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Fetal middle cerebral artery and umbilical artery pulsatility index: effects of maternal characteristics and medical history

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KEYWORDS: cerebroplacental ratio; Doppler; pyramid of pregnancy care; third-trimester screening

ABSTRACT

Objective *To define the contribution of maternal variables which influence the measured fetal middle cerebral artery (MCA) and umbilical artery (UA) pulsatility index (PI) in the assessment of fetal wellbeing.*

Methods *Maternal characteristics and medical history were recorded and fetal MCA-PI and UA-PI (*n = *36 818) were measured in women with singleton pregnancies attending a routine hospital visit at 30 + 0 to 37 + 6 weeks' gestation. For pregnancies delivering phenotypically normal live births or stillbirths ≥ 30 weeks' gestation, variables among maternal demographic characteristics and medical history that are important in the prediction of MCA-PI and UA-PI were determined by multiple linear regression analysis.*

Results *Significant independent contributions to MCA-PI were provided by gestational age at assessment, East Asian racial origin, being parous and birth-weight Z-score of the neonate of the previous pregnancy. Significant independent contributions to UA-PI were provided by gestational age at assessment, Afro-Caribbean, East Asian and mixed racial origin, cigarette smoking, being parous and birth-weight Z-score of the neonate of the previous pregnancy. Multiple linear regression analysis was used to define the contribution of maternal variables that influence the measured MCA-PI and UA-PI and express the values as multiples of the median (MoMs). The cerebroplacental ratio (CPR) MoM was calculated by dividing MCA-PI MoM by UA-PI MoM. The model was shown to provide an adequate fit of MoM values for all covariates, both in pregnancies that delivered small-for-gestational-age neonates and in those without this pregnancy complication.*

Conclusions *A model was fitted to express MCA-PI, UA-PI and CPR as MoMs after adjusting for variables from maternal characteristics and medical history that affect this measurement.* *Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Fetal hypoxemia is associated with increased impedance to flow in the umbilical artery (UA) and decreased impedance in the fetal middle cerebral artery (MCA)[1–4]. Consequently, Doppler measurement of UA and MCA pulsatility index (PI) plays a central role in the assessment and monitoring for fetal oxygenation in pregnancies with impaired placentation. Most studies have investigated the use of UA-PI and MCA-PI in pregnancies with small-for-gestational-age (SGA) fetuses, with the aims of firstly, distinguishing between those which are constitutionally small from those that are growth restricted and therefore at increased risk of perinatal death and long-term neurological morbidity and secondly, deciding the best time, place and mode of delivery[5–8]. Recent evidence suggests that a high UA-PI and low MCA-PI, regardless of fetal size, is associated independently with intrapartum fetal compromise, low neonatal blood pH and neonatal unit admission[9–12]. MCA-PI, UA-PI and their ratio (cerebroplacental ratio (CPR)) may have an important role to play in third-trimester assessment of fetal wellbeing and screening for fetal hypoxemia.

Our approach to risk assessment and screening for pregnancy complications is to apply Bayes' theorem to combine the *a-priori* risk from maternal characteristics and medical history with the results of various combinations of biophysical and biochemical measurements. However, in the application of Bayes' theorem it is essential to standardize the measured values of biomarkers for any variables included in the prior model. The risk of delivering SGA neonates is affected by maternal weight, height, racial origin, cigarette smoking, medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), assisted conception, delivery of a SGA neonate in the previous pregnancy and interpregnancy interval[13,14]. Consequently, for the effective

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use of MCA-PI, UA-PI and CPR in risk assessment, these variables need to be taken into account and this can be achieved by standardizing the measured levels into multiples of the normal median (MoM) values.

The objectives of this study were to first, identify and quantify the effects of variables from maternal characteristics and medical history on fetal MCA-PI and UA-PI levels, second, present a model for standardizing MCA-PI and UA-PI measurements into MoM values and calculating CPR MoM and third, summarize the distribution of MoM values in pregnancies with normal outcomes and those that deliver SGA neonates. The main focus of this paper is on pregnancies with a normal outcome. Further details of the distribution of MoM values in pregnancies with complications are the subject of other publications.

METHODS

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending a routine third-trimester hospital visit at King's College Hospital, University College London Hospital or Medway Maritime Hospital, UK, between March 2011 and December 2014. This visit, initially at $30+0$ to $34+6$ weeks and subsequently at $35+0$ to $37+6$ weeks' gestation, included the recording of maternal characteristics and medical history and an ultrasound examination for estimation of fetal size from transabdominal ultrasound measurement of fetal head circumference, abdominal circumference and femur length. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or the fetal head circumference at 19–24 weeks[15,16]. Transabdominal color Doppler ultrasound was used to visualize the UA and MCA and pulsed-wave Doppler was then used to assess impedance to flow, and PI was measured when three similar consecutive waveforms were obtained[17,18].

Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital. The inclusion criteria for this study were singleton pregnancy delivering a phenotypically normal live birth or stillbirth ≥ 30 weeks' gestation. Pregnancies with aneuploidies or major fetal abnormalities were excluded.

Patient characteristics

Patient characteristics that were recorded include maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous/assisted conception requiring the use of ovulation drugs/*in-vitro* fertilization (IVF)), cigarette smoking during pregnancy (yes/no), medical history of chronic hypertension (yes/no), diabetes mellitus (yes/no), SLE or APS (yes/no), family history of pre-eclampsia (PE) in the mother of the patient (yes/no) and obstetric history including parity (parous/nulliparous if no previous pregnancies ≥ 24 weeks), previous pregnancy with PE (yes/no), gestational age at delivery and birth weight of the neonate in the last pregnancy and interval (years) since last delivery and estimated date of conception of the current pregnancy. Maternal height was measured at the first visit only and maternal weight at each visit. The birth-weight *Z*-score of the neonate in the current and last pregnancy was derived from our reference range of birth weight for gestational age at delivery[19].

Statistical analysis

The effect of the following variables from maternal characteristics and medical history on MCA-PI and UA-PI levels were examined: maternal age, weight and height, racial origin, history of chronic hypertension, diabetes mellitus Type 1 or Type 2, SLE or APS, parity, previous pregnancy with PE, gestational age at delivery and birth-weight *Z*-score of the neonate in the last pregnancy and interpregnancy interval, method of conception, smoking during pregnancy and gestational age at assessment.

Multiple linear regression models were fitted to $\log_{10}$ values of MCA-PI and UA-PI for the full set of explanatory variables, as outlined above. Continuous variables were coded initially into groups and represented as factors to identify suitable parametric forms. Backward elimination was used to identify potentially important terms in the model by sequentially removing non-significant ($P > 0.05$) variables. Effect sizes were assessed relative to the standard deviation (SD) and a criterion of 0.1 SD was used to identify terms that had little substantive impact in model predictions. Residual analyses were used to assess the adequacy of the model. Graphical displays of the relationship between gestational age and MCA-PI and UA-PI and the effects of variables from maternal characteristics and medical history on MoM values were produced for the final model. A full analysis of residuals, including an investigation of interactions, was used to check the model fit and, on the basis of this model, refinements were made. The CPR MoM was derived by dividing the MCA-PI MoM by UA-PI MoM.

The statistical software package R was used for data analyses[20].

RESULTS

Characteristics of the study population

The maternal characteristics and medical history of women that delivered SGA neonates with birth weight $< 5^{th}$ percentile and those with unaffected pregnancies are compared in Table 1.

Variables affecting fetal middle cerebral artery and umbilical artery pulsatility index

Significant independent contributions to MCA-PI were provided by gestational age (Figure 1), East Asian

Table 1 Maternal and pregnancy characteristics of women with singleton pregnancies affected by small-for-gestational age (SGA) with birth weight < 5th centile and those unaffected by SGA, attending for routine visits between March 2011 and December 2014

Characteristic	*Non-SGA* (n = *34 773*)	*SGA* (n = *2045*)
Maternal age (years)	31.3 (26.8–35.0)	30.1 (25.4–34.7)
Maternal weight (kg)	76.2 (68.4–86.8)	70.0 (62.8–80.0)
Maternal height (cm)	165.0 (160.0–169.0)	162.0 (157.5–166.0)
GA at examination (weeks)	32.5 (32.1–33.6)	32.5 (32.0–33.7)
Racial origin		
Caucasian	24 712 (71.1)	1146 (56.0)
Afro-Caribbean	6401 (18.4)	522 (25.5)
South Asian	1789 (5.1)	240 (11.7)
East Asian	1019 (2.9)	64 (3.1)
Mixed	852 (2.5)	73 (3.6)
Medical history		
Chronic hypertension	457 (1.3)	57 (2.8)
Diabetes mellitus	349 (1.0)	19 (0.9)
SLE/APS	66 (0.2)	6 (0.3)
Cigarette smoker	3002 (8.6)	400 (19.6)
Family history of PE	1027 (3.0)	76 (3.7)
Obstetric history		
Nulliparous	17 197 (49.5)	1255 (61.4)
Parous with no previous PE	16 566 (47.6)	723 (35.4)
Parous with previous PE	1010 (2.9)	67 (3.3)
Interpregnancy interval (years)	3.0 (2.0–4.9)	3.4 (2.1–5.7)
GA at delivery of previous pregnancy (weeks)	40.0 (39.0–40.0)	40.0 (38.0–40.0)
Birth weight of previous pregnancy (g)	3377 (3036–3700)	2894 (2525–3206)
Mode of conception		
Spontaneous	33 519 (96.4)	1969 (96.3)
Ovulation induction	336 (1.0)	25 (1.2)
In-vitro fertilization	918 (2.6)	51 (2.5)

Data are given as median (interquartile range) or *n* (%). APS, antiphospholipid syndrome; GA, gestational age; PE, pre-eclampsia; SLE, systemic lupus erythematosus.

racial origin, being parous and birth-weight *Z*-score of the neonate of the previous pregnancy. Significant independent contributions to UA-PI were provided by gestational age (Figure 1), Afro-Caribbean, East Asian and mixed racial origin, cigarette smoking, being parous and birth-weight *Z*-score of the neonate in the previous pregnancy. Linear mixed models, with random effects to represent random effects between women, were fitted to the subset of variables that contributed substantively to the linear regression models (Table 2).

Figure 2 shows MCA-PI MoM diagnostics according to racial origin, history of chronic hypertension and diabetes mellitus, method of conception and smoking in women that delivered SGA neonates and those unaffected by SGA. Figure 3 shows MCA-PI MoM diagnostics according to gestational age, maternal weight and birth-weight *Z*-score of the neonate in the last pregnancy, in women that delivered SGA neonates and those unaffected by SGA.

Figure 4 shows UA-PI MoM diagnostics according to racial origin, history of chronic hypertension and diabetes mellitus, method of conception and smoking in women that delivered SGA neonates and those unaffected by SGA. Figure 5 shows UA-PI MoM diagnostics according to gestational age, maternal weight and birth-weight *Z*-score of the neonate in the last pregnancy in women that delivered SGA neonates and those unaffected by SGA.

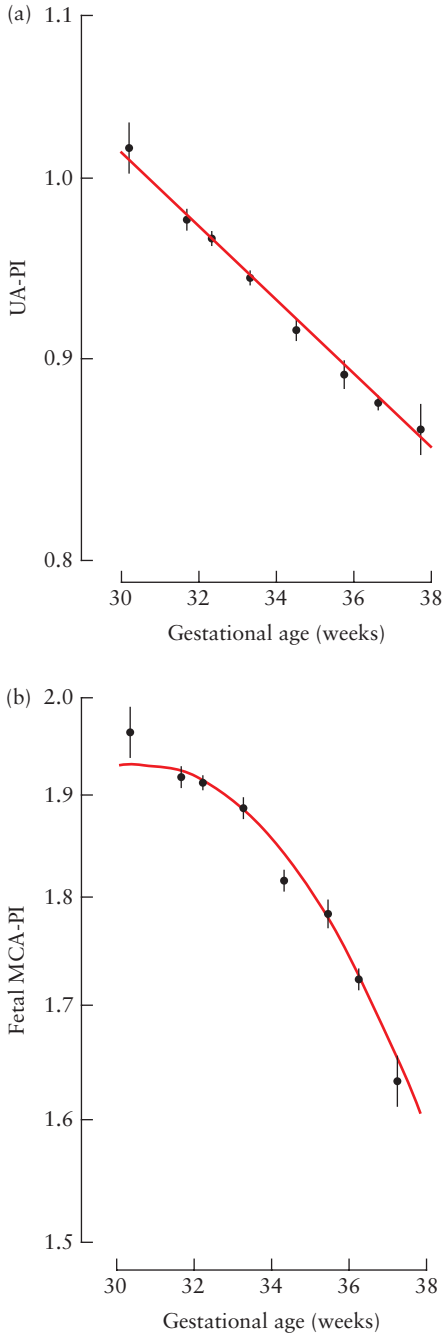

Figure 1 Relationship between median levels of (a) umbilical artery (UA) and (b) fetal middle cerebral artery (MCA) pulsatility index (PI) (with 95% CI) and gestational age.

Distributional properties of UA-PI, MCA-PI and cerebroplacental ratio MoMs

Figure 6 shows the Gaussian distribution of MCA-PI MoM, UA-PI MoM and CPR MoM. The median

Table 2 Regression models for calculating multiples of the median values for $\log_{10}$ fetal middle cerebral artery pulsatility index (PI) and umbilical artery PI

Term	*Estimate*	*95% CI*	*SE*	P
Middle cerebral artery PI				
Intercept	0.28430436	0.28028279 to 0.28832593	0.00205182	< 0.0001
Gestational age				
Gestational age (−210)*	0.00040077	0.00007205 to 0.00072950	0.00016772	0.0169
(Gestational age (−210))^2*	−0.00003322	−0.00003893 to −0.00002752	0.00000291	< 0.0001
Racial origin				
East Asian	−0.00920879	−0.01301226 to −0.00540531	0.00194055	< 0.0001
Obstetric history				
Parous	0.00646360	0.00517455 to 0.00775265	0.00065768	< 0.0001
Parous: birth-weight *Z*-score of last pregnancy	0.00108107	0.00030641 to 0.00185572	0.00039523	0.0062
Umbilical artery PI				
Intercept	0.00858155	0.00685556 to 0.02201845	0.00088061	< 0.0001
Gestational age				
Gestational age (−210)*	−0.00148188	−0.00154397 to −0.00450806	0.00003168	< 0.0001
Racial origin				
Afro-Caribbean	−0.01109663	−0.01284907 to −0.03628080	0.00089410	< 0.0001
East Asian	−0.00830560	−0.01229572 to −0.03240521	0.00203577	< 0.0001
Mixed	−0.00747836	−0.01177884 to −0.03056489	0.00219413	0.0007
Cigarette smoking	0.01116566	0.00882210 to 0.02845698	0.00119569	< 0.0001
Obstetric history				
Parous	−0.00093131	−0.00228675 to 0.00541333	0.00069155	0.1781
Parous: birth-weight *Z*-score of last pregnancy	−0.00352972	−0.00433959 to −0.01203532	0.00041320	< 0.0001

Continuous variables were centered by subtracting the mean from each measured value: *210 from gestational age in days. SE, standard error.

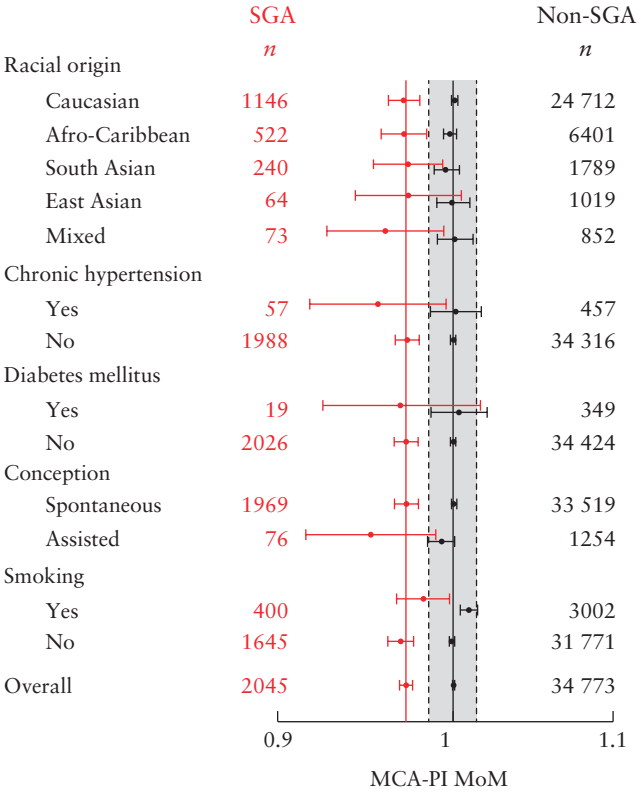

Figure 2 Median fetal middle cerebral artery pulsatility index (MCA-PI) multiples of the median (MoM) (with 95% CI) derived from the model, according to racial origin, chronic hypertension, diabetes mellitus, method of conception and smoking in women who delivered small-for-gestational-age (SGA) neonates and those unaffected by SGA. Median MoM of 1.0 (——) and median MoM ± 0.1 SD (----) are indicated. Median MoM for pregnancies with SGA neonates = 0.9725 (——).

and 5th, 10th, 90th and 95th percentiles for MCA-PI MoM were 1.0000 (95% CI, 0.99732–1.00224) and 0.77536 (95% CI, 0.77228–0.77812), 0.81656 (95% CI, 0.81428–0.81920), 1.19265 (95% CI, 1.19022–1.19523) and 1.23968 (95% CI, 1.23731–1.2413), respectively. The estimated SD for $\log_{10}$ MCA-PI was 0.062648 (95% CI, 0.062176–0.063128).

The median and 5th, 10th, 90th and 95th percentiles for UA-PI MoM were 1.00000 (95% CI, 0.99821–1.00225) and 0.76936 (95% CI, 0.76706–0.77123), 0.81325 (95% CI, 0.81090–0.81517), 1.20084 (95% CI, 1.19740–1.20361) and 1.25103 (95% CI, 1.24750–1.25396), respectively. The estimated SD for $\log_{10}$ UA-PI was 0.064993 (95% CI, 0.064503–0.065491).

The median and 5th, 10th, 90th and 95th percentiles for CPR MoM were 1.00000 (95% CI, 0.99735–1.00273) and 0.72373 (95% CI, 0.72055–0.72712), 0.77650 (95% CI, 0.77379–0.77953), 1.28422 (95% CI, 1.27931–1.28883) and 1.37924 (95% CI, 1.37346–1.38597), respectively. The estimated SD for $\log_{10}$ CPR was 0.085515 (95% CI, 0.084871–0.086170).

DISCUSSION

Main findings of the study

The findings of this study demonstrate that, during the third-trimester of pregnancy, MCA-PI decreases with gestational age, is lower in women of East Asian racial origin and it is higher in parous than in nulliparous women and increases with birth-weight *Z*-score of the neonate in the previous pregnancy. Similarly, UA-PI decreases with gestational age, it is lower in women of Afro-Caribbean,

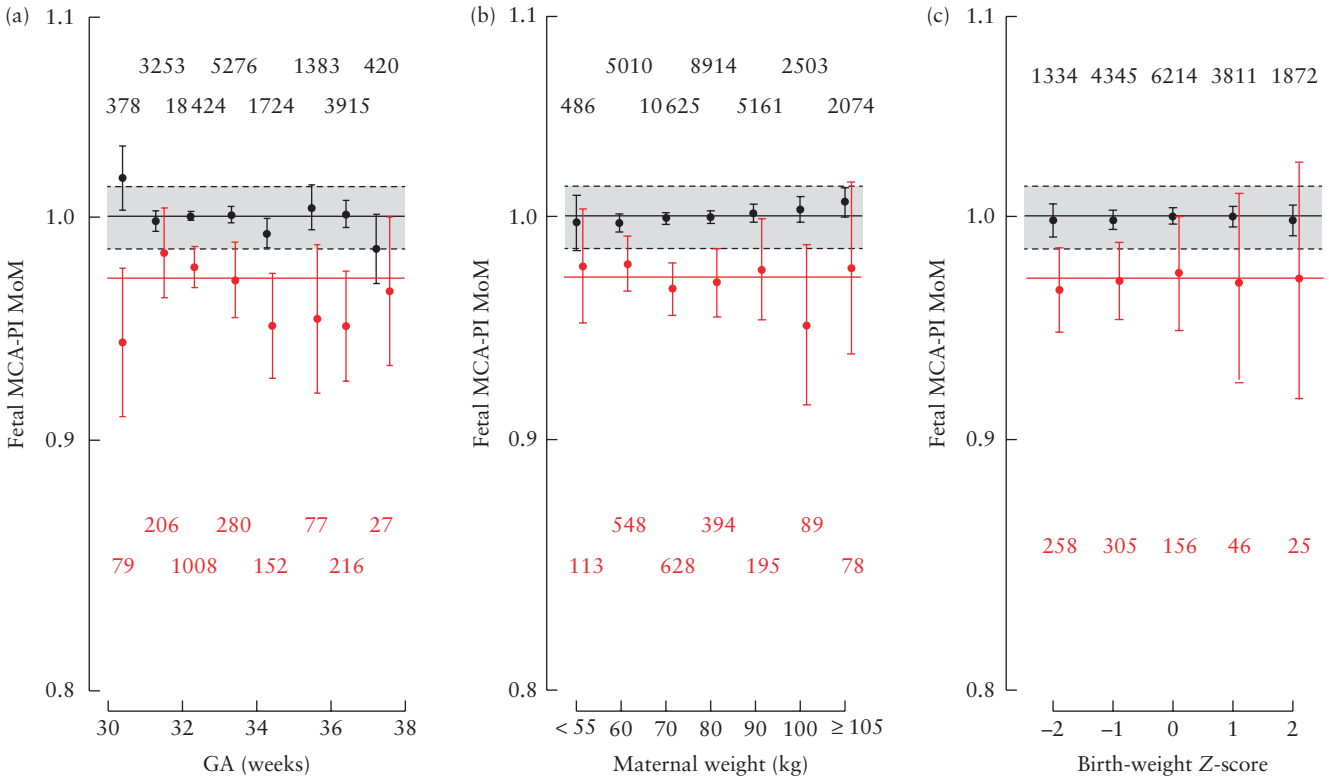

Figure 3 Median fetal middle cerebral artery pulsatility index (MCA-PI) multiples of the median (MoM) (with 95% CI) derived from the model, according to gestational age (a), maternal weight (b) and birth-weight *Z*-score of neonate in last pregnancy (c), in women who delivered small-for-gestational-age (SGA) neonates (red values) and those unaffected by SGA (black values). Median MoM of 1.0 (——) and median MoM ± 0.1 SD (----) are indicated. Median MoM for pregnancies with SGA neonates (——) is shown. GA, gestational age.

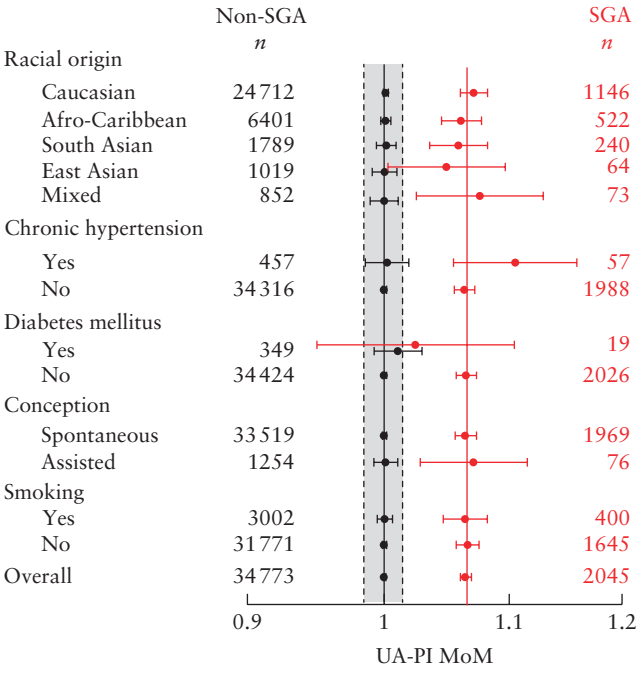

Figure 4 Median umbilical artery pulsatility index (UA-PI) multiples of the median (MoM) (with 95% CI) derived from the model, according to racial origin, chronic hypertension, diabetes mellitus, method of conception and smoking, in women who delivered small-for-gestational-age (SGA) neonates and those unaffected by SGA. Median MoM of 1.0 (——) and median MoM ± 0.1 SD (----) are indicated. Median MoM for pregnancies with SGA neonates = 1.0647 (——).

East Asian and mixed racial origin than in Caucasian women, higher in cigarette smokers than in non-smokers, it is lower in parous than in nulliparous women and higher in parous women with a low birth-weight *Z*-score of the neonate in the previous pregnancy and lower in parous women with a high birth-weight *Z*-score of the neonate in the previous pregnancy.

Multiple linear regression was used to define the contribution of maternal variables that influence the measured MCA-PI and UA-PI and express the values as MoMs. The model was shown to provide an adequate fit of MoM values for all covariates both in pregnancies that delivered SGA neonates and those unaffected by SGA.

Strengths and limitations of the study

The strengths of this study are firstly, prospective examination of a large population of pregnant women attending for routine care in the third-trimester of pregnancy for assessment of fetal anatomy, growth and wellbeing, secondly, measurement of MCA-PI and UA-PI by appropriately-trained sonographers and thirdly, application of multivariable regression analysis to define the contribution and interrelations of variables that influence the measured values of MCA-PI and UA-PI. The main limitation of the study is that the data were confined to the third-trimester of pregnancy.

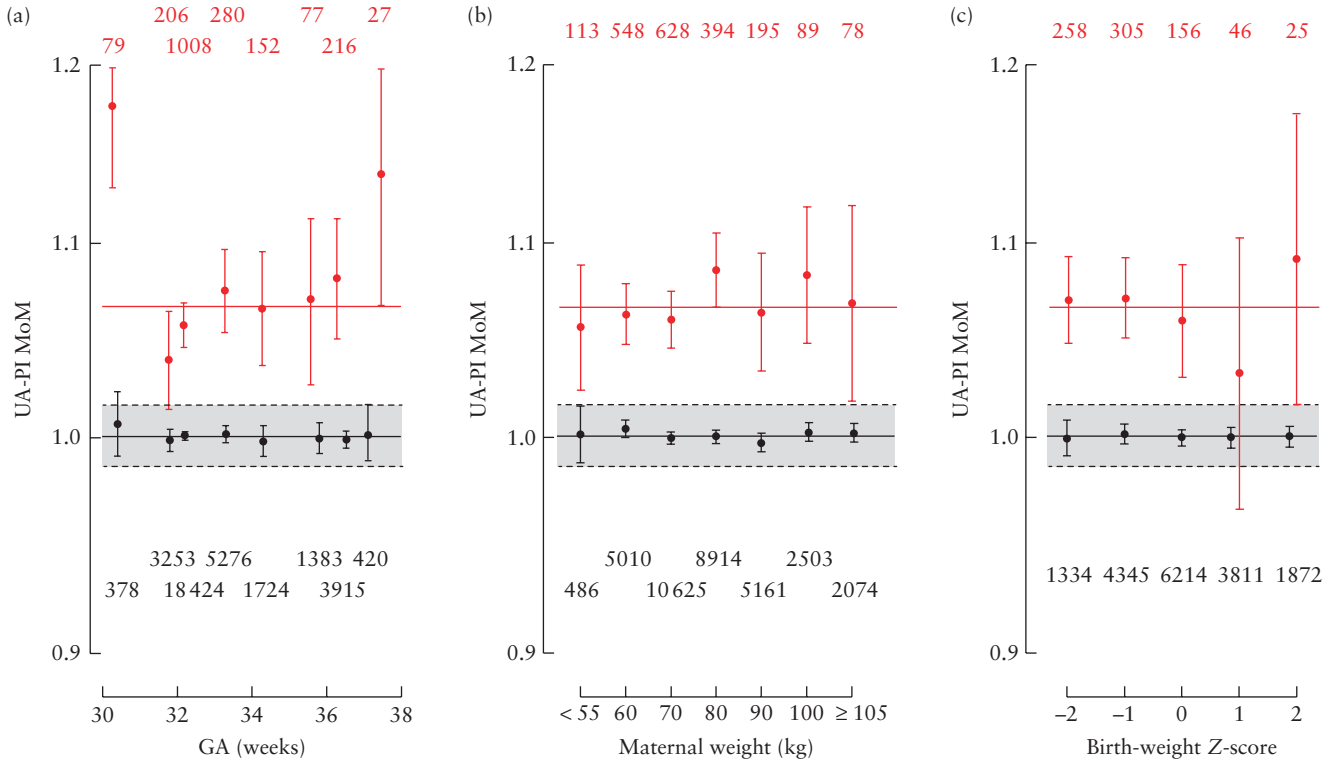

Figure 5 Median umbilical artery pulsatility index (UA-PI) multiples of the median (MoM) (with 95% CI) derived from the model, according to gestational age (a), maternal weight (b) and birth weight *Z*-score of neonate in last pregnancy (c), in women who delivered small-for-gestational-age (SGA) neonates (red values) and those unaffected by SGA (black values). Median MoM of 1.0 (——) and median MoM ± 0.1 SD (----) are indicated. Median MoM for pregnancies with SGA neonates (——) is shown. GA, gestational age.

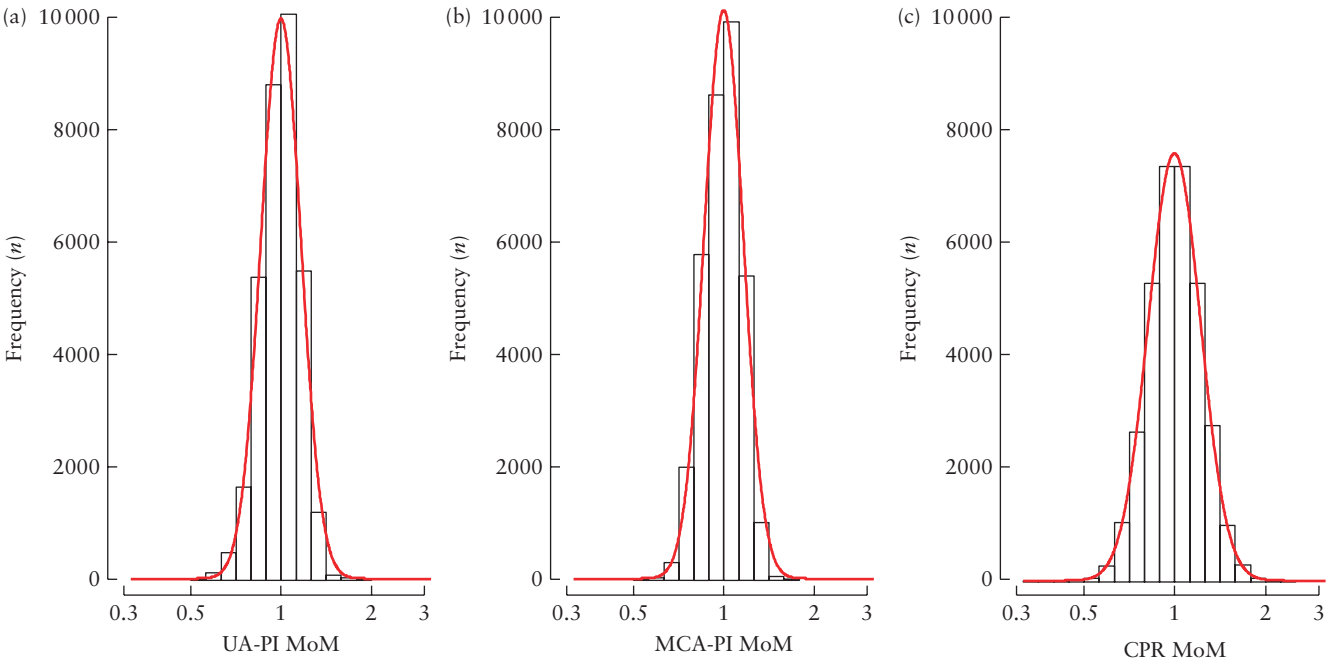

Figure 6 Gaussian distribution of: (a) umbilical artery pulsatility index (UA-PI), (b) fetal middle cerebral artery pulsatility index (MCA-PI) and (c) cerebroplacental ratio (CPR) multiples of the median (MoM) values.

Comparison with findings of previous studies

We found that UA-PI and MCA-PI decrease with increasing gestational age and these findings are compatible with those of previous studies[17,21–23]. We found that, in parous women, MCA-PI is higher and UA-PI is lower than in nulliparous women; one previous study involving women at 37–42 weeks' gestation, reported that MCA-PI was higher in parous than in nulliparous women, but UA-PI was not significantly different[24]. We found that UA-PI, but not MCA-PI, is higher in cigarette smokers than in non-smokers and these findings are compatible with those of previous studies[25–27]. We found that UA-PI, but not MCA-PI, is lower in women of Afro-Caribbean racial origin than in Caucasian women; one previous study reported that impedance to flow in the UA at 30–36 weeks' gestation was decreased in women of African racial origin[28].

Implications for clinical practice

Measurement of MCA-PI, UA-PI and CPR is useful in screening for fetal hypoxemia. The effective use of these Doppler indices in risk assessment and screening necessitates that gestational age and variables from maternal characteristics and medical history which affect these measurements in normal pregnancies are taken into account.

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