAS Institute Inc., Cary, NC, USA, 2002–2003).

CRL measurements were considered as related to GA. A linear mixed-effects model for longitudinal data was built 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 relationship between GA and CRL based on the scatter plots). Multiple linear mixed-effects models were developed incorporating the fixed effect of BMI and its interaction with GA (and $GA^2$) for analysing the relationship of CRL measurements with GA (Verbeke and Molenderghs, 2000). Models were developed considering BMI as a continuous variable and as a categorical one. The categories followed the WHO classification for obesity (WHO, 1989): underweight BMI $<18.50$, normal BMI $= 18.50–24.99$, overweight BMI $= 25.00–29.99$, obese class I BMI $= 30.00–34.99$, obese class II BMI $= 35.00–39.99$, obese class III BMI $>40.00$.

Interaction terms between maternal BMI and GA (or $GA^2$) were included to verify whether growth in CRL differed between women with different BMI. The covariance structure for the fixed effect was set to a simple structure with only the variances equal to $\sigma^2$, 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). 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, BMI as a continuous variable and BMI as a categorical variable, 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 but all data were available in 264, undergoing 740 scans. This provided 649 CRL measurements. The mean GA at first TVS was 56 (range 33–84) days from LMP. The median maternal age was 32 (17–44) years, median parity was 0 (0–6) and the median number of previous pregnancies in non-primigravid women was 2 (1–12). The proportion of white, black and Asian women was 61.0, 15.5 and 5.3% respectively. The median BMI was 23.55 (range 16–45). The most common reasons for exclusion of the 1564 pregnancies were miscarriage or termination prior to 11–14 weeks. Comparison of the included pregnancies to the excluded ones showed that in the included pregnancies there were more Asian women (but no other differences in ethnicity), fewer women who reported vaginal bleeding and more women who reported abdominal pain, anxiety or one or more previous miscarriages, but no other significant differences (including differences in BMI). Maternal characteristics and indication for attendance are summarized in Table I.

The linear mixed-effects model of CRL as a function of GA and BMI showed that this relationship was neither significantly influenced when modelling BMI as a continuous variable ($P = 0.7529$), nor when

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**Table I Maternal age, ethnic background, indication for attendance, previous obstetric history and BMI for women included in the study (total, $n = 264$).**

| | *n* (%) |
|---|---|
| Age (years) | |
| Mean 32 (range 17–44) | |
| <20 | 7 (2.7) |
| 20–24 | 27 (10.2) |
| 25–29 | 35 (13.3) |
| 30–34 | 92 (34.8) |
| 35–39 | 83 (31.4) |
| 40< | 20 (7.6) |
| Ethnic background | |
| White | 161 (61.0) |
| Black | 41 (15.5) |
| Asian | 14 (5.3) |
| Mixed/Other | 48 (18.2) |
| Indication for attendance* | |
| Bleeding | 111 (42.0) |
| Pain | 114 (43.2) |
| Previous miscarriage | 150 (56.8) |
| Anxiety | 26 (9.8) |
| Previous obstetric history | |
| Primigravida | 131 (49.6) |
| Nulliparous | 133 (50.4) |
| Body mass index (BMI) | |
| Median 23.55 (range 16–45) | |
| BMI <18.50 | 8 (3.0) |
| BMI = 18.50–24.99 | 158 (59.8) |
| BMI = 25.00–29.99 | 60 (22.7) |
| BMI >30.0 | 38 (14.4) |

*Women could present with more than one symptom.

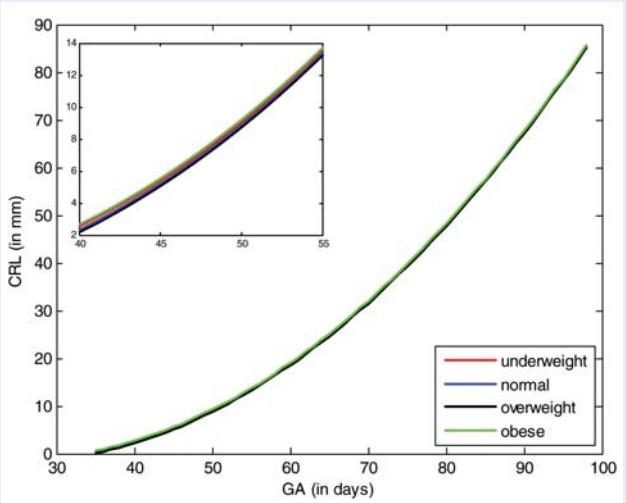


**Figure 1** Growth model for CRL versus GA as a function of BMI using the WHO classification; growth curve for underweight patients (red line), growth curve for normal weight patients (blue dashed line), growth curve for overweight patients (dash-dotted black line), growth curve for obese patients (dotted green line). The insert is a zoom-in of the curves for better visualization. CRL, crown-rump length; GA, gestational age; BMI, body mass index.

modelling it as a categorical variable using the WHO classification ($P = 0.8904$). As the interaction between BMI and GA was not significant, the linear and quadratic slope of CRL versus GA is the same for all women, independent of BMI. The curves only differ slightly in intercept, although this is not statistically significant (see Fig. 1). The linear slope of CRL versus GA equals $-0.794$ (SE = 0.055), the quadratic slope is 0.016 (SE = 0.0004). The AIC of the model was 3405.3.

# Discussion

This study has shown that maternal BMI does not influence embryonic and early fetal growth. This is the first study systematically examining the effect of maternal BMI on embryonic and early fetal growth rate and a validation study in a large independent data set is now planned.

The influence of a high BMI is generally expressed as fetal overgrowth. However, apart from the immediate peripartum complications of fetal macrosomia (Jolly *et al.*, 2003), there might be long-term consequences as well: adolescents born with high birthweights have a greater fat mass in adolescence and a higher incidence of insulin resistance (Murtaugh *et al.*, 2003). Conversely, reduced growth in early life is strongly linked with impaired glucose tolerance, non-insulin dependent diabetes and high blood pressure (Hales *et al.*, 1991).

Approximately 20% (Kanagalingam *et al.*, 2005) of all pregnancies are associated with obesity. We have already shown that maternal ethnicity and age affect early embryonic growth (Bottomley *et al.*, 2009). It is known that obesity is a recognized risk factor for delivering a macrosomic baby (Galtier-Dereure *et al.*, 2000; Sebire *et al.*, 2001; Weiss *et al.*, 2004) and, given that maternal characteristics can influence first trimester growth, and that second and third trimester growth is influenced by BMI, we hypothesized that maternal body weight may influence early embryonic growth. Our study does not support this. A possible explanation could be that the pathophysiology leading to fetal macrosomia due to increased maternal BMI is not relevant during early embryonic development.

The patient characteristics of the women excluded from the study were similar to those of the women included. The only difference was that in the former group more women reported vaginal bleeding. This was expected as the study was designed for 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 EPU for reassurance scans. Although in this cohort of patients, a number of maternal factors that may influence first trimester fetal growth has been studied in the past (Bottomley *et al.*, 2009), other factors that have not been evaluated, such as smoking history and paternal characteristics, may confound the result.

All ultrasound examinations were performed by experienced trained sonographers and doctors. The inter-observer variability in

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acquisition of CRL is a possible confounding factor. However, this would result in random rather than systematic error in women of a specific BMI. Nevertheless, it is possible that in women of increased BMI the CRL is systematically under- or overestimated, especially at the 11–14 week scan, which is transabdominal. This could lead to a true biological association of CRL versus BMI to be missed. Such a systematic error has not been reported in the literature, although there are no studies specifically looking at this in early pregnancy. A total of 264 women were included in the study. It is possible that the study was underpowered to detect an effect of BMI on growth rate. However, all included women had more than one ultrasound examination with 740 scans performed in total and therefore growth rates could be examined. Given our findings, it is unlikely that any effect of maternal BMI on early fetal growth would be large.

## Conclusion

Dating by CRL influences subsequent growth assessment and previous studies have suggested that first trimester fetal growth rates may be influenced by maternal characteristics. Our data suggest that maternal BMI has no significant influence on early fetal growth. Not all potential variables have been explored and other predictors, such as maternal anthropometric variables or smoking history, should also be explored prospectively. It may be possible to improve current charts of embryonic size for assessing GA on the basis of such detailed individualized information.

## Authors' roles

I.S. contributed to acquisition of data, interpretation of data and wrote the manuscript; C.B. contributed to acquisition of data, study design and reviewed the manuscript; A.D. analysed the data and reviewed the manuscript; A.P. contributed to the study design and reviewed the manuscript; D.T. contributed to the study design and reviewed the manuscript; T.B. contributed to the study design and reviewed the manuscript; A.P. contributed to the study conception, interpretation of data and co-wrote the manuscript.

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## References

Bahado-Singh RO, Lynch L, Deren O, Morroti R, Copel JA, Mahoney MJ, Williams J 3rd. First-trimester growth restriction and fetal aneuploidy: the effect of type of aneuploidy and gestational age. *Am J Obstet Gynecol* 1997;**176**:976–980.

Bora SA, Bourne T, Bottomley C, Kirk E, Papageorghiou AT. Twin growth discrepancy in early pregnancy. *Ultrasound Obstet Gynecol* 2009;**34**:38–42.

Bottomley C, Daemen A, Mukri F, Papageorghiou AT, Kirk E, Pexsters A, De Moor B, Timmerman D, Bourne T. Assessing first trimester growth: the influence of ethnic background and maternal age. *Hum Reprod* 2009; **24**:284–290.

Bukowski R, Smith GC, Malone FD, Ball RH, Nyberg DA, Comstock CH, Hankins GD, Berkowitz RL, Gross SJ, Dugoff L *et al.* Fetal growth in early pregnancy and risk of delivering low birth weight infant: prospective cohort study. *BMJ* 2007a;**334**:836.

Bukowski R, Smith GC, Malone FD, Ball RH, Nyberg DA, Comstock CH, Hankins GD, Berkowitz RL, Gross SJ, Dugoff L *et al.* Human sexual size dimorphism in early pregnancy. *Am J Epidemiol* 2007b;**165**:1216–1218.

Choong S, Rombauts L, Ugoni A, Meagher S. Ultrasound prediction of risk of spontaneous miscarriage in live embryos from assisted conceptions. *Ultrasound Obstet Gynecol* 2003;**22**:571–577.

Ehrenberg HM, Mercer BM, Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. *Am J Obstet Gynecol* 2004;**191**:964–968.

Falco P, Milano V, Pilu G, David C, Grisolia G, Rizzo N, Bovicelli L. Sonography of pregnancies with first-trimester bleeding and a viable embryo: a study of prognostic indicators by logistic regression analysis. *Ultrasound Obstet Gynecol* 1996;**7**:165–169.

Galtier-Dereure F, Boegner C, Bringer J. Obesity and pregnancy: complications and cost. *Am J Clin Nutr* 2000;**71**:1242S–1248S.

Gardosi J. Dating of pregnancy: time to forget the last menstrual period. *Ultrasound Obstet Gynecol* 1997;**9**:367–368.

Grisolia G, Milano K, Pilu G, Banzi C, David C, Gabrielli S, Rizzo N, Morandi R, Bovicelli L. Biometry of early pregnancy with transvaginal sonography. *Ultrasound Obstet Gynecol* 1993;**3**:403–411.

Hadlock FP, Shah YP, Kanon DJ, Lindsey JV. Fetal crown-rump length: reevaluation of relation to menstrual age (5-18 weeks) with high-resolution real-time US. *Radiology* 1992;**182**:501–505.

Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991;**303**:1019–1022.

Healy MJ. Outliers in clinical chemistry quality-control schemes. *Clin Chem* 1979;**25**:675–677.

Jolly MC, Sebire NJ, Harris JP, Regan L, Robinson S. Risk factors for macrosomia and its clinical consequences: a study of 350,311 pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2003;**111**:9–14.

Kanagalingam MG, Forouhi NG, Greer IA, Sattar N. Changes in booking body mass index over a decade: retrospective analysis from a Glasgow Maternity Hospital. *BJOG* 2005;**112**:1431–1433.

Leung TN, Pang MW, Daljit SS, Leung TY, Poon CF, Wong SM, Lau TK. Fetal biometry in ethnic Chinese: biparietal diameter, head circumference, abdominal circumference and femur length. *Ultrasound Obstet Gynecol* 2008;**31**:321–327.

Mantoni M, Pedersen JF. Fetal growth delay in threatened abortion: an ultrasound study. *Br J Obstet Gynaecol* 1982;**89**:525–527.

Mongelli M, Gardosi J. Reduction of false-positive diagnosis of fetal growth restriction by application of customized fetal growth standards. *Obstet Gynecol* 1996;**88**:844–848.

Mukri F, Bourne T, Bottomley C, Schoeb C, Kirk E, Papageorghiou AT. Evidence of early first-trimester growth restriction in pregnancies that subsequently end in miscarriage. *BJOG* 2008;**115**:1273–1278.

Murtaugh MA, Jacobs DR Jr, Moran A, Steinberger J, Sinaiko AR. Relation of birth weight to fasting insulin, insulin resistance, and body size in adolescence. *Diabetes Care* 2003;**26**:187–192.

Pexsters A, Daemen A, Bottomley C, Van Schoubroeck D, De Catte L, De Moor B, D'Hooghe T, Lees C, Timmerman D, Bourne T. A new crown-rump length curve based on over 3500 pregnancies. *Ultrasound Obstet Gynecol* 2010; in press.

Reljic M. The significance of crown-rump length measurement for predicting adverse pregnancy outcome of threatened abortion. *Ultrasound Obstet Gynecol* 2001;**17**:510–512.

Robinson HP. Sonar measurement of fetal crown-rump length as means of assessing maturity in first trimester of pregnancy. *Br Med J* 1973;**4**:28–31.

Salpou D, Kiserud T, Rasmussen S, Johnsen SL. Fetal age assessment based on 2nd trimester ultrasound in Africa and the effect of ethnicity. *BMC Pregnancy Childbirth* 2008;**8**:48.

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Schemmer G, Wapner RJ, Johnson A, Schemmer M, Norton HJ, Anderson WE. First-trimester growth patterns of aneuploid fetuses. *Prenat Diagn* 1997;**17**:155–159.

Sebire NJ, Jolly M, Harris JP, Wadsworth J, Joffe M, Beard RW, Regan L, Robinson S. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. *Int J Obes Relat Metab Disord* 2001; **25**:1175–1182.

Smith GC, Smith MF, McNay MB, Fleming JE. First-trimester growth and the risk of low birth weight. *N Engl J Med* 1998;**339**:1817–1822.

Verbeke G, Molenderghs G. *Linear Mixed Models for Longitudinal Data*. New York: Springer, Inc, 2000.

Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, Saade G, Eddleman K, Carter SM, Craigo SD *et al.* Obesity, obstetric complications and cesarean delivery rate–a population-based screening study. *Am J Obstet Gynecol* 2004;**190**:1091–1097.

WHO MONICA Project. Risk factors. *Int J Epidemiol* 1989;**18**:S46–S55.

Yu CK, Teoh TG, Robinson S. Obesity in pregnancy. *BJOG* 2006; **113**:1117–1125.

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